The Woven Sensorium: An Examination of Aberrant Cross-Sensory Experiences in Hyperexcitable Cortex

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Declaration

I declare that the work presented in this thesis is, to the best of my knowledge and belief, original and my own work. The material has not been submitted, either in whole or in part, for a degree at this, or any other university. For transparency, research from my MSc provided pilot work for Chapter 2, but this Chapter 2 bears no resemblance to the MSc thesis and is original. This thesis does not exceed the maximum permitted word length of 80,000 words including tables, figures, and footnotes, but excluding the thesis abstract, bibliography, and appendices.

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Abstract

A heightened predisposition to anomalous perceptual experiences is associated with aberrant patterns of neuronal activity in the cerebral cortex, referred to as cortical hyperexcitability. Increasingly evidence across clinical and neurotypical populations suggests that, where an individual experiences anomalous perceptual experiences, these predominantly occur across multiple sensory domains, and are not confined to a single modality. This has led to the suggestion that cortical hyperexcitability may be a domain-general property of predisposition to aberrant perceptual experiences. The present thesis examined this hypothesis in relation to both state-based and trait-based factors of cortical hyperexcitability in neurotypical individuals. The underlying motivation was that high gain states associated with cortical hyperexcitability may lead to a misattribution of neuronal filtering, creating susceptibility to sensory 'cross-talk' from one domain into another.

In Chapter 2 an Exploratory Factor Analysis with Parallel Analysis was conducted to form a trait-based measure of cortical hyperexcitability across auditory and visual domains - the Audiovisual Aberration Scale (AVAS). In Chapter 3 a multisensory adaptation of the visual Pattern Glare test was used to demonstrate a cross-sensory enhancement effect of aberrant visual experiences. Here experiences of Pattern Glare (visual irritation and distortions) associated with the presentation of irritating visual gratings were enhanced by the concurrent presentation of an irritating auditory tone. In Chapter 4 a rhythmic contrast reversal was introduced to Pattern Glare gratings, somewhat similar to photic visual flicker, to elicit visual hallucinations alongside distortions and irritation. Here hallucinations and irritation, but not distortions, demonstrated a similar cross-sensory enhancement effect with concurrent auditory stimulation. Crucially, across both Chapters 3 and 4, predisposition to cross-sensory enhancement was found to vary in sympathy with both state-based and trait-based indications of cortical hyperexcitability. Finally, in Chapter 5 a decoupling effect (*i.e.*

abolition of cross-sensory enhancement) was demonstrated by applying intermittent theta burst stimulation (iTBS) to the left Temporoparietal Junction (TPJ) prior to completing the multisensory Pattern Glare test introduced in Chapter 3. This decoupling effect was also found to vary in sympathy with both state-based and trait-based indications of cortical hyperexcitability.

Together these findings have demonstrated that cortical hyperexcitability may well work beyond the confines of a single sensory domain in modulating predisposition to anomalous perceptual experiences. A hodotopic interpretation of these results was presented, suggesting that localised gain processes at the TPJ may mediate state-based cortical hyperexcitability, and diffuse gain processes may mediate trait-based cortical hyperexcitability.

Chapter 1

Introduction

Aberrant Experiences

Broadly, perturbations in everyday veridical conscious experiences can be defined as ‘aberrant’ or ‘anomalous’ experiences. Aberrant experiences occur within one of three (non-mutually exclusive) categories: aberrant perceptual experiences, aberrant self-experiences, and aberrant beliefs (Braithwaite et al., 2011; Frith, 1996; Frith, Blakemore & Wolpert, 2000; Frith, 2005a; Frith, 2005b; Powers, Mathys & Corlett, 2017). Aberrant perceptual experiences refer to perturbations in exteroceptive sensory information – these broadly encompass hallucinations, perceptual distortions, and experiences of sensory irritation (Aleman & Larøi, 2008; Waters et al., 2014; Braithwaite et al., 2015a; Fong, Takahashi & Braithwaite 2019). Aberrant self-experiences refer to a perturbed representation of one’s sense of ‘self’, underscored primarily by non-veridical representations of bodily ownership, bodily control, and self-location (Blackmore, 1984; Ehrsson, 2012; Longo, 2015; Blackmore & Troscianko, 2024, pp. 569 – 597). Aberrant beliefs, more commonly termed delusions, refer to mistaken beliefs about oneself or the external world which are often extreme or unusual in nature and inflexible to change in light of counterevidence (Fletcher & Frith, 2009; Dudley et al., 2016; Corlett & Fraser, 2025). Both aberrant self-experiences and aberrant beliefs are beyond the scope of this thesis, which will focus on aberrant perceptual experiences particularly in the visual and auditory domains, as well as aberrant multisensory experiences – where perceptual anomalies occur across multiple sensory domains (Amad et al., 2014; Bere et al., 2024; Fernyhough, 2019; Montagnese et al., 2021; Moseley & Mitrenga, 2022; Toh, Bere & Rossell, 2022)

Aberrant Perceptual Experiences

Categories of hallucinations, distortions, and sensory irritation can be distinguished in terms of their phenomenological aspects. Although the exact definition remains disputed (for discussion see Blom, 2010), hallucinations broadly pertain to unreal percepts of sensory phenomena without a corresponding veridical source of sensory information in the environment (Sacks, 2012). These differ from perceptual distortions, where veridical stimuli within the environment are misperceived in terms of their sensory characteristics (Sacks, 2012). Sensory irritation refers to an unpleasant sense of sensory stress, discomfort, or pain, which often has a more visceral or physiological component compared to hallucinations and distortions (Wilkins, 1995; Swedo et al., 2022).

Sensory Irritation

Visual irritation, often termed '*visual stress*', refers to an unpleasant sense of discomfort or pain often induced by specific physical properties of visual stimuli (Wilkins, 1995). This pain or discomfort is often described in terms of physical sensations around the head and eyes (headaches, eye pain, eye strain) accompanied by visceral or vestibular sensations such as dizziness and nausea (Wilkins et al., 1984; Wilkins, Huang & Cao, 2004; Wilkins & Evans, 2010; Evans, Allen & Wilkins, 2017). In extreme cases, the occurrence of visual irritation has also been associated with the occurrence of seizure (Wilkins et al., 1999; Fisher et al., 2005). Overwhelmingly, the origins of visual stress are thought to be in aberrant neural activity in the visual cortex (Wilkins et al., 1984; Wilkins, Huang & Cao, 2004; Huang et al., 2011; Wilkins, 2012; Evans & Allen, 2016; Wilkins & Evans, 2022).

Auditory irritation may arise in two distinct phenomenological categories: hyperacusis and misophonia. Hyperacusis refers to an aberrant and uncomfortable perception of loudness of sound indicated by unusual intolerance and inappropriate responses to sound (Vernon, 1987; Klein et al., 1990; Baguley, 2003). In contrast, misophonia refers to a reduced tolerance to specific sounds (independent of their loudness) which are experienced as unpleasant or distressing and evoke strong negative emotional, physiological, and behavioural reactions (Jastreboff & Jastreboff, 2002; Swedo et al., 2022). Although thought to be independent in mechanism, both hyperacusis (Salvi, Wang & Ding, 2000; Sun et al., 2012; Chen et al., 2015; McGill et al., 2022) and misophonia (Schröder et al., 2014; Kumar et al., 2017; Schröder et al., 2019; Aryal & Prabu, 2024) have been linked to aberrant neural activity in the auditory cortex.

Perceptual Distortions

Visual distortions encompass changes in visual characteristics of stimuli such as clarity, form, brightness, colour, or motion, as well as erroneous persistence or disappearance (Gibson, 1966; Coren et al., 1976; Coren, 1986; Coren, Ward & Porac, 1989; de Wit et al., 2015; Silverstein & Lai, 2021). Visual distortions are particularly common when reading written text, described phenomenologically as illusory motion or disappearance of letters (Wilkins et al., 1992; Harle, Shepherd & Evans, 2006; Wilkins, Huang & Cao, 2007; Wilkins & Evans, 2010; Evans & Allen, 2016). The occurrence of visual distortions of varying phenomenology are associated with aberrant neural activity in the visual cortex (Huang et al., 2003; Braithwaite, Mevorach & Takahashi, 2015; Fong et al., 2020; Fong et al., 2022).

Auditory distortions manifest as difficulties in discrimination of auditory information (Weiner, 1967; Thompson & Lassman, 1969; Houtsma & Smurzynski, 1990). The most common phenomenological descriptions of auditory distortions are aberrations in loudness or pitch of sounds (Herny & McAuley, 2013; Marks, 1979; Neuhoff, Wayand & Kramer, 2002;

Stevens, 1955), or distortions of the properties or content of speech (Gray et al., 1980; Sanders & Goodrich, 1971; Stern et al., 2007). Distortions of loudness (Dommes et al., 2009; Röhl & Uppenkamp, 2012), pitch (Bendor & Wang, 2005; Penagos, Melcher & Oxenham, 2004), and speech (Miettinen et al., 2010; Miettinen et al., 2011; Wild, Davis & Johnsrude, 2012) are associated with aberrant neural activity in the auditory cortex.

Hallucinations

Visual hallucinations are typically divided into 'simple' and 'complex' hallucinations (Siegel, 1977). Simple hallucinations, sometimes termed Klüver constants or form constants, refers to perception of sprawling geometric shapes which may also possess properties such as motion, depth, or colour (Klüver, 1927; Klüver, 1930; Klüver, 1942; Siegel, 1977). Complex hallucinations refers to perception of salient figurative elements of realistic forms such as faces, objects, or landscapes (Collerton, Perry & McKeith, 2005; Kölmel, 1985; Manford & Andermann, 1998; Teeple, Caplan & Stern, 2009). Both simple (Billock & Tsou, 2007; 2012; Bressloff et al., 2001; Bressloff et al., 2002) and complex (Ffytche et al., 1998; Mocellin, Walterfang & Velakoulis, 2006; van Ommen et al., 2023) hallucinations are associated with aberrant neural activity in the visual cortex. However, complex hallucinations are also associated with aberrant neural activity in a broader network of cortical and subcortical structures including the prefrontal cortex, hippocampus, and thalamus (Amad et al., 2014; Behrendt, 2006; Blanke, Landis & Seeck, 2000; Carter & Ffytche, 2015; Ford et al., 2015).

Auditory hallucinations typically manifest as auditory verbal hallucinations, or the experience of hearing a voice without a corresponding external source (David, 2004; Johns, 2014; Larøi et al., 2012; McCarthy-Jones, 2017). However non-verbal hallucinations, sometimes referred to as auditory phantom perception, may also occur – typically manifesting as perception of noises such as clicking, hissing, beeping, or repetitive tinnitus-like sounds (Ahn et al., 2022; Penfield & Perot, 1963; Weisz et al., 2007). Both verbal (Allen et al., 2008; Kompus et al., 2013; Moseley, Fernyhough & Ellison, 2014) and non-verbal (De Ridder et al., 2014; Penfield & Perot, 1963) hallucinations are associated with aberrant patterns of activity in the auditory cortex. However, auditory-verbal hallucinations are also typically associated with aberrant activity in a broader network of parietal, frontal, and subcortical areas (Alderson-Day, McCarthy-Jones & Fernyhough, 2015; Allen et al., 2008; Kompus, Westerhausen & Hugdahl, 2011; Sommer et al., 2008).

Aberrant Perceptual Experiences in Clinical Populations

Aberrant perceptual experiences may in some cases occur in association with some form of underlying psychopathology or neuropathology. Non-exhaustive examples of this association are discussed below.

Schizophrenia and Psychosis

Auditory hallucinations, particularly voice-hearing experiences, are a common symptom of psychotic disorders and schizophrenia (Johns et al., 2014; Larøi et al., 2014; Waters et al., 2006; Waters et al., 2012). Though less common, increasing attention has been paid to the occurrence of visual hallucinations in schizophrenia and psychotic disorders, with an estimated prevalence between 27 – 33% of patients (Allen et al., 2023; Blom & Sommer, 2011; van Ommen et al., 2016; Waters et al., 2014). Furthermore, the occurrence of visual distortions is now considered as a potential early indication of the transition to psychosis or schizophrenia (Adámek, Langová & Horáček, 2022; Franzen et al., 2025; Silverstein, Keane & Corlett, 2021; Silverstein & Lai, 2021).

Epilepsy

Both auditory and visual hallucinations occur commonly in individuals with epilepsy primarily in the prodromal / pre-ictal (before seizure) phase, as well as during ictal (seizure) and inter-ictal (between seizures) phases (Coebergh et al., 2019; Elliot, Joyce & Shorvon, 2009a; Elliot, Joyce & Shorvon, 2009b; Panayiotopoulos, 1994; Panayiotopoulos, 1999). In addition to hallucinations, individuals with epilepsy commonly report perceptual distortions and symptoms of sensory irritation (Angeli et al., 2024; Furia et al., 2022; Kasper et al., 2010; Panayiotopoulos, 1994; Panayiotopoulos, 1999; Russell & Whitty, 1955). Amongst epilepsies, aberrant perceptual experiences across all phenomenological categories are most commonly associated with Temporal Lobe Epilepsy (Blair, 2012; Gibbs, 1951; Hermann et al., 2000; Mulder & Daly, 1952).

Migraine

Visual hallucinations and distortions in migraine, termed migraine ‘aura’, are a common symptom occurring in approximately 25 – 30 % of individuals with migraine (Kikkeri & Nagalli, 2025; Quieroz et al., 1997; Rasmussen & Olesen, 1992; Russell & Olesen, 1996; Vincent & Hadjikhani, 2007). Increasingly attention has been drawn to the occurrence of auditory aura in migraine, although an exact prevalence remains to be established (Li et al., 2024; Miller et al., 2015; Toh et al., 2024; van der Feltz-Cornelis, Biemans & Timmer, 2012). In addition, individuals with migraine report symptoms of sensory sensitivity across all stages of migraine, which heightens in the pre-ictal and ictal (during migraine headache) phases (Chronicle & Mulleners, 1996; Haigh et al., 2023; Harle & Evans, 2004; Vingen et al., 1998; Wilkins, Huang & Cao, 2007; Wilkins, 1995; Woodhouse & Drummond, 1993).

Migraineurs are of particular interest in the study of aberrant perceptual experiences, as they do not typically show a tendency towards aberrant beliefs which are observed in populations such as individuals with epilepsy (Elliot, Joyce & Shorvon, 2009a; Elliot, Joyce & Shorvon, 2009b; Devinsky & Lai, 2008) or psychosis / schizophrenia (Corlett et al., 2007; Corlett et al., 2009; Dudley et al., 2015). Therefore, migraine may serve as a window into aberrant perceptual experiences in clinical populations in the absence of typically associated aberrant beliefs.

Aberrant Perceptual Experiences in Non-clinical Populations

Strikingly, there is growing evidence that aberrant perceptual experiences observed in neurological and psychological populations also occur spontaneously in a significant proportion of the neurotypical population (*i.e.* individuals without evidence of underlying neurological or psychological conditions; Johns & van Os, 2001; Linscott & van Os, 2010; van Os et al., 1999; van Os, 2003; van Os et al., 2009; Verdoux & van Os, 2002). A substantial number of investigations in non-clinical populations demonstrate examples of auditory verbal hallucinations (Alderson-Day et al., 2017; Barkus et al., 2007; Moseley et al., 2022 ; Sommer et al., 2010a; Sommer et al., 2010b), and simple and complex visual hallucinations (Aynsworth et al., 2023; Braithwaite et al., 2015a; Fong, Takahashi & Braithwaite, 2019; Mocellin, Walterfang & Velakoulis, 2007; Rogers et al., 2024; Toh et al., 2020). However, there is also evidence for the occurrence of auditory and visual distortions (Allen et al., 2006; Bell et al., 2011; Braithwaite et al., 2015a; Fong, Takahashi & Braithwaite, 2019), and heightened auditory and visual irritation (Braithwaite et al., 2015a; Fong, Takahashi & Braithwaite, 2019; Haigh, Haggerty & Delgado, 2025; Haigh et al., 2013; Haigh et al., 2023) in neurotypical populations.

In addition to spontaneous experiences, aberrant perceptual experiences may be intentionally elicited to examine predisposition (*i.e.* the degree to which aberrant perceptual experiences occur readily) in non-clinical individuals. Such methods include conditioned (sometimes 'Pavlovian') hallucinations (Powers, Mathys & Corlett, 2017), rhythmic visual flicker (Billock & Tsou, 2007; Purkinje, 1819; Walter, 1954) and irritative visual stimuli such as Pattern Glare (Braithwaite et al., 2013; Evans & Stevenson, 2008; Wilkins et al., 1984) amongst others (for reviews see Hoffman, 1999; Rogers et al., 2021). Together, investigations of both spontaneous and elicited experiences highlight that aberrant perceptual experiences can, and do, occur in neurotypical individuals in the absence of aberrant beliefs or underlying neurocognitive impairment.

Cortical Hyperexcitability

Across clinical and non-clinical populations, the occurrence of aberrant perceptual experiences is associated with aberrant underlying patterns of neurophysiological activity in the cerebral cortex - referred to as cortical hyperexcitability (Chronicle, Pearson & Mulleners, 2006; Jardri et al., 2016; Mulleners et al., 2001; Palmer et al., 2000; van der Kamp, et al., 1996; Wilkins, 1995). Cortical hyperexcitability is characterised by heightened neuronal responsiveness, typically seen in neural responses which are aberrantly large in amplitude and short in latency (Coutts et al., 2012; Haigh, Cooper & Wilkins, 2015; Zaehle et al., 2011). This is thought to reflect failures of neuronal 'gating' - the process by which neuronal responses in post-synaptic neurons are controlled and / or attenuated in cases of strong input from pre-synaptic neurons (Badawy, Harvey & Macdonell, 2009a; Badawy, Harvey & Macdonell, 2009b; Telias & Segal, 2022; Welch et al., 1990; Welch, 2005).

Cortical hyperexcitability is increasingly viewed as two distinct but related concepts of state-based and trait-based cortical hyperexcitability (Braithwaite et al., 2015; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Joshi et al., 2024). State-based hyperexcitability refers to temporally specific, transient fluctuations in neural activity that occur in the present moment (in the here and now) and are directly linked to the occurrence of a particular aberrant perceptual experience. In contrast, trait-based hyperexcitability represents a more stable latent background context, contributing to a heightened long-term susceptibility or predisposition to aberrant perceptual experiences over time.

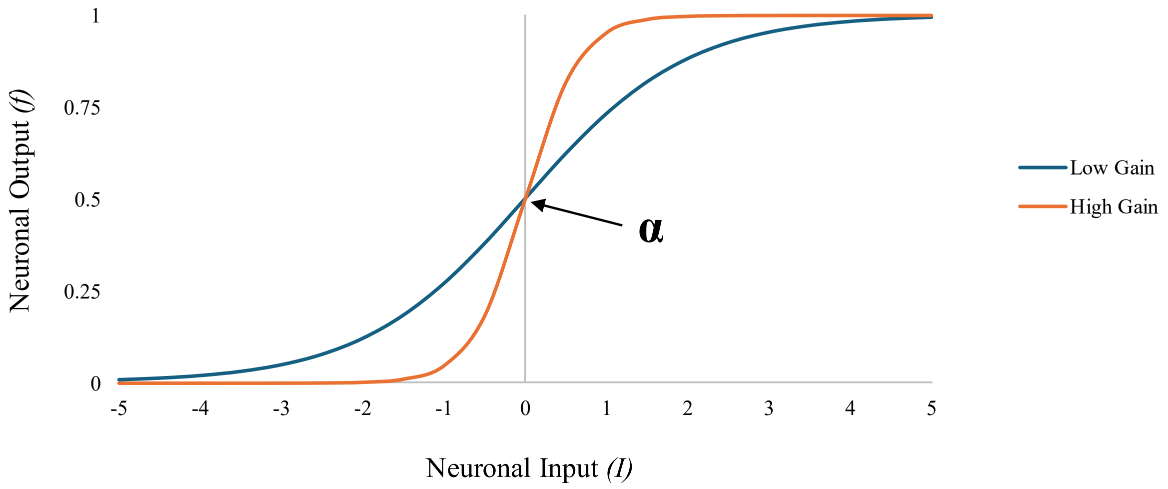
Importantly, it has been shown in the auditory domain that the relationship between state and trait-based factors mediating predisposition to aberrant perceptual experiences is not a straightforward one. For example, Kühn and Gallinat (2012) reported a dissociation where the immediate experience of hallucinations (‘state’) was linked to heightened activity in speech production regions, while a more general predisposition to hallucinations (‘trait’) was associated with aberrant activity in auditory processing areas (see also Mo et al., 2024; Zmigrod et al., 2016). Similarly, in the visual domain, neural factors of trait predisposition to hallucinations are often found in the neural connections between the visual cortex and frontal (Collerton et al., 2005; van Ommen et al., 2023) or subcortical (Erskine et al., 2019; Ford et al., 2015a; Ford et al., 2015b) structures, whilst the hallucination state is associated with more localised hyperexcitability within the visual cortex itself (Abraham & Duffy, 2001; Bressloff et al., 2002; Ffytche, 2008). These findings highlight that aberrant perceptual experiences arise through a complex interaction of state-based and trait-based factors (more extensive discussion of evidence for both state-based and trait-based hyperexcitability in aberrant perceptual experiences is presented below).

Cortical Hyperexcitability and Cortical Gain

One explanatory framework for the relationship between cortical hyperexcitability and aberrant perceptual experiences is that of cortical gain control (McColl & Wilkinson, 2000; Porciatti et al., 2000; Tsai et al., 2011). Computationally, cortical gain is defined as the slope of a neuron's input – output function, typically modelled conceptually as a sigmoid transfer function (see Figure 1; Astolfi et al., 2005; Azouz, 2005; Schwartz & Simoncelli, 2001; Wilson & Cowan, 1972; Wilson & Cowan, 1973).

Figure 1.

Sigmoid Transfers Depicting Relatively Low and High Gain



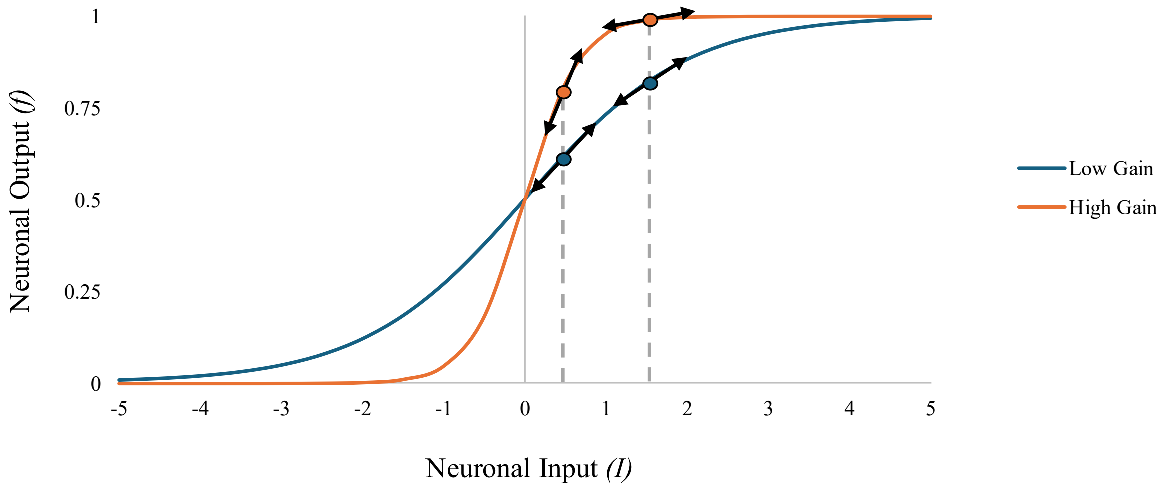
Point marked *α* depicts the inflection point of both high gain and low gain sigmoids – this is the point at which the steepness of the *f(I)* slope is maximal.

Figure 1 depicts sigmoid curves of varying steepness, representing the intrinsic gain (*g*) of two neurons. This sigmoid transfer function, *f(I),* indicates a quantified relationship between neuronal input (*I*) and resultant firing rate (neuronal output, *f)*. As such, the sigmoid transfer function can model the relative responsivity for a range of neuronal inputs and can compare the relative responsivity of neurons of differing intrinsic gain (high *g*, low *g*) for the same neuronal input. The inflection point (α) represents a fixed point along the intrinsic gain curve at which the neuronal output is maximal relative to neuronal input (i.e. steepest point of the curve; Wilson & Cowan, 1972; Wilson & Cowan, 1973).

Whilst intrinsic gain is defined by the steepness of the sigmoid transfer function, cortical gain is a highly transient property defined by the tangential slope at the Operating Point (*OP*) of the system (see Figure 2). *OP* represents the so-called 'gain state' of the system at a given point in time, and the local tangential slope at the operating point therefore determines *f(I)* for the system at a given point in time. Where *f(I)* is steep (i.e. closer to the inflection point) this would reflect a system operating in a high cortical gain state, and where the *f(I)* is shallow this would reflect a system operating in a low cortical gain state. This characterises high-gain and low-gain states; high-gain states see rapid increases in neuronal output for a change in neuronal input, whilst low-gain states see modest perturbations in neuronal output for the same change in input (Carandini & Heeger, 2012; Ferguson & Cardin, 2020). However, in high-gain states neuronal responses may also 'saturate' – whereby neuronal output is maximal, leading to little change in neuronal output for a change in neuronal input – more quickly than in low-gain states (shallow *f(I)*; see Figure 2).

Figure 2.

Example Operating Points and Corresponding f(I) Slopes for Low and High Gain



Note – for low gain function, the *f(I)* slope shows relatively little variation for a change in neuronal input, whereas under high gain the same variation in neuronal input produces a notable shift in the *f(I)* slope. In addition, at the higher input *f(I)* is relatively shallow for high gain, but not for low gain, suggesting little neuronal output – this demonstrates saturation under high gain, a neuronal '*ceiling effect*'.

Cortical gain mechanisms act to modulate responsiveness of neuronal populations to incoming sensory evidence relative to its salience, acting as a dynamic filter for signal-to-noise ratio for sensory information (Aston-Jones & Cohen, 2005; Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001). Here neurons enact a process of neuronal sensory gating, *i.e.* enhancing signals pertaining to salient sensory information, whilst suppressing irrelevant or noisy neural signals (Grunwald et al., 2003; Vogels & Abbott, 2009). Under typical gain control conditions excitatory and inhibitory mechanisms remain balanced, supressing noise in neural signals via inhibitory mechanisms and enhancing salient inputs via excitatory mechanisms (Ferguson & Cardin, 2020; Greenhouse, 2022; Hasselmo et al., 1997).

However, in circumstances where cortical gain control mechanisms are misallocated or diminished (*e.g.* in cases of cortical hyperexcitability) this gating process may become ineffective, or severely diminished (McColl & Wilkinson, 2000; Porciatti et al., 2000; Tsai et al., 2011). As a result, the system may fail to adequately filter noisy or irrelevant signals from salient sensory signals, creating conditions of 'perceptual uncertainty' – where neural representations of sensory information become unstable or unreliable (Hillyard, Vogel & Luck, 1998; Hénaff et al., 2020; Scolari & Serences, 2009; Woolley et al., 2005). These unstable representations increase the likelihood of erroneous perceptual manifestations including anomalous perceptual experiences.

Cortical Hyperexcitability and Precision-Weighted Predictive Coding

Predictive coding provides a conceptual framework for the interaction between high-level cognitive mechanisms and unstable sensory representations where anomalous perceptual experiences occur. Predictive coding proposes that perceptual representations are constructed through a Bayesian process of active inference; here afferent (incoming) sensory information is shaped by our prior expectations around external events (or 'priors'; Bastos et al., 2012; Corlett, Frith & Fletcher, 2009; Corlett et al., 2019; Friston, 2005; Powers, Kelley & Corlett, 2017; Powers, Mathys & Corlett, 2017; Rao & Ballard, 1999; Sterzer et al., 2018). Where perceptual signals are highly unstable or unreliable (*i.e.* low in perceptual precision), the active inference process allows for priors to 'fill in' or override imprecise sensory information within these perceptual signals (Friston, 2005; Powers, Kelley & Corlett, 2017; Powers, Mathys & Corlett, 2017). This process of active inference can be thought of as a dynamic bias, with greater reliance on either incoming sensory information or priors to construct perceptual representations dependent on the degree of perceptual uncertainty in sensory signals at a given point in time.

Where a mismatch arises between sensory evidence and priors this generates a ‘prediction error’ which must be resolved to create stable perceptual representations – those perceptual representations arising under prediction error are more likely to over-rely on priors and hence feature aberrations from veridical sensory information (Corlett et al., 2019; Horga et al., 2014; Powers, Mathys & Corlett, 2017). However, crucially not all prediction errors are treated equally. Rather, prediction error signals are thought to be weighted in terms of their reliability, and this weighting is thought to scale the influence of prediction error signals on perceptual representations (a proxy for perceptual precision; Clark, 2024; Haarsma et al., 2021; Palmer et al., 2019; Pezzulo, Parr & Friston, 2024). Under precision-weighted predictive coding models, cortical gain control is thought to be the neurobiological mechanism by which this precision-weighting process is implemented (Kanai et al., 2015).

To summarise, under conditions of cortical hyperexcitability neuronal representations of sensory information may become unstable, and hence low in perceptual precision (McColl & Wilkinson, 2000; Porciatti et al., 2000; Tsai et al., 2011). Typically, cortical gain control processes would filter to optimise signal-to-noise ratio and stabilise underlying neural signals, however under high-gain this process is diminished, and hence sensory signals remain low in perceptual precision (Hillyard, Vogel & Luck, 1998; Hénaff et al., 2020; Scolari & Serences, 2009; Woolley et al., 2005). Predictive coding processes attempt to override unstable sensory representations with priors, which creates a prediction error due to the low perceptual precision of unstable sensory signals (Clark, 2024; Haarsma et al., 2021; Palmer et al., 2019; Pezzulo, Parr & Friston, 2024). Under high-gain there may be an overweighting of this prediction error signal, leading to even greater reliance on priors in constructing perceptual representations, creating conditions conducive to aberrant perceptual experiences (Kanai et al., 2015; Powers, Mathys & Corlett, 2017).

Measuring Cortical Gain and Hyperexcitability in Aberrant Perceptual Experiences

Both state-based and trait-based cortical hyperexcitability in the context of aberrant perceptual experiences have been investigated using a range of behavioural measures. Although covering these in their entirety is beyond the scope of this thesis (for complete reviews see Aynsworth, Collerton & Dudley, 2017; Rogers et al., 2021; Smailes et al., 2022), a select few which hold direct relevance to this thesis are outlined below. These methodologies are often deployed in tandem with neuroimaging and / or brain-stimulation methods to directly manipulate or measure cortical hyperexcitability and cortical gain.

In neuroimaging, electroencephalography (EEG) and magnetoencephalography (MEG) measure electrical and magnetic fields produced by neuronal activity in the cortex, providing an index of electrophysiological activity which may vary in sympathy with cortical hyperexcitability (Biasiucci, Franceschiello & Murray, 2019; Cohen, 2017; Proudfoot et al., 2014; Singh, 2014). Typically these measure either: i) evoked potentials, localised neural activity time-locked and phased locked to the occurrence of a single event, or ii) neural oscillations, a spectral measure of ongoing rhythmic neural activity in various frequency bands which indicate summative generations of action potentials at multiple spatial and temporal scales (Biasiucci, Franceschiello & Murray, 2019; Cohen, 2017; Proudfoot et al., 2014; Singh, 2014; Thut, Schyns & Gross, 2011).

Alternatively, the haemodynamic (*i.e.* blood-flow) response of the brain can be measured with functional Near-infrared Spectroscopy (fNIRS), which monitors changes in the concentration of oxygenated and deoxygenated haemoglobin in neural tissue (an indirect measure of neural activity based on correlations with metabolic demand; Chen et al., 2020; Owen-Reece et al., 1999; Pinti et al., 2020).

Finally, Magnetic Resonance Imaging (MRI) can be used to generate detailed images of cerebral tissue and ongoing neural activity through strong magnetic fields which measure the distribution of water molecules via proton displacement (Grover et al., 2015; Turner & Jones, 2003; Vlaardingerbroek & Boer, 2013). Functional MRI (fMRI) detects changes in relative blood oxygenation levels which are thought to be a direct consequence of neurotransmitter action on metabolic processes (Glover, 2011; Matthews & Jezzard, 2004).

Neurostimulation methods of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) may be used to temporarily alter cortical excitability in neural structures and observe effects on behaviour (Nitsche et al., 2008; Nitsche & Paulus, 2011; Pascual-Leone, Walsh & Rothwell, 2000; Siebner & Rothwell, 2003).

Pattern Glare

The Pattern Glare (PG) test is an eminent behavioural measure of predisposition to aberrant visual experiences associated with cortical hyperexcitability; PG consists of presenting square-wave grating patterns at various spatial frequencies, some of which are known to be visually irritating and hence overwhelm visual neurons (Braithwaite et al., 2013; Evans & Stevenson, 2008; Wilkins et al., 1984; Wilkins, 1995). These grating patterns consist of: i) a low-frequency control grating at 0.5 cycles-per-degree (cpd), ii) the crucial highly irritating medium-frequency grating at 3 cpd, iii) a high-frequency control grating at 14 cpd. Medium-frequency grating patterns (optimal around 3 cycles-per-degree) are uncomfortable to our perceptual system due to the unusual relationship between the amplitude (s) and spatial frequency (f) of light waves emitted from them. Natural scenes adhere to a typical relationship of $s \approx 1/f^a$, where a is marginally less than 1 (Field, 1987). Visual scenes which depart severely from this relationship, as these medium-frequency grating patterns do, can overwhelm visual neurons leading to experiences of visual irritation (Penacchio & Wilkins, 2015; Wilkins, Penacchio & Leonards, 2018). In addition to visual irritation, these medium-frequency gratings can also elicit experiences of visual distortions and hallucinations (collectively Associated Visual Distortions, AVDs) in individuals with a heightened degree of cortical hyperexcitability (Braithwaite et al., 2013; Braithwaite, Mevorach & Takahashi, 2015; Evans & Stevenson, 2008; Harle et al., 2006; Shepherd, 2000; Wilkins et al., 1984; Wilkins, 1995).

A heightened degree of PG has been observed in a range of clinical and neurological populations typically displaying signs of elevated cortical hyperexcitability including migraine (Aurora & Wilkinson, 2007; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Fong et al., 2022; Haigh et al., 2012; Harle & Evans, 2004; Huang et al., 2003), stroke (Beasley & Davies, 2012; 2013), and epilepsy (Wilkins, Darby & Binnie, 1979; Wilkins et al., 1984; Wilkins, 1995). Crucially, elevated PG has been observed in several non-clinical populations associated with elevated cortical hyperexcitability including individuals reporting out-of-body experiences (Braithwaite et al., 2013a; Braithwaite et al., 2013b), and in association with non-clinical schizotypal traits (Torrens et al., 2023; Torrens et al., 2024). Moreover, Braithwaite, Mevorach and Takahashi (2015) found that excitatory tDCS over the visual cortex significantly increased the intensity of AVDs reported by nonclinical participants, suggesting a direct relationship between cortical hyperexcitability and Pattern Glare. This suggests that PG is an effective tool for measuring predisposition to aberrant visual experiences mediated by cortical hyperexcitability across both clinical and neurotypical populations.

Several fMRI studies have repeatedly supported this positive association between the degree of cortical hyperexcitability in the visual cortex and the intensity of AVDs in PG

(Huang & Wilkins, 2021; Huang & Zhu, 2017; Huang et al., 2003; Huang et al., 2011). In migraineurs the reported intensity of AVDs in response to medium-frequency gratings is positively associated with the amplitude of the BOLD response in the visual cortex (Huang et al., 2003), and the attenuation of these AVDs using coloured lenses (ophthalmic treatment for visual stress) is associated with an attenuation of this BOLD response (Huang et al., 2011). This provides a direct relationship between hyperexcitability in the visual cortex and experiences of PG. However, the observed increase in visual cortex activation is associated with a widespread increase in functional connection within the visual cortex itself, and with broader brain regions (Huang & Wilkins, 2021; Huang & Zhu, 2017). This may suggest that whilst hyperexcitability in the visual cortex may underlie the occurrence of AVDs, this hyperexcitability may be modulated by complex interactions with broader neural regions beyond the visual cortex.

Both fNIRS and EEG investigations support aberrations in cortical gain control as an underlying mechanism for PG susceptibility. In individuals with heightened cortical hyperexcitability the haemodynamic response to medium-frequency gratings is generally greater in amplitude and shorter in latency (Coutts et al., 2012; Haigh, Cooper & Wilkins, 2015; Haigh et al., 2013; Muthukumaraswamy et al., 2012), suggestive of a steeper neuronal input-output slope (*f(I)*). Evoked potential correlates of the heightened PG response demonstrate aberrations in early negative components of the neural response in the visual cortex (Fong et al., 2020; Haigh et al., 2019; Tempesta et al., 2021), likely reflective of aberrations in early gating of visual signals under conditions of high gain. Together, these findings indicate that PG is a suitable method for examining predisposition to aberrant visual experiences associated with cortical hyperexcitability and aberrations in cortical gain control mechanisms.

Trait-based Questionnaire Measures

Several trait-based measures of cortical hyperexcitability have been developed to examine predisposition to aberrant perceptual experiences over time. For example, the Launay-Slade Hallucination Scale (Launay & Slade, 1981) Meares-Irlen Scale (Hollis & Allen, 2006), and Visual Discomfort scale (Conlon et al., 1999) have each been developed to assess predisposition to experiences of hallucinations, distortions, and visual discomfort over time. However, each of these are entirely intuitive as their underlying latent variable structure has not been formally analysed through statistical methods such as factor analysis or parallel analysis (see overview of methodology). Other commonly used measure such as the Cardiff Anomalous Perception Scale (CAPS; Bell, Halligan & Ellis, 2006) and Positive and Negative Symptom Scale for schizophrenia (PANSS; Kay, Fiszbein & Opler, 1987), for which formal factor analysis has been conducted, however each have limitations. Both were devised to primarily measure symptoms which occur in clinical populations (psychosis, schizophrenia), rather than across clinical and non-clinical populations. In addition, the questions in these measures capture broad phenomenological aspects of aberrant perceptual experiences, rather than capturing trait predisposition to experiences which have specifically demonstrated an association with cortical hyperexcitability.

To more directly measure trait-based cortical hyperexcitability in the visual domain, the Cortical Hyperexcitability Index (CHi_II: Braithwaite et al., 2015; Fong et al., 2019) was developed. The CHi_II forms a proxy trait-based measure of cortical hyperexcitability by probing the frequency and intensity with which aberrant visual experiences associated with cortical hyperexcitability occur over time. When formally examined with exploratory factor analysis and parallel analysis, this revealed three distinct (but related) factors of: i) Heightened Visual Sensitivity and Discomfort (HVSD), ii) Aura-like Visual Hallucinatory Experiences (AVHE), and iii) Distorted Visual Perception (DVP). This fractionation of trait-based underlying the concept of cortical hyperexcitability has been strengthened further in several subsequent investigations.

This fractionation has been further supported with factors predicting selective components of behavioural (Fong et al., 2019) and electroencephalographic (Fong et al., 2020) outcomes from Pattern Glare. In addition, participants' score on the factor AVHE has been shown to mediate the efficacy of optimised multi-channel tDCS (Joshi et al., 2024). As such, the CHi_II emerges as the predominant, experimentally-validated trait-based measure of cortical hyperexcitability.

Photic Flicker Hallucinations

Rhythmic photic stimulation, or repetitive flicker of a light source, has long been known to induce visual hallucinations (von Helmholtz, 1866; Purkinje, 1819; Walter, 1954). Today, this principle has been adopted in the laboratory for the photic flicker paradigm, using repetitive flicker of a light source for the purpose of examining neurocognitive and phenomenological aspects of visual hallucinations (Allefeld et al., 2011; Amaya et al., 2023a; Amaya et al., 2023b; Amaya, Nierhaus & Schmidt, 2025; Bartossek, Kemmerer & Schmidt, 2021; Becker et al., 2009; Billock & Tsou, 2007; 2012; Ffytche, 2008; Shenyan et al., 2024). Participants primarily report the occurrence of simple visual hallucinations (sometimes Klüver of form constants), consisting of geometric shapes and patterns with characteristics of colour, motion, depth, and texture (for phenomenological overview see Billock & Tsou, 2007; 2012). However, participants may also report complex hallucinations, typically described as salient figurative elements of realistic forms, such as faces, objects, or landscapes (Shenyan et al., 2024).

Ffytche (2008) conducted a combined EEG-fMRI examination of the neurological underpinnings of flicker-induced hallucinations. Here EEG evidence suggested that the occurrence of visual hallucinations coincided with an increase in phase coherence of neural oscillations in the alpha band (8 – 13 Hz) across late areas of the visual cortex (V2 to V5). Several further studies have demonstrated the association between alpha oscillations and flicker-induced hallucinations, noting that the occurrence of visual hallucinations is associated with increased amplitude of alpha oscillations (Adrian & Mathews, 1934; Amaya et al., 2023a; Amaya et al., 2023b; Bartossek, Kemmerer & Schmidt, 2021; Becker et al., 2009; Billock & Tsou, 2012; Herrmann, 2001; Schwartzman et al., 2019).

Alpha oscillations are thought to play a role in gating neuronal responses to sensory information in the visual cortex by functionally inhibiting irrelevant inputs and increasing excitability in regions associated with processing anticipated sensory information (Foxe & Snyder, 2011; Jensen & Mazaheri, 2010). One explanation for this function is that alpha activity may have layer-specific roles in the visual cortex to modulate the overall firing rate of neurons (Haegens et al., 2011; Osipova, Hermes & Jensen, 2008; Spaak et al., 2012; van Diepen, Foxe & Mazaheri, 2019). The exact gain-control mechanism associated with alpha oscillations is debated (for summary see van Diepen, Foxe & Mazaheri, 2019). However, it has been suggested that alpha oscillations[1] gate visual signals by inhibiting or facilitating the rate of salient and irrelevant signals information through the visual pathway to optimise signal-to-noise ratio, with regular periods of excitation and inhibition exerted in different phase-angles of the oscillatory cycle (Haegens et al., 2011; Haegens et al., 2015; Mazaheri & Jensen, 2010; Spaak et al., 2012). With aberrations in cortical gain control this optimisation

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[1] Note alpha oscillations may not be solely implicated in this process – rather the interaction between alpha and gamma oscillations (30 – 200 Hz) may be implicated here (Fries, 2009; van Kerkoerle et al., 2014).

process may become ineffective, thus visual signals become low in perceptual precision and conducive to perceptual aberrations (*i.e.* hallucinations).

Ffytche (2008) also demonstrated with fMRI that the occurrence of visual hallucinations was associated with a decrease in functional connectivity between late areas of the visual cortex (V2 to V5) and the Lateral Geniculate Nucleus of the thalamus (LGN). Further fMRI investigations have extended these findings to demonstrate an increase in functional connectivity between higher-order ventroanterior thalamic nuceli and the visual cortex (Amaya et al., 2023; Amaya, Nierhaus & Schmidt, 2025).

A functional disconnection between LGN and visual cortex may indicate a shift in LGN's firing mode, from tonic mode where retinal signals are faithfully transmitted to the cortex, to burst mode where thalamic inputs become decoupled (Ffytche, 2008; Sherman, 2001). This shift to burst firing mode has been demonstrated to occur in thalamocortical circuits operating in high-gain states in vitro (Le Masson et al., 2002; Mease et al., 2016). In addition, higher-order thalamic nuclei are implicated in co-ordinating cortical activity by reducing perceptual thresholds (*i.e.* steeper input-output slope, or $f(I)$), suggesting their increased functional connectivity may further increase localised gain state (Aru et al., 2019; Takahashi et al., 2020). This may explain how low-precision sensory signals occur (decreased LGN functional connectivity), yet their advance through the visual system is enhanced (increased weighting from higher-order thalamic nuclei), resulting in highly salient aberrant visual percepts. This demonstrates that flicker hallucinations arise through a complex interaction of cortical gain processes associated within the visual cortex itself, and those gain processes which co-ordinate neural activity between diffuse neural regions.

Dysconnection Hypothesis

This relationship between aberrant perceptual experiences and neural connectivity also lends support to the Dysconnection hypothesis, which states that aberrant interactions between brain regions is an underlying pathophysiological factor which predisposes individuals to aberrant experiences (Catani & Ffytche, 2005; Friston, 1998; Friston, 1999; Friston et al., 2016; Geschwind, 1965; 1974; Stephan, Baldeweg & Friston, 2006; Stephan, Friston & Frith, 2009)[2]. This may implicate hyperexcitability at a network level, as well as localised shifts in cortical hyperexcitability, in the occurrence of aberrant perceptual experiences.

Hyperexcitability at a network-level has previously been associated with aberrant patterns of connectivity between brain regions, particularly in the context of epilepsy (Bear, 1979; Courtiol et al., 2020; Vaudano et al., 2009; Varotto et al., 2012). This relationship has been observed for functional connectivity indexed by coherence of neural oscillations in EEG signals in distinct neural regions (Samaha, Gosseries & Postle, 2017; Vetter et al., 2025), and structural neuronal connectivity between distinct neural regions (Dayan et al., 2018; Kora et al., 2023; Lopes et al., 2020; Messé, Hütt & Hilgetag, 2025). As epilepsy is a neurological condition characterised by both elevated cortical hyperexcitability and heightened predisposition to aberrant perceptual experiences (Coebergh et al., 2019; Elliot, Joyce & Shorvon, 2009a; Elliot, Joyce & Shorvon, 2009b; Panayiotopoulos, 1994; Panayiotopoulos, 1999), these findings support the notion that network-level cortical hyperexcitability may emerge (at least partially) through aberrant patterns of connectivity in cortical networks.

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[2] Note – *Dysconnection* refers to both hyper and hypo-connection within and between neural systems, not necessarily a functional or structural *disconnection*

The Hodotopic Framework

One specific branch of the Dysconnection hypothesis has emerged in the Hodotopic framework, which proposes a Dysconnective explanation for the occurrence of visual hallucinations, distortions, and irritation (Ffytche, 2008; Silverstein & Lai, 2021). Broadly, the hodotopic framework proposes that the hallucination state arises through topological (localised) changes in neural activity within a neural system, whilst the hallucination trait reflects hodological (long-range connectivity) aberrations between neural systems (Ffytche et al., 1998; Catani & Ffytche, 2005; Ffytche, 2008).

In the earlier discussed study, Ffytche (2008) demonstrated light-flicker induced hallucinations were associated with a relative decrease in hodological connectivity between the LGN and late visual cortex, yet a localised increase in neural excitability and increased functional connectivity across late areas of the visual cortex (V2 – V5). This suggests that a trait tendency towards high-gain states in hodological corticothalamic circuits within late visual cortex can subsequently create a state predisposition to topological high-gain states and cortical hyperexcitability.

Notably, Ffytche (2008) did not find significant changes in phase-coherence within the primary visual cortex (V1). Therefore, Silverstein and Lai (2021) extended the hodotopic framework, suggesting a role for early visual cortex (V1) and associated corticothalamic loops in creating predisposition to lower complexity perceptual aberrations such as distortions. Here the authors proposed a continuum of mechanism whereby low-complexity aberrant visual experiences (specifically distortions) are associated with weak pre-cortical signals from the retina, and aberrant hodological connection in early visual corticothalamic circuits between V1 and the LGN. In addition, they suggest that as the complexity of aberrant experiences increases these early visual pathways are de-emphasised, and greater emphasis is placed on the role of neurotransmitters such as acetylcholine and dopamine in higher-order cognitive networks such as the basal forebrain and striatum. In cortical gain terms, the Hodotopic framework may be seen as reflective of both localised (circuit-level) and more global (neuromodulatory) gain mechanisms contributing to the overall predisposition to these aberrant visual experiences (Aston-jones & Bloom, 1981; Ferguson & Cardin, 2020; Friston et al., 2012; Foote, Aston-jones & Bloom, 1980). However, the exact localised and global mechanisms may not be identical across the continuum of complexity.

It is important to note that these mechanisms reflect a continuum rather than two distinct models (Silverstein & Lai, 2021). However, this does support the Dysconnection hypothesis' notion that aberrant perceptual experiences may arise through complex interactions of localised and distributed cortical networks, which may differently reflect state- and trait-based factors of predisposition to aberrant perceptual experiences. In addition, the Hodotopic framework suggests that these factors may differ somewhat across different types of aberrant perceptual experiences (*i.e.* hallucinations, distortions, irritation). Therefore, examining interactions between and within cortical networks represents a crucial step in understanding neurocognitive factors of predisposition to aberrant perceptual experiences.

Aberrant Multisensory Experiences

One approach to examining the role of Dysconnection and Hodotopic processes may be through aberrant multisensory experiences, which are occurrences of aberrant perception across multiple sensory domains (Amad et al., 2014; Bere et al., 2024; Fernyhough, 2019; Montagnese et al., 2021; Moseley & Mitrenga, 2022; Toh, Bere & Rossell, 2022).

Investigations on the occurrence of aberrant multisensory experiences are limited. However, there is growing evidence to suggest that the majority of individuals who report aberrant sensory experiences do so across multiple sensory domains, including populations such as: schizophrenia (53%; Lim et al., 2016), psychosis (estimates vary from 71 - 96%; Dudley et al., 2018; Dudley et al., 2023a; Dudley et al., 2023b; Dudley et al., 2024), migraine (> 50%; Li et al., 2024; Toh et al., 2024), and neurotypical individuals who experience hallucinations (no clear estimate; Rogers et al., 2024; Toh et al., 2020).

This elevated prevalence of multisensory aberrant experiences may support a Dysconnection view of cortical hyperexcitability, suggesting that hyperexcitability may occur as a central neuronal theme rather than within isolated sensory cortices (Welch et al., 1990; Schoenen, 1996). This has given rise to the notion that cortical hyperexcitability may have cross-sensory effects on aberrant perceptual experiences, essentially creating an aberrant form of cross-modal correspondence (Driver & Spence, 2000; Spence, 2011).

Cross-modal Correspondence

A cognitive explanation has been posed for cross-sensory interactions between sensory domains via the cross-modal correspondence framework, which suggests that associations may be drawn across sensory domains due to a perceived continuity of certain attributes or dimensions of stimuli (Parise & Spence, 2008; 2009; Spence & Driver, 2004; Spence, 2011; Walker, Walker & Francis, 2012; 2015; Walker et al., 2010; Walker, 2012). From an evolutionary standpoint, cross-modal correspondence may be seen as an effective tool for resolving the '*binding problem*' – the neural process for determining which sensory signals should be bound together at a given moment (Goodale et al., 1991; Goodale et al., 1994; Roskies, 1999). Veridical resolution of the binding problem may therefore support effective multisensory integration, however aberrations in this process may result in intrusions of sensory information into irrelevant sensory representations.

Continuity between perceptual streams is typically drawn in terms of so-called ‘synaesthetic’ congruence, or temporal congruence (Spence, 2011). Synaesthetic congruence refers to non-redundant perceptual features which are deemed equivalent across sensory domains, such as lightness / brightness in the visual domain and pitch in the auditory domain (Gallace & Spence, 2006; Parise & Spence, 2008; Parise & Spence, 2009). A classic example of synaesthetic correspondence is the ‘bouba / kiki’ effect, where participants are asked to rate the strength of the association between these two words and two shapes – one with more rounded edges, and one with more angular edges (see Ćwiek et al. 2022). Typically, participants report a stronger association between the word ‘bouba’ and rounded shape, and between the word ‘kiki’ and angular shape (Ćwiek et al. 2022). Correspondence between streams is thought to occur at the neural level due to higher-order statistical regularities across sensory systems which convey spatial, phonetic, or semantic features (Körding et al., 2007; Noppeney, 2021; Sato et al., 2007; Shams & Beierholm, 2010).

Temporal congruence refers to time-bound continuity across perceptual streams, such as matched stimulus onset and offset (Di Stefano & Spence, 2025; Shore, Barnes & Spence, 2006; Spence, 2007). One such example of temporal congruence is in the sound-induced flash illusion (SIFI), where the presentation of two short auditory tones paired with a single visual flash can lead to the illusory perception of a second flash (Shams, Kamitani & Shimojo, 2000; 2002). Temporal correspondence is thought to be conveyed at the neural level through rhythmic regularities in neuronal signals underlying separate sensory streams (Di Stefano & Spence, 2025).

Although this provides a framework for understanding why cross-modal correspondences occur at a cognitive level, it lacks a coherent underlying neurobiological framework. One might tentatively suggest that cortical gain control may partially mediate correspondences between sensory domains. As high-gain states are characterised by insufficient filtering of salient signals from irrelevant background noise (Hillyard, Vogel & Luck, 1998; Hénaff et al., 2020; Scolari & Serences, 2009; Woolley et al., 2005), this may suggest that high-gain states reduce the available sensory information to resolve the binding problem. High-gain states may therefore increase the likelihood of a cross-sensory prediction error, and hence an overreliance on priors to determine the extent to which two sensory signals are bound (Corlett et al., 2019; Horga et al., 2014; Powers, Mathys & Corlett, 2017). As in unisensory perception, this overreliance on priors to 'fill in' low precision sensory information may therefore increase susceptibility to aberrations in multisensory integration. This would suggest that cortical gain control provides an eminent framework for developing a comprehensive neurocognitive framework for aberrations in cross-modal correspondence and aberrant multisensory experiences more generally.

Neural Frameworks for Multisensory Integration

Two prominent, and not necessarily mutually exclusive, suggestions for how cross-sensory signals are integrated at the neural level have been explored. Broadly the convergence of signals from separate sensory domains is thought to be enacted by multisensory neurons, which were first detected in the superior colliculus in animal models (Meredith & Stein, 1986). Multisensory neurons receive presynaptic inputs across all modalities and can enhance or depress their synaptic output dependent on spatial and temporal convergence of pre-synaptic inputs (for overview see Stein & Stanford, 2008). Where there is congruence between presynaptic inputs a high-gain state will increase the synaptic output to increase the weighting of the 'bound' sensory signal, or where there is incongruence a low-gain state will decrease synaptic output to decrease the weighting of the bound signal (Meredith, Nemitz & Stein, 1987; Meredith & Stein, 1986; Wallace & Stevenson, 2014). However, there is some disagreement on how exactly this process supports multisensory integration in humans.

Multisensory Neocortex Hypothesis

There is a suggestion that sensory information does not operate independently at the cortical level, and rather multisensory neurons may exist across the entire human neocortex including in ‘unisensory’ cortical regions (Ghazanfar & Schroeder, 2006). Evidence for the so-called multisensory neocortex has been demonstrated in several EEG and MEG investigations, which have noted neuronal activations in ‘irrelevant’ sensory cortices during unisensory tasks. For example, activation of the primary auditory cortex has been demonstrated during silent lip-reading (*i.e. visual linguistic task*) but not silent observation of general facial movements (*i.e. visual non-linguistic task;* Calvert et al., 1997). Other studies have noted an increased amplitude (Foxe et al., 2000) and decreased latency (van Wassenhove, Grant & Poeppel, 2005) of auditory ERPs with bimodal stimuli relative to auditory-only stimuli. Here the gating of each sensory input may occur via a process of mixed selectivity, whereby a single neuron responds to two independent presynaptic inputs through a dynamic weighting procedure - this may reflect a linear sum of these two inputs or a non-linear weighting process (for overview see Tye et al., 2024). From a cortical gain perspective this would suggest that sensory gating, the filtering of salient signals from irrelevant noise signals, is enacted by individual neurons which may be sited anywhere within the neocortex.

However, the fact that coalescence of sensory information from different domains can occur within a single neuron in a ‘unisensory’ cortical region does not necessarily mean that later, systems-level integrative processes are obsolete (Meredith et al., 2020). For example, although multisensory processing may occur in auditory cortical neurons, the summative output of multisensory neurons in the auditory cortex amounts to a fraction of ongoing spontaneous activity from local unisensory neurons (Meredith & Allaman, 2015). This would suggest that in terms of the overall signal-to-noise ratio, these localised multisensory processes do not meaningfully impact sensory signals at the perceptual level. This suggests there may be later cross-modal processes which can further gate the influence of neuronal inputs from one modality on another so that cross-modal correspondences manifest at the perceptual level.

Multisensory Hubs

As such, an alternative account proposes that designated multisensory hubs at later stages of sensory processing may serve a role in gating cross-sensory neuronal signals (Calvert & Thesen, 2004; Ehrsson, Holmes & Passingham, 2005; Stein & Stanford, 2008). These regions are thought to support cross-modal integration by receiving inputs from sensory cortices further down the sensory processing pathway and increasing neuronal firing where spatial or temporal aspects of neuronal activity are aligned across the two modalities (Matsuhashi et al., 2004).

There are several system-level functions by which these multisensory hubs may co-ordinate neural oscillatory activity across sensory cortices to support integration of sensory signals (for overview see Senkowski & Engel, 2024). Multisensory systems may co-regulate the amplitude of ongoing neural oscillations, increasing or decreasing oscillatory power (*i.e.* synchrony of neuronal firing) across the system to allow gain control mechanisms to appropriately weight cross-sensory prediction errors (Arnal, Wyart & Giraud, 2011; Biau et al., 2022; Roa Romero et al., 2016). As well as amplitude, multisensory systems may align temporal aspects of oscillations across the system. Multisensory hubs may co-ordinate oscillations through phase resetting, the re-alignment of oscillations into a matched point of their cycle across corresponding sensory cortices (Lakatos et al., 2009; Senkowski et al., 2005). Alternatively multisensory hubs may support entrainment, whereby oscillatory activity becomes phase-locked to repetitive external stimulation across sensory cortices leading to mutual enhancement of oscillatory power (Crosse, Butler & Lalor, 2015; Power et al., 2012; Simon & Wallace, 2017).

Typically, multisensory hubs are thought to co-ordinate neural activity at a systems level through both phase and amplitude of neural signals in functional coupling processes, which increase functional connectivity throughout the system (Senkowski & Engel, 2024). Several studies have indicated that increases in functional connectivity between sensory cortices and intermediate multisensory hubs support cross-modal integration (*e.g.* Galindo-Leon et al., 2019; Keil et al., 2014; Leonardelli et al., 2015). Although the exact mechanisms may be context-dependent and system-dependent, this suggests multisensory hubs play an important role in co-ordinating cortical gain processes across sensory cortices, and therefore in co-ordinating cross-modal correspondences at the cortical level.

The Temporoparietal Junction

One such example of a multisensory hub is the Temporoparietal Junction (TPJ), a cortical structure at the intersection of the temporal and parietal lobes comprising of the angular gyrus and posterior section of the superior temporal sulcus (Patel, Sestieri & Corbetta, 2019). Aberrations in neuronal activity at the TPJ have long been associated with the out-of-body experience (OBE), the anomalous integration of aberrant visual, motor, and vestibular sensory information leading to an observer perceiving themself from a vantage point outside their body (Blanke & Arzy, 2005; Blanke et al., 2004; Blanke et al., 2005; Blanke, 2004). In addition, associations have been demonstrated between predisposition to OBE’s and cortical hyperexcitability (Braithwaite et al., 2013a; 2013b), as well as aberrations in multisensory integration processes (Braithwaite, Watson & Dewe, 2017; Ehrsson, 2012; 2020). Of course, the OBE is not purely an aberrant perceptual experience per se and may more accurately be described as a distortion of body ownership (Ehrsson, 2012; 2020). However, there are indeed aspects of perceptual aberration experienced in the OBE, and so this does indicate that aberrations in neuronal activity at the TPJ may occur in association with aberrant cross-modal correspondence.

There are two key roles associated with the TPJ which may implicate it in state-based and trait-based predisposition to aberrant multisensory experiences across visual and auditory domains.

TPJ and Audiovisual Integration

Structural Magnetic Resonance Imaging of the TPJ has demonstrated extensive anatomical connections to both auditory (Cammoun et al., 2015; Petit et al., 2023; Wu et al., 2016; Yakar et al., 2023) and visual cortices (Niu & Palomero-Gallagher, 2023; Uddin et al., 2010; Wu et al., 2016). The TPJ is therefore anatomically suitable to form an intermediate multisensory region between lower-level visual and auditory sensory cortices. Functional Magnetic Resonance Imaging of the TPJ during multisensory tasks would support the role of the TPJ as an intermediate hub between auditory and visual cortical regions. In humans, co-activation of the TPJ with auditory and visual cortices is observed during simultaneity judgements, where the onset of auditory and visual stimuli is staggered gradually away from synchronous onset whilst participants report whether stimuli were presented simultaneously or not (Binder, 2015; Love et al., 2018; van Kemenade et al., 2017). The neuronal response at the TPJ is thought to indicate the formation of a ‘bound’ audiovisual signal, where two component unisensory signals are coalesced at the neural level as occurring from a common external source (Binder, 2015). This would suggest the TPJ forms an intermediate multisensory hub between visual and auditory cortices and is associated with determining cross-modal correspondence at the neural level.

Although the exact functions of the TPJ await clarification, it has been suggested that the TPJ coalesces sensory signals from relevant sensory cortices through precise information around temporal congruence across sensory domains (Davis, Christe & Rorder, 2009; Spierer, Bernasconi & Grievel, 2009). This may suggest that the TPJ serves the function of a neuronal temporal binding window – defining the period within which two sensory signals must co-occur (*i.e.* arrive at the TPJ) to be bound together (Powers, Hevey & Wallace, 2012; Zmigrod & Zmigrod, 2015). Animal models would predict that the more temporally aligned two signals from different sensory domains are, the greater the resulting increase in gain state at the TPJ (Meredith, Nemitz & Stein, 1987; Meredith & Stein, 1986; Wallace & Stevenson, 2014), and this may well be reflected by the increased BOLD response observed at the TPJ in temporal order judgement tasks (Binder, 2015; Love et al., 2018; van Kemenade et al., 2017). This could be seen therefore as the resolution of a cross-sensory prediction error, whereby localised gain states increase or decrease the weighting of the bound audiovisual signal depending on whether component unisensory signal fall within a single TBW (Kanai et al., 2015). Where component signals do fall within the same TBW they are bound and treated as a unitary source in perceptual representation; where component signals are separated by the TBW they are filtered and treated as separate sources in perceptual representation.

Cross-sensory TBWs are strongly associated with neural oscillatory activity in the parietal region, particularly within the alpha frequency band (8 -13 Hz; Chancel, Iriye & Ehrsson, 2022; D’Angelo et al., 2025; Graziano, Cooke & Taylor, 2005; Grivaz, Blanke & Serino, 2017; Limanowski & Blankenburg, 2016). Each phase, or complete oscillatory cycle, of the alpha wave is thought to represent a window in time within which two component inputs must co-occur to be treated as ‘bound’ at the neural level (Cecere, Rees & Romei, 2015; Schoffelen, Pesci & Noppeney, 2024; Venskus & Hughes, 2021). This account has been extended to address the interaction between alpha oscillations and gamma oscillations (30 – 200 Hz; Keil & Senkowski, 2018). Here gamma oscillations are though to form a feedforward mechanism carrying sensory signals to higher regions of the sensory processing pathway, such as the TPJ, where TBW mechanisms may enact gating mechanisms to up-weight or down-weight the binding of sensory signals (Galindo-Leon et al., 2019; Keil & Senkowski, 2018; Osipova, Hermes & Jensen, 2008; Roux et al., 2013).

The role of the TPJ in determining cross-sensory TBWs may partially explain its role in cross-modal correspondence at the neural level. By receiving neuronal inputs from auditory and visual cortices and determining the degree of temporal correspondence in their underlying neuronal signals, localised processes at the TPJ may help decode sensory evidence for continuity across modalities.

TPJ as a Hub of the Default Mode Network

In addition, the TPJ is one of several hubs of the neural default mode network (DMN). Although its exact function remains a topic of consideration, the DMN is generally considered to be a higher order system implicated in complex processes which support conscious perceptual experiences such as awareness, or the conscious processing of internal and external stimuli (Fernández-Espejo et al., 2012; Raichle, 2015). Within the DMN, the TPJ is implicated in the process of functional integration, where bottom-up sensory systems and top-down higher order cognitive processes are co-ordinated (Hagmann et al., 2008; Raichle, 2015; van den Heuvel & Sporns, 2011).

This may bear significance to cortical gain as it suggests the TPJ may have a crucial role in the precision-weighting process by integrating incoming sensory information and priors so that the degree of prediction error for a given input can be determined (Hoemann & Feldman-Barrett, 2019; Rockland & Graves, 2023; Seghier, 2013; 2022). In the case of sensory cross-talk, sensory information about temporal coherence from the TBW in combination with priors for cross-sensory inputs may help determine the degree of cross-sensory prediction error. This would align with the notion that co-activation of the DMN with sensory cortices may reflect unresolved perceptual prediction errors (Berkes et al., 2010; Carhart-Harris & Friston, 2010; Carhart-Harris et al., 2013). Where the DMN and lower-level sensory systems are highly functionally connected and co-activated, conscious awareness (and by extension perceptual precision) of external stimuli is thought to be low, and so perceptual representations are dominated by priors creating a heightened susceptibility to perceptual aberrations (Carhart-Harris & Friston, 2010; Carhart-Harris et al., 2013). In the case of sensory cross-talk, coactivation of the TPJ and sensory cortices may reflect a heightened degree of cross-sensory prediction error, creating susceptibility to aberrant multisensory perception.

The TPJ could therefore be seen as a junction between sensory systems co-ordinating cross-modal correspondence, and higher-order systems which integrate sensory information into conscious perceptual representation. Or from a hodological perspective, the TPJ may from a junction between more localised and more diffuse mechanisms implicated in sensory cross-talk (Ffytche, 2008; Silverstein & Lai, 2021).

The Temporoparietal Junction and Aberrant Multisensory Experiences

A number of structural and functional MRI investigations have been conducted examining the neural underpinnings of multisensory hallucinations, and how these differ from unisensory hallucinations (for review see Fernyhough, 2019; Montagnese et al., 2021). Generally, findings suggest a network-level dysfunction between sensory cortices and intermediate multisensory hubs such as the TPJ may underpin multisensory hallucinations (Fernyhough, 2019; Montagnese et al., 2021).

A handful of investigations have compared state-based neural activity during multisensory and unisensory hallucinations using opportunistic methods in schizophrenia and psychosis – asking participants to press a button to indicate the onset and offset of a unisensory or multisensory hallucination during constant imaging (Silbersweig et al., 1995; Jardri et al., 2013). Whilst both unisensory and multisensory hallucinations were associated with a BOLD response in relevant sensory cortices, multisensory hallucinations were additionally associated with a BOLD response at the TPJ (Silbersweig et al., 1995; Jardri et al., 2013). This mirrors the sensory cortex and TPJ coactivation patterned observed in temporal order judgement tasks, where the TPJ is thought to play a mediating role in binding sensory signals across sensory domains (Binder, 2015; Love et al., 2018; van Kemenade et al., 2017). This may suggest the TPJ plays a similar role in the state-based occurrence of multisensory hallucinations, binding sensory signals across sensory domains into a single hallucinatory percept – a form of aberrant sensory cross-talk.

In addition, several resting-state comparisons have been made between individuals experiencing unisensory and multisensory hallucinations within clinical populations to examine trait-based factors of predisposition to aberrant multisensory experiences (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015). Collectively, these investigations demonstrate that multisensory hallucinations are associated with aberrations in functional connectivity between the TPJ and other hubs of the DMN, as well as subcortical structures such as the DMN and hippocampus (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015). Interpreting these findings is more challenging with the debate around the DMN's exact function, however from a precision-weighted predictive coding perspective this may reflect aberrations of higher-order systems associated with determining prediction errors, leading to overweighting of cross-sensory prediction errors and hence 'short-cuts' from the DMN in overweighting priors relative to sensory evidence (Carhart-Harris & Friston, 2010; Carhart-Harris et al., 2013).

Together, these findings may suggest a hodotopic interpretation of the TPJ's role in aberrant multisensory experiences in clinical populations. Here an interaction between both localised (state-based) cortical gain mechanisms, and more diffuse (trait-based) cortical gain mechanisms may be considered. This presents a fascinating avenue for establishing a comprehensive explanatory framework of neurocognitive factors underlying predisposition to anomalous multisensory experiences.

Thesis Motivations and Chapter Overviews

Thesis Motivations

Despite the notable prevalence of aberrant multisensory experiences across clinical and non-clinical populations (Dudley et al., 2018; Dudley et al., 2023a; Dudley et al., 2023b; Dudley et al., 2024; Lim et al., 2016; Li et al., 2024; Rogers et al., 2024; Toh et al., 2020), the neurocognitive mechanisms underlying their occurrence await clarification. This may in part be due to the difficulty in capturing aberrant multisensory experiences in the laboratory. Up to now, investigations have relied on the chance occurrence of aberrant multisensory experiences during neuroimaging (Jardri et al., 2013; Silbersweig et al., 1995) or resting-state imaging which speaks only to trait-based mechanisms (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015). In addition, these investigations are limited to clinical populations such as in psychosis and schizophrenia where the divide between mechanisms underlying the occurrence of aberrant perceptual experiences, and mechanisms underlying aberrant beliefs about those experiences, may be unclear (Corlett et al., 2007; Corlett et al., 2009; Devinsky & Lai, 2008; Dudley et al., 2015; Elliot, Joyce & Shorvon, 2009a; Elliot, Joyce & Shorvon, 2009b).

This is one of the preeminent criticisms of research in the field of aberrant perceptual experiences – the lack of standardised tools and methodological techniques, with many researchers relying on the chance occurrence of perceptual anomalies in clinical populations (Tackett et al., 2019; Moseley et al., 2021; Smailes et al., 2022). The development of novel methodologies for examining aberrant multisensory experiences in a systematic manner, and deploying these methodologies in neurotypical populations, represents a pertinent direction for this area of research. This may allow researchers to deploy a '*functional systems*' approach to examining multisensory aberrant perceptual experiences, identifying which underlying factors of predisposition are domain-general, and which factors are domain-specific (Fernyhough, 2019).

Collectively, this thesis addresses these issues by examining the state-based and trait-based neurocognitive factors associated with predisposition to aberrant multisensory experiences, predominantly in neurotypical populations. Each investigation examined how predisposition to aberrant multisensory experiences varies in sympathy with signs of elevated cortical hyperexcitability, motivated by the suggestion that cortical hyperexcitability may occur as a central neuronal theme rather than within isolated sensory cortices (Welch et al., 1990; Schoenen, 1996).

Although a comprehensive neurocognitive account of multisensory aberrant experiences awaits further clarification, the cross-modal correspondence framework provides a helpful explanation of how aberrant cross-sensory interactions occur at the perceptual level (Spence, 2011). Here 'cross-talk' of sensory information occurs through inaccuracies in resolving the binding problem – the neural process for determining which sensory signals should be bound together at a given moment (Goodale et al., 1991; Goodale et al., 1994; Roskies, 1999). Aberrant multisensory experiences could therefore be seen as a cross-talk of aberrant sensory information from one domain into another, leading to a cross-sensory amplification of anomalous perceptual experiences.

This concept of sensory cross-talk in cortical hyperexcitability was examined in terms of two key frameworks: i) aberrations in cortical gain control, and ii) the hodotopic framework for aberrant perceptual experiences (Ffytche, 2008; Silverstein & Lai, 2021). Cortical gain control was of interest given the association between cortical hyperexcitability and the failure of cortical gain control to regulate the stability of perceptual representations (McColl & Wilkinson, 2000; Porciatti et al., 2000; Tsai et al., 2011). Sensory cross-talk was therefore considered theoretically as a failure of cortical gain control mechanisms to gate sensory signals in cross-sensory perceptual representation, leading to inefficient regulation of signal-to-noise ratios which may aberrantly enhance the salience of anomalous perceptual experiences (Aston-Jones & Cohen, 2005; Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001).

The hodotopic framework was considered as an explanation for interactions between state-based and trait-based cortical gain mechanisms for sensory cross-talk, adapting principles outlined in relation to aberrant visual experiences into multisensory domains (Ffytche, 2008; Silverstein & Lai, 2021). The hodotopic framework might predict that localised perturbations in cortical gain control would underlie the state-based occurrence of sensory cross-talk, and aberrations in more diffuse (global) cortical gain mechanisms would underlie a trait predisposition to sensory cross-talk (Ffytche, 2008; Silverstein & Lai, 2021). Neuroimaging evidence of multisensory hallucinations in clinical populations would support this view, with localised mechanisms between TPJ and sensory cortices associated with the state occurrence of multisensory hallucinations (Jardri et al., 2013; Silbersweig et al., 1995), whilst distributed network-level disfunction centred around the TPJ is associated with trait-based susceptibility (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015).

Considering both cortical gain processes and their potential hodotopic implementation therefore provides a theoretically motivated framework for examining the role of cortical hyperexcitability as a neurocognitive factor of predisposition to aberrant multisensory experiences.

Rationale For Alternative Format

Chapters 2 to 5 of this thesis are written in a publishable manuscript format which will be submitted for peer review. Each chapter in this thesis details a different investigation into how cortical hyperexcitability may be a domain-general factor of predisposition to aberrant perceptual experiences, containing a range of behavioural and neuroscientific findings. The chapters, despite forming distinct papers for submission, are logically connected and provide a comprehensive narrative regarding how cortical hyperexcitability may form both a state-based and trait-based factor of predisposition to aberrant perceptual experiences across sensory domains, how the cortical gain and hodotopic frameworks may explain this association, and how multisensory hubs such as the TPJ may play a role in co-ordinating these state-based and trait-based mechanisms.

Experimental Chapter Overviews

Chapter 2

Mainly methodologically motivated, Chapter 2 developed a novel tool for measuring predisposition to aberrant auditory and visual experiences associated with cortical hyperexcitability – the Audiovisual Aberration Scale (AVAS). Building on the solid foundations of the CHi_II in the visual domain (Braithwaite et al., 2015; Fong et al., 2019), several items were added for aberrant auditory items associated with cortical hyperexcitability. The underlying latent variable structure within the AVAS was examined via Exploratory Factor Analysis, supplemented with Parallel Analysis for more objective determination of the number of factors. Comparisons were made between Migraineurs-with-Aura, Migraineurs-without-Auara, and neurotypical participants on each AVAS factor.

Chapter 3

Here an adaptation to the visual Pattern Glare Test (Braithwaite et al., 2013; Evans & Stevenson, 2008; Wilkins et al., 1984; Wilkins, 1995) was made, pairing visual Pattern Glare gratings with auditory pure tones of various irritating and non-irritating frequencies. The intensity of Pattern Glare experiences (Associated Visual Distortions; AVDs) was examined for each visual grating and auditory tone combination. The aim was to examine whether pairing an irritating visual grating with and irritating auditory tone may enhance the intensity of AVDs – a sensory cross-talk effect. The propensity for sensory cross-talk was examined in terms of its association with a state-based measure of cortical hyperexcitability calculated from Pattern Glare test scores (ΔAVD), as well as trait-based cortical hyperexcitability as measured by the AVAS. Some exploratory analyses were also conducted comparing the propensity for sensory cross-talk between Migraineurs-with-Aura, Migraineurs-without-Auara, and neurotypical participants.

Chapter 4

A further adaptation to the Pattern Glare test was made, introducing rhythmic phase reversals to emulate the visual flicker effect used to induce photic flicker hallucinations (Allefeld et al., 2011; Amaya et al., 2023a; Amaya et al., 2023b; Amaya, Nierhaus & Schmidt, 2025; Ffytche, 2008). Gratings were phase reversed at various irritating and non-irritating frequencies, some of which are known to induce hallucinations in photic flicker (Billock & Tsou, 2007; 2012). Participants were asked to rate the intensity of various visual hallucinations, distortions, and irritation symptoms. In addition, reversed gratings were paired with frequency-modulated auditory tones, modulated at a matched rate to the visual reversal to examine whether auditory tones may enhance the intensity of aberrant visual experiences. Each subcategory of aberrant visual experience was examined separately for indications of sensory cross-talk, allowing for variation in the propensity of different types of aberrant sensory experience to be modulated by cross-sensory enhancement. Sensory cross-talk was again examined in terms of its association with state-based cortical hyperexcitability (ΔAVD), as well as trait-based cortical hyperexcitability as measured by the AVAS. An exploratory qualitative examination on participant reports of phenomenological diversity of aberrant experiences induced by phase reversal Pattern Glare is also presented.

Chapter 5

The role of the left Temporoparietal Junction (TPJ) in the occurrence of sensory cross-talk is examined. The left TPJ was selected based on neuroimaging evidence of its role in both state-based and trait-based predisposition to multisensory hallucinations (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015; Silbersweig et al., 1995). Here participants complete the adapted audiovisual Pattern Glare test (Chapter 3) before and after receiving Theta Burst Stimulation (TBS), a high-frequency form of subthreshold Transcranial Magnetic Stimulation, applied to the left TPJ. This experimental procedure was completed twice across two separate experimental sessions; once with an inhibitory form of TBS, and once with an excitatory form of TBS. Indications of sensory cross-talk were examined before and after TBS to determine whether each protocol may enhance sensory cross-talk, or attenuate sensory cross-talk. The effects of TBS on sensory cross-talk were examined in terms of their association with state-based cortical hyperexcitability (ΔAVD), as well as trait-based cortical hyperexcitability as measured by the AVAS. This aimed to reveal whether the disruption of neural processes at the TPJ by TBS may be mediated by state-based and / or trait-based cortical hyperexcitability.

Chapter 2

The Audiovisual Aberration Scale: Developing A Novel Tool to Examine Predisposition to Aberrant Visual and Auditory Experiences Associated with Cortical Hyperexcitability

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Abstract

The development of the Cortical Hyperexcitability Index (CHi_II; Braithwaite et al., 2015; Fong et al., 2019) represented several significant methodological improvements in developing a tool to quantify trait predisposition to aberrant perceptual experiences. However, the CHi_II takes a modular, domain-specific approach to cortical hyperexcitability as it is limited to measuring experiences in the visual domain only. Using Exploratory Factor Analysis with Parallel Analysis in a large sample study (*N* = 337), we explore how (or if) aberrant perceptual experiences in auditory and visual domains cluster together with regard to their frequency and intensity. Factor clustering forms the basis of a novel proxy questionnaire measure of cortical hyperexcitability – the Audiovisual Aberration Scale (AVAS). Perceptual hypersensitivities in both auditory and visual domains formed a single cluster, but not for hallucinations and distortions. Voice-hearing experiences formed a distinct factor separate from visual hallucinations and distortions. However, all three factors did show moderate-to-strong correlations, consistent with the notion of cortical hyperexcitability as a shared underlying factor of predisposition to aberrant experiences across sensory domains. Significant Migraine group differences were also observed, with Migraineurs-with-Aura demonstrating indications of elevated trait-based cortical hyperexcitability relative to both Migraineurs-without-Aura and neurotypical controls, consistent with findings around Migraine and cortical hyperexcitability (Fong et al., 2020; Fong et al., 2022). The AVAS therefore represents a promising tool for implementation alongside contemporary neuroscientific methods to better link specific aberrant brain processes to atypical conscious experiences in multisensory domains.

Introduction

1.1 Cortical Hyperexcitability

Anomalous perceptual experiences, including alterations in sensory sensitivity, hallucinatory experiences, and distorted sensory perception, are associated with aberrant patterns of electrophysiological activity in the cerebral cortex (Sowa & Pituck, 1989; Walker et al., 1995; Wilkins, 1995; van der Kamp et al., 1996; ; Ffytche et al., 1998; Palmer et al., 2000; Mulleners, et al., 2001; Chronicle, Pearson & Mulleners, 2006; Stevenson et al., 2012 ; Braithwaite et al., 2015; Fong et al., 2019; Fong et al., 2020). These aberrant patterns of activation can reflect underlying processes referred to as 'neural disinhibition' (a failure within inhibitory systems) or cortical hyperexcitability (aberrations within excitatory systems) – though both lead to an increase / elevated pattern of neural activity (Wilkins, 1995; van der Kamp et al., 1996; Palmer et al., 2000).

Elevated cortical hyperexcitability has now been identified across a legion of neurological disorders, (as well as neurotypical groups) and appears to play a central role in mediating anomalous conscious experiences. Examples include migraine with aura (Fong et al., 2020; Palmer et al., 2000; de Tommaso et al., 2014; Harriott & Schwedt, 2014), complex partial seizures of the temporal lobe (epilepsy: Panayiotopolous, 1999; Badawy et al., 2007; Badawy et al., 2013a; Badawy et al., 2013b), Charles Bonnet syndrome (CBS) (Burke, 2002; Ffytche, 2005; Ffytche, 2007; Ffytche, 2008), schizophrenia and psychosis (Ulhaas & Singer, 2010; Baumeister et al., 2017; Grent-'t-Jong et al., 2018), visual stress (Braithwaite, Mevorach, & Takahashi, 2015), and instances of spontaneous hallucinations in neurotypical individuals with no tractable pathology (Barkus et al., 2007; Braithwaite et al., 2011; Braithwaite, Broglia, Brincat, et al., 2013; Braithwaite et al., 2015).

Cortical hyperexcitability can be decomposed into both state-based and trait-based factors (Braithwaite et al., 2015; Fong et al., 2019). State-based hyperexcitability pertains to instances happening in the here and now (instance based), which may be subject to external stimulation from sensory information. Trait-based hyperexcitability reflects the latent background predisposition to these instances which are ever present over time.

1.2 Trait-based Cortical Hyperexcitability and Aberrant Experiences

One noteworthy observation mentioned above is that the same relationship between trait-based hyperexcitability and predisposition to aberrant experiences has also been observed in populations with no known underlying psychological or neurological condition (Lewis-Hanna et al., 2011; Fong et al., 2019; Honcamp et al., 2024) This suggests trait-based cortical hyperexcitability may be a key component contributing to the creation of a continuum of predisposition to aberrant experiences (Johns & van Os, 2001; Johns et al., 2004).

Previous investigations have typically focused on the role of trait-based cortical hyperexcitability in predisposition to visual hallucinations, particularly in the context of neurological conditions such as migraine and Charles-Bonnet Syndrome (Jürgens et al., 2014; Puledda et al., 2019). However, trait-based cortical hyperexcitability has also been associated with a range of other aberrant sensory experiences outside the visual domain in both clinical (Schoenen et al., 2003; Vincent & Hadjikhani, 2007; Kühn & Gallinat, 2012; Petrusic et al., 2013) and neurotypical (Ferri et al., 2017; Honcamp et al., 2024) populations. This is unsurprising given that a majority of both clinical (Dudley et al., 2023; Bere et al., 2024; Li et al., 2024; Toh et al., 2024) and neurotypical (Larøi et al., 2019; Toh et al., 2020; Rogers et al., 2024) hallucinators report experiencing hallucinations in multiple sensory domains. Collectively, these findings support the notion that trait-based cortical hyperexcitability could reflect a domain-general factor of predisposition to aberrant experiences (Welch et al., 1990; Aurora & Wilkinson, 2007; Coppola et al., 2007; Petrusic et al., 2018; Silvestro et al., 2022). It is pertinent therefore to examine the importance of trait-based cortical hyperexcitability to aberrant experiences in non-visual domains.

1.3 Trait-based Cortical Hyperexcitability and Aberrant Auditory Experiences

Aberrant auditory experiences have received relatively less attention in the context of cortical hyperexcitability, although there is evidence for a relationship in both clinical and non-clinical populations. Most notable is the experience of auditory verbal hallucinations, or voice-hearing, which also occurs in non-clinical populations despite common classification as a psychotic symptom (Larøi et al., 2012; Daalman et al., 2013; Daalman et al., 2016). In non-clinical populations elevated trait-based cortical hyperexcitability has been linked to susceptibility to voice-hearing experiences (Lewis-Hanna et al., 2011; Honcamp et al., 2024). In addition, experiences of voice-hearing have been observed several times in clinical populations who show elevated trait-based cortical hyperexcitability including migraine (Li et al., 2024; Toh et al., 2024) and schizophrenia (Spencer et al., 2009; Li et al., 2017). Reported phenomenology of voice-hearing can vary between observers, with some reporting single voices whilst others report multiple voices, and some voices which converse whilst others talk directly to the observer (Hamed, 2010; Lo et al., 2011; van der Feltz-Cornelis et al., 2012; Miller et al., 2015; Vreebrug et al., 2016). Reports of dissociative-type voice hearing (e.g. hearing voices telling the observer what to do, commenting on the observer's thoughts and actions) may also occur, although these have not been directly examined in terms of their relationship to cortical hyperexcitability to date (Nayani & David, 1996; Kucukgoncu et al., 2014; Moslkowitz & Corstens, 2018; Sengul, Sengul & Tunc, 2018; Saçmacı, Cengiz &

Aktürk, 2020). As such, a wide phenomenological range of voice-hearing experiences appear to be linked to elevated trait-based cortical hyperexcitability.

Additional (non-verbal) auditory signs of elevated trait-based cortical hyperexcitability have also been observed in the literature. First, symptoms of auditory hypersensitivity have been observed in clinical conditions associated with elevated trait-based cortical hyperexcitability such as migraine (Harriott & Schwedt, 2014; Demarquay & Mauguière, 2015) and schizophrenia (Freedman & Chapman, 1973; Landon et al., 2016). Again, the relationship between auditory hypersensitivity and elevated trait-based cortical hyperexcitability is also observed in non-clinical populations (Schreiner & Malone, 2015; McGill et al., 2023). Often co-occurring with auditory hypersensitivity are various forms of ‘noise-hearing’, sometimes equated with tinnitus, although the exact phenomenology of noise-hearing shows some variability (Kumar, 2014; Boucher et al., 2015; Levine & Oron, 2015). Again, these experiences are frequently exhibited in clinical populations who show elevated rates of trait-based cortical hyperexcitability (Rubin et al., 2002; Volcy et al., 2005; Miller et al., 2015; Mathew & Robertson, 2016; Lai & Dilli, 2020). Alongside voice hearing, these two categories of auditory hypersensitivity and noise-hearing also present aberrant auditory experiences whose presence may be indicative of elevated trait-based cortical hyperexcitability.

1.4 Questionnaire Measures of Trait-based Cortical Hyperexcitability

A significant issue with examining trait-based cortical hyperexcitability has been the lack of empirically validated tools. Examples such as the Meares-Irlen Scale (Irlen, 1983; Hollis & Allen, 2006) and Visual Discomfort Scale (Conlon et al., 1999) are entirely intuitive, and have not been formally explored through factor analysis or validated against state-based measures of cortical hyperexcitability. They therefore assume a unitary factor structure and neglect to examine whether a latent variable structure of distinct but related factors may underlie the central concept they seek to measure. In addition, such measures often suffer from poor item wording, with questions asking participants to consider multiple symptoms or concepts grouped together in a single item and provide a single response to all of them. Again, this fails to consider whether distinctions between individual symptoms or concepts which are grouped together in a single item may represent subtly distinct variables underlying the central tenant of the questionnaire. A more sensitive approach which considers a latent variable structure may offer deeper insights into the structure of cortical hyperexcitability as a construct and help refine theoretical models.

More recently, the Cortical Hyperexcitability Index (CHi_II: Braithwaite et al., 2015; Fong et al., 2019) was developed as a proxy trait-based measure of cortical hyperexcitability in the visual domain. An exploratory factor analysis with parallel analysis revealed three distinct but related clusters of aberrant experiences within its factor structure, consisting of: i) Heightened Visual Sensitivity and Discomfort (HVSD), ii) Aura-like Visual Hallucinatory Experiences (AVHE), and iii) Distorted Visual Perception (DVP), suggesting a fractionation of the previous unitary notion surrounding cortical hyperexcitability. This fractionation has been further supported with factors predicting differential components of behavioural (Fong et al., 2019) and neurophysiological (Fong et al., 2020) measures of state-based cortical hyperexcitability. In addition, participants' score on the factor AVHE has been shown to mediate the efficacy of optimised multi-channel transcranial direct-current brain stimulation (Joshi et al., 2024), supporting the efficacy of the CHi_II in capturing important individual differences in baseline brain states.

However, many of the measures available appear to focus on vision. This likely reflects the role of aberrant processes in conditions like visual stress and migraine.

Nonetheless, important questions remain as to whether hyperexcitability typically remains confined within the boundaries of specific sensory cortex or whether it could manifest itself as a more domain-general factor impacting multiple senses at the cortical level.

Overview of the Present Study

This study aimed to develop and establish a new multisensory proxy measure of trait-based signs reflecting cortical hyperexcitability across two sensory domains. This development built on the original foundation of the Cortical Hyperexcitability Index, and the revised Cortical Hyperexcitability Index_II (CHi_II; Braithwaite et al., 2015; Fong et al., 2019) though extended here into the auditory domain. The CHi_II was chosen because; (i) it has been verified empirically via an exploratory factor analysis / parallel analysis, (ii) has successfully delineated performance on a behavioural pattern-glare task which also included quantitative neurophysiological measures (Fong et al., 2020), and has revealed distinct effects on objective autonomic processes in relation to computer-modelled optimised brain stimulation (multi-channel transcranial direct-current stimulation: Joshi et al., 2024).

Two main developments were made. First, the wording of all questions was slightly modified. Previously the opening wording of these items varied with phrases such as '*Do you ever…*' and '*Have you ever…*'. In this study all items were adapted to start '*Have you ever…*' to unify items with incidence-neutral phrasing. Second, a series of new items were added that reflected anomalous auditory experiences such as heightened auditory sensitivity and voice-hearing – which are known to reflect increased cortical hyperexcitability (Spencer et al., 2009; Demarquay & Mauguière, 2015). These changes were subjected to a new exploratory factor analysis / parallel analysis on an independent large sample. Two a-priori predictions were that the new items may distribute themselves across the pre-existing factor structure – as many of the new items represented hallucinations (voice-hearing) or forms of distortions which the CHi_II represents. Alternatively, they may form their own anomalous auditory (voices) factor.

The final questionnaire, termed here the *Audiovisual Aberration Scale* (AVAS), measures the frequency and intensity of these experiences.

Methods

2.1 Participants

Three-hundred and thirty-seven participants (74.18% female, 23.44% male, 2.37% Non-binary / Third gender) aged 18-59 (*M* = 20.91, *SD* = 4.94) were recruited via Lancaster University's SONA recruitment system and private social media forums for Lancaster University students and staff. All participants received research credits or a £5 Amazon voucher as compensation for their participation.

2.2 Materials

2.2.1 Pre-Screen Questionnaire

A brief preliminary questionnaire asked participants to declare any relevant psychological and neurological disorders / experiences, including: neurosurgery, epilepsy or seizures of unknown origin, migraine, tinnitus or reoccurring noises of unknown origin, hyperacusis (hypersensitivity to sound), neurological conditions requiring medication, psychiatric conditions requiring medication, ocular conditions (e.g., astigmatisms, colour blindness), or hearing loss (partial or complete). Prevalence rates of these within the sample are available in Table 1.

Table 1.

Summary of Pre-Screen Items and Prevalence in Study Sample

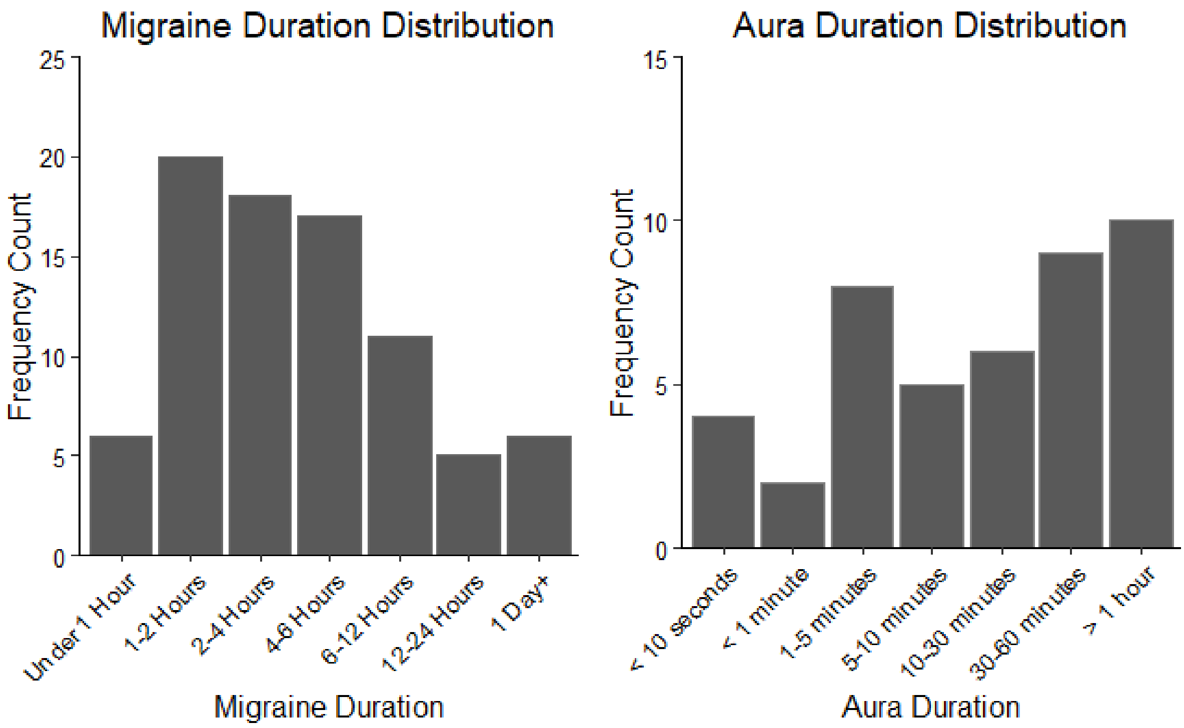
Shortened Pre-screen Item	Prevalence (%)
History of migraine?	24.93
Any ocular conditions (astigmatisms, colour blindness etc.)?	17.51
Suffered from psychological condition requiring medication?	13.95
History of hypersensitivity to sound affecting everyday life?	13.35
History of tinnitus or reoccurring noises of unknown origin?	8.61
History of hearing loss (partial or complete)?	6.23
Undergone neurosurgery, including eye or ear?	5.93
Suffered from neurological condition requiring medication?	3.56
History of epilepsy or seizures of unknown origin?	1.48

2.2.2 Migraine Characteristics Questionnaire

Those who responded ‘yes’ to having a history of migraine completed a further preliminary questionnaire (see Appendix A) to gauge the phenotypic characteristics of migraine present in the sample. Seventy participants declared themselves as migraineurs; of these, 58.81% experience migraine-with-aura and 41.19% experience migraine-without-aura. Figure 1 shows distributions for both migraine duration and aura duration.

Figure 1.

Migraine and Aura Durations in Study Sample



Several questions then gauged the phenomenological aspects of migraine in this sample. On a series of Likert scale responses, participants indicated how frequently their migraines were accompanied by aura (0% = "Never", to 100% = "Always"), and whether they experience sensitivity to light, visual discomfort, auditory discomfort, and vertigo or nausea (0 = "Definitely Not", to 100 = "Definitely Yes") during migraines. Descriptive statistics for responses to these items are presented in Table 2. As can be seen in Table 2, the most common symptoms were visual, followed by vestibular (vertigo / nausea), then auditory. Approximately 36% of migraines experienced by our sample are accompanied by aura.

Table 2.

Migraine Characteristics.

Shortened Pre-screen Item	Mean	Standard Deviation (±)
Visual Discomfort?	64.01	32.48
Sensitivity to light?	62.85	30.36
Vertigo or Nausea?	53.33	34.87
Accompanied by aura?	36.23	37.41
Auditory Discomfort?	35.62	31.99

2.2.3 Audiovisual Aberration Scale - AVAS

Cortical Hyperexcitability Index (CHi_II). The previously devised CHi_II questionnaire (Fong et al., 2019) is an indirect proxy measure of trait-based cortical hyperexcitability. It sought to characterise aberrant visual experiences (illusions, distortions, hallucinations) that are known to reflect elevated levels of underlying cortical hyperexcitability in the visual domain. The CHi_II has also been examined via electrophysiological activity with the factor structure reliably indexing differential components in the EEG (with migraine and controls: Fong et al., 2020) and indicated that baseline brain states mediate the efficacy of optimised multi-channel transcranial direct-current brain stimulation (Joshi et al., 2024).

An exploratory factor analysis (coupled with parallel analysis) revealed that the CHi_II had a 3-factor structure representing the types of visual experiences associated with cortical hyperexcitability. These factors were; i) Heightened Visual Sensitivity and Discomfort (HVSD), ii) Aura-like Visual Hallucinatory Experiences (AVHE), and iii) Distorted Visual Perception (DVP). Responses are collected on two 7-point Likert scales assessing the frequency (0 = ‘Never’, 6 = ‘All the time’) and intensity (0 = ‘Not at all’, 6 =

'Extremely Intense') of these experiences, which are then pooled to give a maximum score for each item (max 12) and the overall questionnaire.

Auditory Item Selection. The present study sought to build on this solid foundation and extend it in the auditory domain with some additional improvements to assist in the precision of the measure. The resultant measure here is referred to as the '*Aberrant Visual and Auditory Scale'* (AVAS). For creation of the AVAS, a series of items pertaining to aberrant auditory experiences (hearing voices / noises) thought also to reflect cortical hyperexcitability were created. The previously discussed literature on auditory hyperexcitability was supplemented with existing measures of aberrant perceptual experiences which were reviewed for their relevance, including the Dissociative Experiences Scale (DES; Bernstein & Putnam, 1986), Cambridge Depersonalisation Scale (CDS; Sierra & Berrios, 2000), Sensory Profile Questionnaire (SPQ; Brown et al., 2001), Hyperacusis Questionnaire (HaQ; Khalfa et al., 2002), and Cardiff Anomalous Perceptions Scale (CAPS; Bell et al., 2006). This resulted in eight items split broadly into three categories of auditory experiences: 'voice-hearing', 'noise-hearing', and 'hypersensitivity'. These additional items are summarised in Table 3.

Table 3.

Auditory Item Shortlist for CHi_II

Auditory Item	Experience
Q31. Have you ever heard a single voice talking aloud when no one else was there?	Voice-hearing
Q32. Have you ever heard two or more voices talking aloud to each other when no one else was there?	Voice-hearing
Q33. Have you ever heard two or more voices talking aloud and directly to you, when no one else was there?	Voice-hearing
Q34. Have you ever heard voices telling you what to do when no one else was there?	Voice-hearing
Q35. Have you ever heard voices commenting on what you are thinking or doing?	Voice-hearing
Q36. Have you ever heard a sound which might be described as a ringing in your ears?	Noise-hearing
Q37. Have you ever heard a sound which can be described as a roaring or whirring, which other people around you cannot hear?	Noise-Hearing
Q38. Have you ever noticed certain sounds appearing louder or more irritating than usual?	Hypersensitivity
Q39. Have you ever become distracted when surrounded by lots of noise?	Hypersensitivity

Items thirty-one to thirty-five concern aberrant voice hearing, which is a cornerstone feature of the literature on cortical hyperexcitability in the auditory domain (Dierks et al., 1999; Spencer et al., 2009; Jardri et al., 2011; Kompus et al., 2011; Allen et al., 2012). Importantly, the AVAS distinguishes between hearing a solitary voice or multiple conversing voices in items thirty-one, thirty-two and thirty-three as suggested by the CAPS (Bell et al., 2006) and several sources of relevant literature (e.g. Lo et al., 2011; Miller et al., 2015). Question thirty-four pertains to hearing voices that tell the individual what to do as suggested by the DES (Carlos & Bernstein, 1986), and question thirty-five pertains to hearing voices commenting on the individual's thoughts or actions as suggested by the DES and CAPS (Carlos & Bernstein, 1986; Bell et al., 2006).

Items thirty-six to thirty-nine concern experiences of 'noise' hearing and hypersensitivity to sound. Question thirty-six concerns tinnitus-like experiences of ringing (Rubin et al., 2002; Miller et al., 2015; Mathew & Robertson, 2016; Traynor, 2018), and thirty-seven concerns other persistent sounds of roaring and whirring which have also been reported but would not be considered tinnitus-like by its conventional descriptions (Sacks, 1970, p. 103; Mathew & Robertson, 2016; Blackmore, 2017, p. 95). Question thirty-eight concerns unusually loud or uncomfortable auditory experiences as suggested by the SPQ, HaQ, and CAPS (Brown et al., 2001; Khalfa et al., 2002; Bell et al., 2006). Question thirty-nine concerns experiences of being distracted in environments with many sounds, as suggested by the SPQ and HaQ (Brown et al., 2001; Khalfa et al., 2002). As with the original CHi-II, all items were measured on two 7-point Likert scales for 'frequency' and 'intensity' of these experiences.

Visual Item Adjustments. As well as adding new items, some adjustments were made to the formatting of the items taken from the CHi_II. Previously the opening wording of these items varied with phrases such as 'Do you ever…' and 'Have you ever…'. In this study all items were adapted to start 'Have you ever…' to unify items with incidence-neutral phrasing. This phrasing was also applied to the new auditory items.

2.3 Analysis

To examine the factor loadings of these auditory items, an exploratory factor analysis (EFA) with supplementary parallel analysis (PA) was conducted (Horn, 1965; Hayton, Allen & Scarpello, 2004). EFA is viewed as more reliable than Principal Component Analysis when constructing a model which incorporates the underlying latent variable structure of the CHi_II (Bryant & Yarnold, 1995; Williams, Onsman & Brown, 2010; Schreiber, 2021). A battery of statistical tests assessed the fitness of the data for EFA in terms of meeting the underlying statistical assumptions; first Kaiser-Meyer-Olkin's sampling adequacy and Bartlett's Sphericity Test determined a sufficient degree of common variance within the data (Kaiser & Rice, 1974; Kaiser, 1981; Williams, Onsman & Brown, 2010; Tabachnick & Fidell, 2013). Both Mardia's and Royston's multivariate normality tests ensured that the data met the assumption of Multivariate Normality; where these assumptions are violated, Principal Axis Factoring would be considered for factor extraction (Costello & Osborne, 2005). EFA, PA, and data fitness analysis were conducted in the R statistical program (version 4.2.2) using the 'psych' and 'MVN' packages.

Results

3.1 Descriptive Statistics

Prior to dissemination of the factor structure, mean total score for the AVAS was 119.47 (Median = 111, SD = 71.85, Range = 0 - 362). The total frequency and intensity scores were positively correlated (r (335) = 0.94, p < .001). The total score was moderately positively skewed with a Skewness of 0.79 and Kurtosis of 3.68. This meets the suggested criteria for normally distributed data of Skewness within +/- 2 and Kurtosis within +/-7 (Hair, Black, Babin & Anderson, 2010; Byrne, 2011). A more stringent Shapiro-Wilk test suggested a non-normal distribution ($W = 0.96$, $p < .001$). This was expected for data with a hypothesised underlying factor structure and mirrors the results of previous investigations which established the CHi and CHi_II (Braithwaite et al., 2015; Fong et al., 2019).

3.2 Factor Extraction and Rotation Methods

Both the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy (MSA = 0.94), and the significance of Bartlett's Sphericity Test ($\chi^2 = 7523.68$ (df = 741), $p < .001$), suggest a degree of common variance between variables, thus supporting the data's factorability (Kaiser & Rice, 1974; Kaiser, 1981; Tabachnick & Fidell, 2007; Williams, Onsman & Brown, 2010). Exploratory Factor Analysis (EFA) is viewed as more reliable than Principal Component Analysis when constructing a model which incorporates the underlying latent variable structure of the AVAS (Bryant & Yarnold, 1995; Williams, Onsman & Brown, 2010; Schreiber, 2021). As with the CHi_II, the data were subjected to tests of multivariate normality to select a method of factor extraction. Both Mardia's (multivariate skewness = 404.3, $p < .001$; multivariate kurtosis = 1998.48, $p < .001$) and Royston's (H = 3296.50, $p < .001$) tests suggest the data do not meet the assumptions of multivariate normality. Principle

Axis Factoring (PAF) is considered the optimal method of factor extraction where assumptions of multivariate normality are violated (Costello & Osborne, 2005).

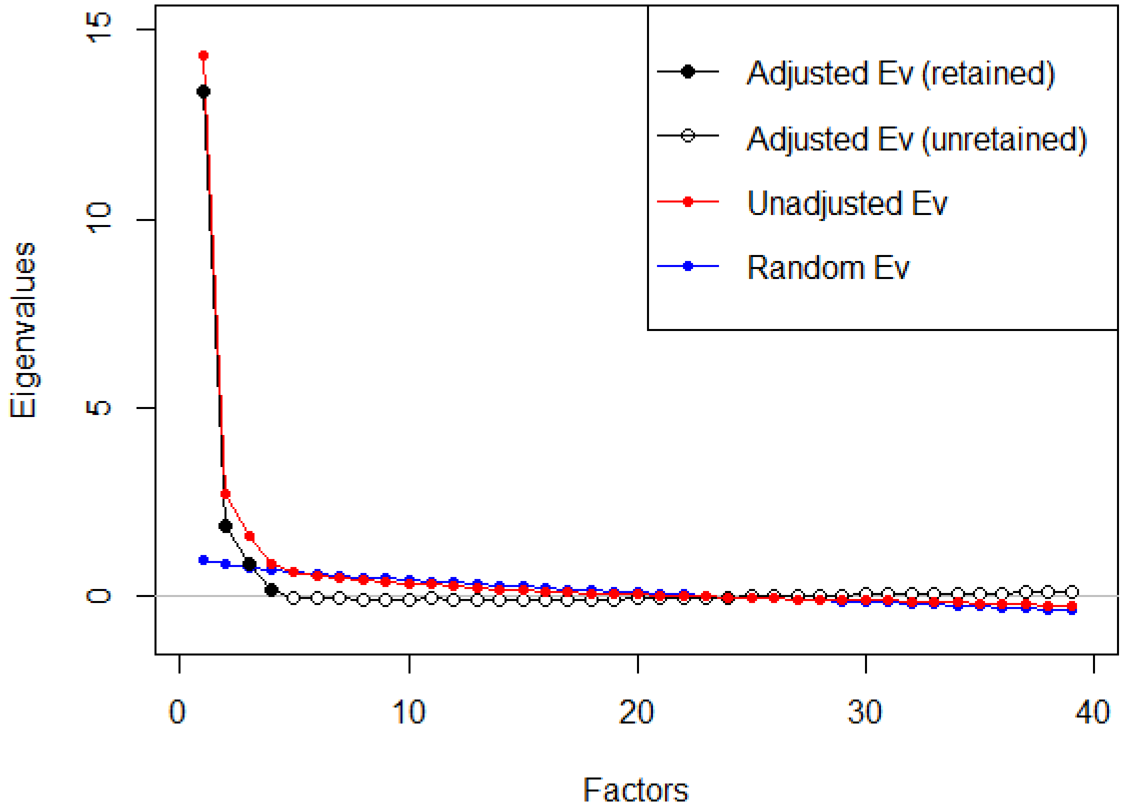
Factor rotation attempts to find the simplest factor solution within which all variables load stably (> .4) onto a single factor extracted in PAF, and poorly (< .1) onto others (Browne, 2001; Osborne, 2015). Previous investigations suggest extracted factors from the CHi_II data correlate significantly (all r > .5) with each other (Braithwaite et al., 2015; Fong et al., 2019). As such, oblique Promax rotations were used over orthogonal methods (Fabrigar, Wegener, MacCallum & Strahan, 1999; Williams, Osman & Brown, 2010; Fabrigar & Wegener, 2012; Howard, 2016).

3.3 Factor Extraction

Initially, a visual analysis of the Scree plot (see Figure 2) suggested a 4-factor model (Cattell, 1966). Data was also subjected to a more objective Parallel analysis (PA); random factors were generated from Monte Carlo simulations under conditions of equal sample size and number of variables to the true data set (Horn, 1965). This was conducted using the 'paran' command from the 'paran' package in Rstudio (version 1.5.3; Dinno, 2018). Alpha was set at 0.01 (99th percentile) to counteract the factor over-extraction flaw in Horn's initial methodology (as suggested by Glorfeld, 1995). PA stipulates that factors with Eigenvalues greater than their simulated counterpart should be retained. Based on these criteria a model which retained 4 factors was proposed, however the fourth factor did not retain more than four stably loading items (> .4), justifying its rejection for the final model (Costello & Osborne, 2005; Osborne, 2015).

Figure 2.

Parallel Analysis Scree Plot



3.4 Final Factor Structure

As a result, Principal Axis Factoring using Promax rotations (converged within 6 iterations) were used to extract 3 factors. This model explained 47.32% of the variance in the data (see Table 4 for overall factor structure). We used a loading value of .40 as a minimum criterion for item retention. Any items without a loading value < .40 were dropped (Tabachnik & Fidell, 2013).

Table 4.

Factor Structure and Cronbach's Alpha for AVAS Questionnaire

	Factor			**Communalities**	
Abbreviated Question	**1**	**2**	**3**	**Initial**	**Extracted**
Q4 - Indoor lights so bright they seem irritating	**1.00**	-0.23	-0.06	0.69	0.31
Q39 - Distracted when surrounded by sound	***0.86***	*-0.23*	*0.01*	*0.52*	*0.48*
Q2 - Overwhelmed by visual information	**0.83**	-0.12	0.02	0.58	0.42
Q16 - Working on computer irritates eyes	**0.81**	-0.11	-0.06	0.50	0.50
Q1 - Sensitivity to external visual information	**0.79**	0.05	-0.18	0.55	0.45
Q18 - Irritation reading under fluorescent lights	**0.78**	-0.08	-0.03	0.50	0.50
Q7 - Certain environments visually uncomfortable	**0.78**	0.01	-0.03	0.58	0.42
Q12 - Days when lights / colours seem more intense	**0.67**	0.11	-0.04	0.54	0.46
Q38 - Sounds appear loud / irritating	***0.67***	*-0.08*	*0.10*	*0.44*	*0.56*
Q11 - Dizzy / nauseous due to lights / visual patterns	**0.63**	0.12	-0.03	0.49	0.51
Q20 - Discomfort / irritation from viewing headlights	**0.58**	0.16	-0.09	0.43	0.57
Q13 - Discomfort looking at certain patterns	**0.6**	0.09	0.07	0.49	0.51
Q17 - Perceptual distortions when tired / fatigued	**0.55**	0.16	0.05	0.49	0.51
Q14 - Headache induced by visual information	**0.52**	0.08	0.09	0.39	0.61
Q21 - Irritation from certain fonts / letters	**0.52**	0.08	0.10	0.41	0.59
Q36 - Ringing sound in ears	***0.50***	*0.03*	*0.14*	*0.37*	*0.63*
Q28 - Spiral, tunnel, or funnel-like shape	-0.24	**0.80**	-0.02	0.42	0.58
Q27 - Loss of vision surrounded by zigzags	-0.18	**0.87**	-0.07	0.52	0.48
Q29 - Illusory spiderweb type patterns	-0.21	**0.72**	0.09	0.42	0.58
Q26 - Coloured balls, or circular shapes / patterns	0.03	**0.67**	-0.10	0.40	0.60
Q9 - Flashes of colour when nothing is there	0.18	**0.63**	-0.12	0.49	0.51
Q30 - World drained of colour / vibrancy	-0.01	**0.58**	0.08	0.39	0.61
Q23 - Flashes of dynamic patterns (e.g., zigzags)	0.07	**0.65**	-0.06	0.44	0.56
Q24 - Isolated spot of blindness in visual field	-0.04	**0.59**	0.03	0.33	0.67
Q22 - Sudden narrowing of visual field	0.03	**0.56**	0.05	0.38	0.62
Q15 - Visual distortions when looking around	0.24	**0.52**	-0.03	0.47	0.53
Q25 - White / black dots resembling static	0.20	**0.44**	-0.01	0.36	0.64
Q6 - Transient flashes / spots of white light	0.34	**0.51**	-0.09	0.50	0.50
Q10 - Appearance of objects / shapes changes	0.15	**0.43**	0.23	0.51	0.49
Q8 - Fleeting shapes when nothing is there	0.32	**0.44**	-0.04	0.46	0.54
Q34 - Voices telling you what to do	*-0.10*	*0.04*	***0.82***	*0.63*	*0.37*
Q32 - Two or more voices talking to each other	*-0.04*	*-0.04*	***0.85***	*0.65*	*0.35*
Q35 - Voices comment on thoughts / actions	*0.01*	*-0.07*	***0.84***	*0.65*	*0.35*
Q33 - Two or more voices talk directly to you	*-0.14*	*0.06*	***0.80***	*0.60*	*0.40*
Q31 - A single voice talking aloud	*0.12*	*-0.13*	***0.73***	*0.52*	*0.48*
Q5 - Everyday objects look different in size	0.30	0.33	0.16	0.40	0.60
Q37 - Roaring or whirring sound in ears	*0.32*	*0.28*	*0.02*	*0.26*	*0.74*
Q3 - Visual perception seems heightened / enhanced	0.30	0.25	0.08	0.32	0.68
Q19 - Had an out-of-body experience	0.06	0.30	0.23	0.36	0.64
Cronbach's Alpha	.94	.91	.89		

Note: Items are listed in order of decreasing relevant loading (in bold). Shaded items did not load. New items are highlighted with italics.

This resulted in four dropped items. Three were items adapted from the CHi_II (‘*Q3. Have you ever felt that your visual perception seems heightened or enhanced?*’; ‘*Q5. Have everyday objects ever looked different in size (e.g., larger / smaller) to you than their typical appearance?*’; ‘*Q19. Have you ever had an out-of-body experience, where you were absolutely convinced that you experienced the world from a vantage point completely outside of your physical body?*’). One was a new, auditory item (‘*Q37. Have you ever heard a sound which can be described as a roaring or whirring, which other people around you cannot hear?*’). Crucially, there were no items cross-loaded onto multiple factors, and all factors contained 5 or more loadings which represents a clear factor structure.

Sixteen items loaded onto factor one including thirteen items adapted from the CHi_II, and three new auditory items (‘*Q36. Have you ever heard a sound which might be described as a ringing in your ears?*’; ‘*Q38. Have you ever noticed certain sounds appearing louder or more irritating than usual*?’; ‘*Q39. Have you ever become distracted when surrounded by lots of noise?*’). Largely replicating the CHi_II, fourteen of the adapted CHi_II items loaded onto factor two, only five of which did not load onto factor two of the CHi_II. Factor three was entirely comprised of five newly created auditory items (‘*Q31. Have you ever heard a single voice talking aloud when no one else was there?*’; ‘*Q32. Have you ever heard two or more voices talking aloud to each other when no one else was there?*’; ‘*Q33. Have you ever heard two or more voices talking aloud and directly to you, when no one else was there?*’; ‘*Q34. Have you ever heard voices telling you what to do when no one else was there?*’; ‘*Q35. Have you ever heard voices commenting on what you are thinking or doing?*’).

Table 5 summarises the intercorrelation of the AVAS factors. All intercorrelations of AVAS factors were ≥ .50, suggesting a minimum of 25% common variance between these factors. This further justifies the selection of Promax factor rotations in the EFA model.

Table 5.

Summary of Intercorrelations of Factors

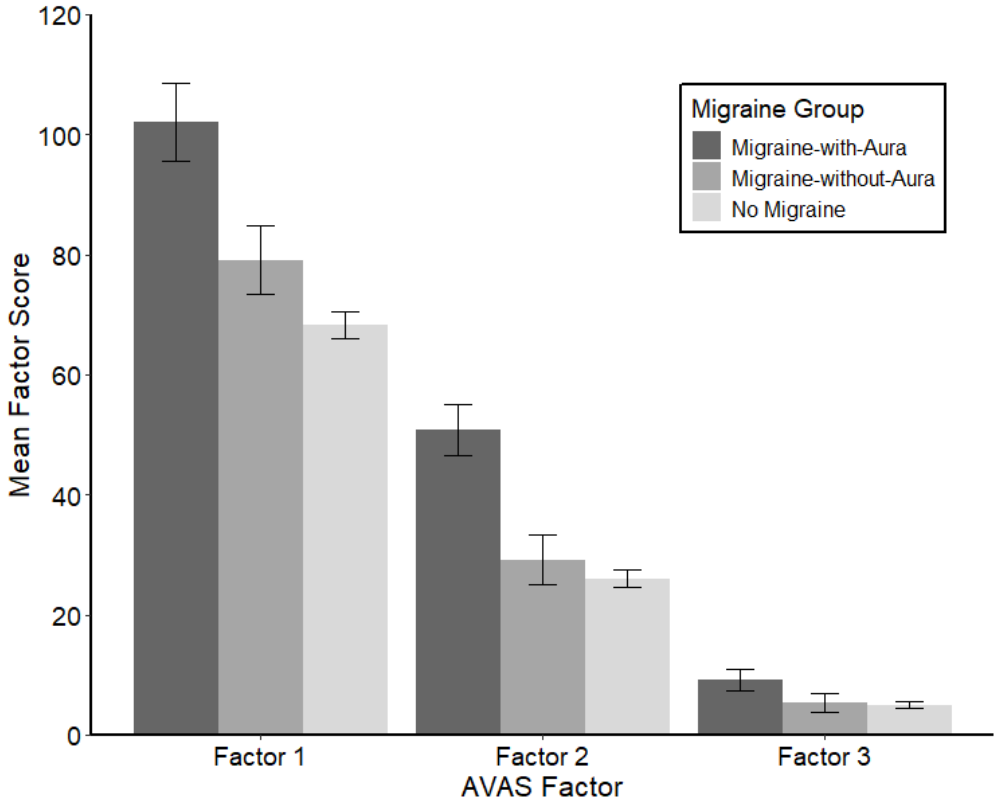
Factor	1	2	3
1			
2	.70		
3	.51	.62	

3.5 Extracted AVAS Questionnaire

Descriptive statistics for the AVAS were recalculated following factor extraction and dropping of non-loading items. Mean total scores for the AVAS across our sample was 109.12 (Median = 101, SD = 64.34, Range = 0 - 325). After non-loading items were extracted, total frequency and intensity scores remained positively correlated (r (335) = 0.94, p < .001). Some additional, exploratory analyses were conducted comparing mean factor scores between migraine groups within our sample (see Figure 3 for descriptive statistics).

Figure 3.

Descriptive Statistics for AVAS Factors by Migraine Group



A one-way MANOVA was conducted to determine whether our migraine groups (MwA, MwoA, No Migraine) differ in terms of their scores on the devolved AVAS Factors (Factor 1, Factor 2, Factor 3). The results suggested a significant multivariate effect, $F(2, 334) = 7.14$, $V = 0.12$, $p < .001$, $\eta^2\rho = 0.06$. Separate univariate ANOVAs revealed a significant effect of migraine group for Factor 1 ($F(2, 334) = 15.87$, $p < .001$, $\eta^2\rho = 0.090$, $BF_{10} > 1000$), Factor 2 ($F(2, 334) = 19.67$, $p < .001$, $\eta^2\rho = 0.110$, $BF_{10} > 1000$), and Factor 3 ($F(2, 334) = 3.57$, $p = .029$, $\eta^2\rho = 0.020$, $BF_{10} = 1.21$) scores separately. Tukey's HSD was applied to each separate univariate ANOVA to determine which migraine groups differed significantly on each separate AVAS Factor (see Table 6). For both Factor 1 and Factor 2, MwA scored higher than both the MwoA and No Migraine groups, whilst MwoA and No

Migraine groups did not significantly differ on either Factor. For Factor 3, MwA scored higher than the No Migraine group, whilst other comparisons were not significant.

Table 6.

Tukey's HSD Comparisons for effects of Migraine Group on AVAS Factor score

Factor 1				
Comparison	Difference	-95 CI	+95 CI	*p*
MwA – No Migraine	33.36	19.22	47.51	< .001***
MwA – MwoA	22.49	3.57	41.41	.015*
MwoA – No Migraine	10.87	-3.86	25.61	.193
Factor 2				
Comparison	Difference	-95 CI	+95 CI	*p*
MwA – No Migraine	24.80	15.49	34.11	< .001***
MwA – MwoA	21.69	9.24	34.15	< .001***
MwoA – No Migraine	3.11	-6.59	12.81	.731
Factor 3				
Comparison	Difference	-95 CI	+95 CI	*p*
MwA – No Migraine	4.11	0.48	7.73	.022*
MwA – MwoA	3.69	-1.16	8.53	.174
MwoA – No Migraine	0.42	-3.36	4.19	.963

*Denotes significance: *** - $p < .001$; * - $p < .05$

The above results show Migraine-with-Aura is associated with significantly elevated proxy signs of trait-based cortical hyperexcitability relative to control participants. For both Factor 1 and Factor 2, participants who reported as Migraine-with-Aura scored significantly higher than participants who reported Migraine-without-Aura, pointing clearly to underlying neural mechanisms beyond the typical pathophysiology of headache. These results demonstrate elevated trait-based cortical hyperexcitability (as measured by the AVAS) is associated with Migraine-with-Aura. For Factor 3 a significant difference was observed between participants reporting Migraine-with-Aura relative to control participants, however there was no significant difference between Migraine-with-Aura and those reporting Migraine-without-Aura. These results do suggest a role for cortical hyperexcitability in the experiences measured by Factor 3, however they suggest a range of wider underlying factors of predisposition alongside cortical hyperexcitability.

Discussion

The outlined study aimed to develop and establish a new multisensory measure revealing trait-based signs of cortical hyperexcitability across two sensory domains. Items were developed based on aberrant visual and auditory experiences thought to be associated with elevated cortical hyperexcitability. The EFA revealed a stable structure of three distinct but correlated clusters of experiences. Interestingly, and supportive of the utility of the AVAS, all items loaded above .40 and not a single item cross-loaded onto multiple factors suggesting each factor represents a meaningful distinction between these phenomenological categories of aberrant experience.

The extracted factors represented: i) Heightened Sensory Sensitivity and Discomfort (HSSD), ii) Migrainesque Visual Aura Symptoms (MVAS), and iii) Voice Hearing Experiences (VHE). Both HSSD and MVAS factors largely replicated the factor structure of the former CHi_II (with some auditory additions to factor HSSD), whist voice hearing items loaded exclusively onto factor VHE. Both the intercorrelations of factors (all $r > .50$), and the elevated scores of all three factors in individuals within the sample who identified as experiencing Migraine-with-Aura, are indicative of cortical hyperexcitability as a key underlying factor of predisposition to aberrant experiences examined by the AVAS. Each factor is now discussed, alongside the theoretical implications of the migraineur differences observed.

4.1 AVAS Factor Structure

4.1.1 Factor 1 – Heightened Sensory Sensitivity and Discomfort (HSSD)

All ten items loading onto Factor 1 of the CHi_II also loaded onto Factor 1 here (Fong et al., 2019), along with two items relating to perception becoming overwhelmed or distorted under conditions of excessive light or fatigue. Two new auditory items which fell under the category of auditory hypersensitivity also loaded into Factor 1, namely experiencing hypersensitivity to auditory information, and becoming overwhelmed by auditory information. These items fit a consistent intuitive theme of heightened sensitivity and perceptual discomfort induced by fatigue or external information.

The phenomenological experiences examined in Factor 1 are extensively reported in association with an elevated degree of underlying cortical hyperexcitability in visual and auditory cortices (Huang et al., 2003; Huang et al., 2011; Schreiner et al., 2015; McGill et al., 2023), and have been shown to occur to a greater extent in migraineurs relative to neurotypical controls (Vingen et al., 1998; Harriott & Schwedt, 2014; Demarquay & Mauguière, 2015 Fong et al., 2021; Fong et al., 2022).

The presence of one item pertaining to tinnitus-like ringing may seem counterintuitive as the only 'noise-hearing' item, however tinnitus in migraineurs has previously been conceived of as an allodynic (i.e. pain / discomfort induced through external stimuli which would not usually cause pain or discomfort) symptom (Volcy et al., 2005). Despite seeming to fit more neatly with hallucinations as a perception of a non-veridical stimulus, in fact the frequency and intensity of tinnitus may, in some cases, reflect a symptom of hypersensitivity to external sensory information which is exacerbated by elevated underlying cortical hyperexcitability. Collectively, the intuitive loadings of these items, as well as substantial replication of the CHi_II and the excellent Cronbach's alpha statistic (.94), support the stability and consistency of this Factor.

4.1.2 Factor 2 – Migrainesque Visual Aura Symptoms (MVAS)

Eight of the nine visual hallucination items which loaded onto Factor Two of the original CHi_II also loaded onto Factor 2 here. In addition, two previously dropped items describing aura-like hallucinations (‘Spider-web type patterns’ and ‘black and white static’) did load onto Factor 2 on this occasion. Importantly, the item pertaining to fortification hallucinations (loss of vision surrounded by zigzags) which are overwhelmingly associated with Migraine-with-Aura loaded strongly onto AVHE ($\lambda = 0.87$).

Here both positive auras consisting of low-level elementary hallucinations (e.g. phosphenes, fortification hallucinations) and negative auras consisting of lost visual information converged onto a single factor, replicating findings from the CHi_II. As Factor 2 was overwhelmingly comprised of items representing hallucinations, this also replicates the factor structure of the CHi_II. The excellent cronbach’s alpha statistic (.90) further supports the stability of the factor structure as well as the internal consistency of Factor 2.

There is some dissidence on this occasion as three items describing visual distortions (e.g., ‘world drained of colour’) loaded onto Factor 2, where previously hallucinations and distortions were delineated. Distortions in perceptual qualities such as colour (Lawden & Cleland, 1993; De Marinis et al., 2007) and motion (Antal et al., 2005) are frequently reported alongside hallucinations in the preictal and ictal phase of migraine where cortical hyperexcitability is significantly elevated. Their frequent co-occurrence in the same sensory domain may mean that they are difficult to distinguish phenomenologically, particularly for migraineurs who would likely experience the most frequent and most intense symptoms. Given the sample collected by Fong et al. (2019) did not contain any migraineurs, the participants may have been better able to distinguish perceptual distortions from hallucinations, leading to their separate factors. This could be addressed in future iterations by including perceptual distortions in other sensory domains, such as somatosensory distortions, to combat this (see Limitations and Future Research for discussion).

Whilst it may appear that removing migraineurs from the sample altogether may resolve the above discussion, this is not necessarily the case. For the present investigation, a relatively small number of migraineurs (N = 70) were recruited meaning that the proportion of migraineurs within the sample (20.77 %) was similar to the population-wide incidence rate estimated between 15 – 23.8 % (Baykan et al., 2015; GBD 2016 Headache Collaborators, 2018). This is effective for EFA to prevent the loading of particular items onto factors being obscured by either over-representation or under-representation of the prevalence of each item within the sample's responses (Child, 2006; Watkins, 2018). Removing migraineurs altogether would lead to significant under-representation of these experiences within the sample relative to their occurrence in the general population, thus obscuring the loading of all items across the questionnaire.

4.1.3 Factor 3 – Voice-Hearing Experiences (VHE)

Factor Three contained five items, all of which reflect auditory verbal hallucinations, or experiences of voice-hearing. These items aimed to cover the broad phenomenological spectrum of voice-hearing, such as hearing single versus multiple voices, and to isolate the sensory experience from the hearer's subjective beliefs about these experiences such as the origin of voices (e.g. hearing the voice of the devil – Bell et al., 2006). Voice-hearing experiences are reported across neurotypical, migraineur, and clinical (particularly schizophrenia) populations in concert with indications of elevated cortical hyperexcitability (Hoffman & Cavus, 2002; Spencer et al., 2009; Kompus, Westerhausen & Hugdahl, 2011; van der Feltz-Cornelis et al., 2012; Jardri et al., 2016; Li et al., 2024; Toh et al., 2024).

4.2 Migraineur Differences

Within this sample the anticipated pattern of migraineur differences was observed for both the HSSD and AVHE factors, as Migraineurs-with-Aura scored significantly higher than both Migraineurs-without-Aura and non-migraineur participants on both factors. This supports the notion that migraineurs generally have a more hyperexcitable cortex than non-migraineurs, but that those who experience Migraine-with-Aura (i.e. experiencing perceptual hallucinations and distortions) have the most elevated level of cortical hyperexcitability within these groups (Datta et al., 2013; Braithwaite et al., 2015; Coppola et al., 2019; Fong et al., 2019). This significantly extends the role of cortical hyperexcitability as a factor of predisposition to aberrant perceptual experiences into multiple sensory domains where previous research has focused primarily on vision (e.g. Evans & Stevenson, 2008; Braithwaite et al., 2015; Fong et al., 2019; Fong et al., 2020).

However, this pattern was not observed for VHE, with significant differences observed only between those experiencing Migraine-with-Aura and non-migraineurs. This difference is a noteworthy finding which points to some role of cortical hyperexcitability in voice-hearing with the most hyperexcitable participants (Migraine-with-Aura) clearly reporting elevated scores in the auditory domain (VHE). However, despite a notable difference score between MwA and MwoA samples, the comparison was not statistically significant with the current sample (Diff = 3.69, $p = .114$).

4.3 Theoretical Implications

The present findings provide new support for the association between cortical hyperexcitability and aberrant perceptual experiences across multiple sensory domains (Schoenen et al., 2003; Vincent & Hadjikhani, 2007; Petrusic et al., 2013; Toh et al., 2024; Li et al., 2024). This meshes well with the notion that cortical hyperexcitability may be expressed (at least in part) as a domain-general factor extended beyond visual cortex and mediating predisposition to aberrant multisensory experiences (Welch et al., 1990; Aurora & Wilkinson, 2007; Coppola et al., 2007; Petrusic et al., 2018; Silvestro et al., 2022). In addition, these findings have important implications for continuum models of aberrant perception (Johns & van Os, 2001; McCreery & Claridge, 2002; Schwartzman et al., 2008; van Os & Reininghaus, 2016). Here one might consider that the grouping and close associations of aberrant perceptual experiences across sensory domains could reflect domain-general processes in bottom-up sensory processes. Recent investigations have shown distinct combinations of multisensory aberrant experiences arise within both clinical (Dudley et al., 2023; Toh et al., 2024; Bere et al., 2024) and neurotypical (Larøi et al., 2019; Toh et al., 2020; Rogers et al., 2024) populations.

As with the CHi and the CHi_II, the newly devised AVAS has considerable merit compared to other measures interested in quantifying cortical hyperexcitability in relation to visual stress. For example, items on the Visual Discomfort Scale (VDS: Conlon et al., 1999) do not have a unidimensional and clear structure – with some items asking about several symptoms at once. For example, VDS items one to three open with "*Do your eyes every feel watery, red, sore, strained, tired, dry, gritty, or do you rub them a lot, when…*" followed by a potential source of visual discomfort, such as striped patterns. VDS therefore assumes that each of these symptoms have a unitary underlying factor of predisposition, where the fractionated variable structure of the AVAS allows for identification of multiple latent factors of predisposition to these experiences which relate through an additional underlying factor of cortical hyperexcitability.

In addition, the VDS measure used a Rasch model approach which assumes that endorsements (or not) of particular items within a scale or measure depend on a single underlying construct (Bond & Fox, 2013). In essence, this assumes the probability of a participant giving a high or low response to each item within a scale can be thought of as a logistic function between the occurrence of a particular construct (e.g. the person's level of visual discomfort), and the degree to which that construct is expressed in the wording of the item. However, if the item includes multiple factors indicating the presence of this construct (e.g. "*Do your eyes every feel watery, red, sore, strained, tired, dry, gritty, or do you rub them a lot…*") at once, this function is violated, as visual discomfort could manifest as any one of the aforementioned symptoms to different extents in different people dependent on a number of other factors beyond their individual level of visual discomfort. For this reason, Rasch models require that all items within the measure are worded in a way that clearly and unambiguously demonstrates unidimensionality (Smith, 2000). As discussed, VDS suffers from poor question formulation, which undermines the effectiveness of the approach used.

The EFA + PA approach deployed in the development of both the CHi_II and AVAS does not make these assumptions, and for good reason. The three-factor structure uncovered strongly suggests that cortical hyperexcitability cannot be boiled down to a simple logistic function, as there are multiple distinct but related factors which together are indicative of an individual's level of cortical hyperexcitability (Braithwaite et al., 2015; Fong et al., 2019). This approach has proven effective in subsequent examinations of the relationship between the AVAS and behavioural, neuroimaging, and brain stimulation measures of cortical hyperexcitability, with the individual factors showing selective associations with these various indicators of cortical hyperexcitability (Fong et al., 2019; Fong et al., 2020; Joshi et al., 2024).

Together, this points to two clear advantages of the AVAS over comparable measures such as the VDS (Conlon et al., 1999). First, the use of EFA + PA over Rasch models provides greater flexibility in uncovering distinct underlying components, rather than forcing items into a rigid scale that may not fully capture the variability within the data. Second, this resulting multi-factor structure can help refine theoretical models by revealing natural groupings of symptoms or traits, offering deeper insights into the structure of cortical hyperexcitability as a construct. Furthermore, the move to a multisensory measure allows for consideration of factors beyond a single sensory domain as indicative of (or contributing to) the underlying construct of cortical hyperexcitability.

4.4 Limitations and Future Research

The present study has examined multisensory trait-based aspects of cortical hyperexcitability across a sample with neurotypical and migraine individuals. This has culminated in the construction of the AVAS measure – a new empirically validated tool with considerable utility in the field of anomalous / aberrant perceptions. This work could be further extended with the inclusion of additional sensory processing modalities – to assess the range of excitability across the cortex. Of particular interest would be somatosensory distortions which have been found to co-occur with visual hallucinations in migraine and are thought to have a shared underlying mechanism (Lanska & Lanska, 2013; Mastria et al., 2023; Fitzek et al., 2024). This would further expand our understanding of the multisensory nature of cortical hyperexcitability.

The extent to which cortical hyperexcitability remains within one primary sensory domain (i.e., vision) or may permeate several, remains an open question, but one the AVAS could shed light on. In addition, the development of a state-based version of the measure, examined alongside more quantitative approaches and neural measures would also be illuminating.

Now that the measure has been empirically established here it could be taken to examine a host of conditions and disorders as well as biases in neurotypical samples. Importantly, although measures exist that seek to quantify voice hearing and aberrant auditory experiences (Launay & Slade, 1981; Chadwick, Lees & Birchwood, 2000), the AVAS does not conflate sensory experience with belief or higher-level interpretations (the voice of the devil, God, and related interpretations). Consequently, it seeks to be more specifically directed towards the presence of the sensory anomaly which, at its core, likely reflects aberrant hyperexcitable processes. Future research might want to further examine the role of auditory aura and migraine with extended samples allowing for an assessment of migraine subtypes particularly given recent evidence for voice-hearing as a form of aura in migraineurs (Toh et al., 2024; Li et al., 2024).

4.5 Conclusion

The present study introduces a new trait-based proxy measure for multi-sensory indicators of cortical hyperexcitability. As with predecessor measures (The CHi and CHi_II) the identification of a three-factor model fractionates and refines the unitary notion of cortical hyperexcitability, allowing for a more precise delineation of the underlying components. Going forward, the AVAS is a promising tool and could be utilised alongside contemporary neuroscientific methods (brain stimulation, brain-imaging, neurophysiology) to better link specific aberrant brain processes to atypical conscious experiences in both visual and auditory domains.

Chapter 3

Sensory Cross-talk In a Novel Multisensory Adaptation of the Pattern Glare Test is Associated with Signs of Elevated Cortical Hyperexcitability

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Abstract

There is increasing evidence that most individuals who report anomalous perceptual experiences do so across multiple sensory domains. However, most neurocognitive investigations take a domain-specific approach to examining underlying factors of predisposition to anomalous perceptual experiences. The present investigation sought to examine whether cortical hyperexcitability may represent a domain-general factor of predisposition to aberrant perceptual experiences. Here a novel multisensory adaptation was made to the visual Pattern Glare test, where the presentation of certain irritating visual grating patterns may elicit aberrant visual experiences in cases of elevated cortical hyperexcitability. Both irritating and non-irritating gratings were paired with concurrent auditory pure tones at various irritating and non-irritating frequencies. A highly specific cross-sensory enhancement effect was observed where aberrant visual experiences elicited by irritating gratings were enhanced by the concurrent presentation of an irritating auditory pure tone. This cross-sensory enhancement effect was found to be elevated in individuals displaying signs of elevated state-based cortical hyperexcitability. In addition, a significant positive association was observed between the sensory cross-talk effect and the Migrainesque Visual Aura Symptoms (MVAS) factor of the trait-based AVAS measure. These findings support the notion that cortical hyperexcitability may be a more domain-general factor of predisposition to aberrant perceptual experiences and hence may be present in more than one cortical network. The complex, fractionated relationship between state-based and trait-based factors is explored. Theoretical implications of these findings are discussed in terms of cortical gain control mechanisms and the cross-modal correspondence framework.

Introduction

1.1 Cortical Hyperexcitability

Anomalous perceptual experiences, including altered sensory sensitivity, hallucinatory experiences, and distorted sensory perception, are associated with aberrant underlying patterns of neurophysiological activity in the cerebral cortex - referred to as cortical hyperexcitability (Chronicle, Pearson & Mulleners, 2006; Mulleners et al., 2001; Palmer et al., 2000; van der Kamp, et al., 1996; Wilkins, 1995).

A growing number of investigations have highlighted important contributions from both background latent trait-based and more temporally specific state-based components underlying cortical hyperexcitability (Braithwaite et al., 2015; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Joshi et al., 2024). State-based hyperexcitability refers to transient fluctuations in neural activity that occur in the present moment (in the here and now) and are directly linked to the occurrence of aberrant perceptual experiences. In contrast, trait-based hyperexcitability represents a more stable latent background context, contributing to a heightened long-term susceptibility or predisposition to aberrant perceptual experiences more generally.

Importantly, it has been shown in the auditory domain that the relationship between state and trait-based factors mediating hallucination proneness is not a straightforward one. For example, Kühn and Gallinat (2012) reported a dissociation where the immediate experience of hallucinations (‘state’) was linked to heightened activity in speech production regions, while a more general predisposition to hallucinations (‘trait’) was associated with aberrant activity in auditory processing areas (see also Mo et al., 2024; Zmigrod et al., 2016). Similarly, in the visual domain, neural factors of trait predisposition to hallucinations are often found in the neural connections between the visual cortex and frontal (Collerton et al., 2005; van Ommen et al., 2023) or subcortical (Erskine et al., 2019; Ford et al., 2015a; Ford et al., 2015b) structures, whilst the hallucination state is associated with more localised hyperexcitability, (possibly also reflecting hyperconnection), within the visual cortex itself (Abraham & Duffy, 2001; Bressloff et al., 2002; Ffytche, 2008).

Collectively, these studies indicate that while a baseline neural vulnerability (trait) may predispose an individual to hallucination, the actual emergence of these phenomena is also strongly influenced by dynamic, situational changes (state) and that there are distinct interdependent underlying neural mechanisms for state and trait predispositions. This complex interaction underscores that the propensity for hallucinations cannot be fully understood by examining either trait or state factors in isolation.

1.2 Cortical Hyperexcitability and Cortical Gain

There are several explanatory frameworks (which may not be mutually exclusive), that address the association between cortical hyperexcitability and anomalous perceptual experiences, one of which is aberrations in cortical gain control (McColl & Wilkinson, 2000; Porciatti et al., 2000; Tsai et al., 2011). Cortical gain is typically defined as the slope of a neuron's input – output function (typically modelled as a sigmoid transfer function: Schwartz & Simoncelli, 2001); high gain states within neuronal populations are characterised by a rapid increase in response (i.e. firing rate) for a change in input, whilst low gain states are characterised by modest perturbations in response for the same change in input (Carandini & Heeger, 2012; Ferguson & Cardin, 2020). Computationally, cortical gain mechanisms regulate the amplitude of neural responses to incoming sensory information relative to its salience (Aston-Jones & Cohen, 2005; Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001). Typically, these processes would exert control over neural responses through inhibitory mechanisms which suppress irrelevant information whilst excitatory mechanisms enhance representation of salient inputs, acting as a neural filter to optimise signal-to-noise ratio (Ferguson & Cardin, 2020; Greenhouse, 2022; Hasselmo et al., 1997).

However, under conditions of aberrant gain control (e.g. in individuals with cortical hyperexcitability) this inhibitory modulation may be weakened, aberrant, or dysfunctional (McColl & Wilkinson, 2000; Porciatti et al., 2000; Tsai et al., 2011). As a result, the system may fail to adequately suppress background noise or to stabilise over-amplified responses to highly salient / irritative stimuli. Consequently, such failures in gain regulation could contribute to 'perceptual uncertainty'- a state in which neural representations of sensory inputs become unstable or unreliable (Hillyard, Vogel & Luck, 1998; Hénaff et al., 2020; Scolari & Serences, 2009; Woolley et al., 2005). These unstable representations, in turn, increase the likelihood of distortions, misperceptions, and anomalous perceptual experiences.

1.3 Predictive Coding

An alternative (though complementary) explanatory framework is that of predictive coding, which states that perception occurs through a Bayesian process of active inference whereby incoming (sensory) information is shaped by our prior expectations around external events (or 'priors'; Bastos et al., 2012; Corlett, Frith & Fletcher, 2009; Corlett et al., 2019; Friston, 2005; Powers, Kelley & Corlett, 2017; Powers, Mathys & Corlett, 2017; Rao & Ballard, 1999; Sterzer et al., 2018). Here, sensory information processed under conditions of cortical hyperexcitability would be represented as highly uncertain at the neural level due to excessive irrelevant neural signals coinciding with the critical sensory signals representing veridical sensory information, resulting in low confidence in the underlying sensory information at the neural level and requiring inference from priors to 'fill in' perceptual signals (Friston, 2005; Powers, Kelley & Corlett, 2017; Powers, Mathys & Corlett, 2017).

Under conditions of low confidence, perceptual representations would be heavily influenced by prior expectations rather than incoming sensory signals, this can be thought of as a dynamic bias, and when sensory information is uncertain this bias leans towards priors over sensory information in constructing perceptual experiences. Where the mismatch between priors and sensory evidence is large (i.e. a 'prediction error'), the resulting perceptual representation would be more likely to feature aberrations from veridical sensory information (i.e. anomalous perceptual experiences; Powers, Mathys & Corlett, 2017). Crucially, not all prediction error signals are treated equally in terms of their salience, prediction error signals are thought to be weighted in terms of reliability (or precision), and this weighting is thought to scale the influence of the error signal on sensory perception (Kanai et al., 2015). The precision-weighted predictive coding framework therefore expresses anomalous perceptual experiences as occurring through mechanisms of top-down control on sensory information.

It is important to note that cortical gain control mechanisms and the predictive coding framework are not necessarily mutually exclusive, these may simply reflect differing levels of explanation for the occurrence of anomalous perceptual experiences. For example, cortical gain control may explain how sensory signals with a high degree of perceptual uncertainty arise, whereas predictive coding may explain how top-down processes modulate the perceptual content of the aberration. In fact, more recently cortical gain has been incorporated into the predictive coding framework as a computational process underlying the weighting of prediction errors, extending to a theory of '*precision weighted predictive coding*' (Kanai et al., 2015).

However, more emphasis may be placed on cortical gain control as an explanatory framework for anomalous perceptual experiences at this stage as the predictive coding framework lacks a comprehensive neurobiological explanation for how precision-weighting occurs. Mechanistically precision weighting may occur via gain of prediction error signals, with gain control enacted by dynamic interactions between excitatory pyramidal neurons and inhibitory interneurons (Barrett & Simons, 2015; Feldman & Friston, 2010; Kanai et al., 2015).

1.4 Visual Cortical Hyperexcitability

In studies on migraine and migraine aura, the presence of cortical hyperexcitability in the visual cortex has been linked to the presence of aberrant visual experiences, ranging from visual distortions to simple and even complex hallucinations which make up the experience of 'aura' (Hadjihkani et al., 2001; Huang et al., 2003; Huang et al., 2011; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Fong et al., 2022; Jurkovičová et al., 2024; Rasmussen & Olesen, 1992; Russell & Olesen, 1996).

However, the association between cortical hyperexcitability and aberrant visual experience is not limited to individuals with migraine. Elevated cortical hyperexcitability has also been observed in various clinical and neurological conditions and disorders characterised by aberrant visual experiences including Charles Bonnet syndrome (Coltheart, 2018; Ffytche et al., 1998; Kazui et al., 2009; Painter et al., 2018), complex partial seizures of the temporal lobes (Bear, 1979; Gloor & Fariello, 1988; Gloor, 1979; Penfield, 1938), psychosis (Jardri et al., 2013; Waters et al., 2014), and schizophrenia (Carment et al., 2019; Lakatos et al., 2013; Oertel et al., 2007; Spencer et al., 2004; Spencer & McCarley, 2005). Interestingly, similar observations have been made in neurotypical groups (albeit in attenuated form) predisposed to visual hallucinations (Braithwaite et al., 2015; Ffytche, 2008; Fong, Takahashi & Braithwaite, 2019). These findings underscore the ubiquitous nature of cortical hyperexcitability and its diverse symptomatology across both clinical and neurotypical populations.

Previous work has sought to quantify state-based visual hyperexcitability with the Pattern Glare (PG) task (Evans & Stevenson, 2008; Wilkins et al., 1984; Wilkins, 1995). PG tasks utilise square wave gratings at differing spatial frequencies, some of which are known to over-stimulate and overwhelm visual neurons and be cortically irritating. Highly potent gratings have a spatial frequency of around 3 cycles-per-degree (cpd) of visual angle. Baseline gratings of around 14 cpd, and 0.5 cpd are also examined where the degree of stimulation to the perceptual system, though present, is thought to be attenuated. The aberrant experiences induced by viewing the gratings are primarily visual distortions (e.g., flicker, shimmer, coloured halos, etc) and are collectively referred to as pattern-glare (PG: Aurora & Wilkinson, 2007; Braithwaite et al., 2013; Evans & Stevenson, 2008; Harle, Shepherd & Evans, 2006; Shepherd, 2000; Wilkins et al., 1984; Wilkins, 1995).

The relationship between PG and cortical hyperexcitability has been demonstrated for neurotypical populations (Braithwaite et al., 2013; Braithwaite et al., 2015; Fong et al., 2019) as well as in neurological disorders such as migraine-with-aura (Aurora & Wilkinson, 2007; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Fong et al., 2022; Haigh et al., 2012; Harle & Evans, 2004; Huang et al., 2003) and stroke (Beasley & Davies, 2012), and supported with findings from brain imaging, neurophysiological measurements and brain stimulation (Braithwaite, Mevorach & Takahashi, 2015; Fong et al., 2020; Fong et al., 2022; Huang et al., 2003; Huang et al., 2011; Jurkovičová et al., 2024).

Critically, and in line with cortical gain theory, these neural responses are typically larger in amplitude and faster in reaching peak amplitude (i.e. larger slope / more responsive) as indicated by haemodynamic responses in functional near infrared spectroscopy (fNIRS; Coutts et al., 2012; Haigh, Cooper & Wilkins, 2015). Collectively, these studies highlight the role of cortical hyperexcitability in generating and mediating aberrant visual experiences across various neurological conditions, disorders, and within neurotypical groups.

1.5 Auditory Cortical Hyperexcitability

Although there is extensive evidence for the relationship between cortical hyperexcitability and aberrant visual experiences, this relationship is not limited to the visual domain. Cortical hyperexcitability has also been implicated in a range of aberrant auditory perceptual experiences such as auditory hypersensitivity / hyperacusis, auditory-verbal hallucinations (voice hearing), and non-verbal auditory hallucinations (Eichhammer et al., 2003; Hoffman & Cavus, 2002; Honcamp et al., 2024; Spencer et al., 2009). A host of such symptoms have also been observed in migraineurs who are known to display an elevated degree of latent cortical hyperexcitability (Ashkenazi et al., 2009; Demarquay & Mauguière, 2016; Li et al., 2024; Mathew & Robertson, 2016; Miller et al., 2015; Toh & Yolland et al., 2024; van der Feltz-Cornelis, Biemans & Timmer, 2012; Vingen et al., 1998; Volcy et al., 2005).

As with aberrant visual experiences, these symptoms are observed in a range of other clinical conditions and pathological disorders associated with cortical hyperexcitability such as Schizophrenia (Allen et al., 2008; McCarthy-Jones, 2012; Waters et al., 2012), Temporal Lobe Epilepsy (Coebergh et al., 2019; Korsnes et al., 2010; Kumar et al., 2022; Perez et al., 2022), and hearing impairment (Cole et al., 2002; Linszen et al., 2019; Marschall et al., 2021; Sanchez et al., 2011), as well as occurring in neurotypical populations (Daalman et al., 2013;

Daalman et al., 2016; Honcamp et al., 2024; Larøi et al., 2012; Toh et al., 2020; Toh & Thomas et al., 2024). As with visual hyperexcitability, the disorders/psychopathologies and symptoms associated with auditory hyperexcitability are diverse in reflection of the wide range of neural factors which underlie state-based and trait-based cortical hyperexcitability.

1.6 Multisensory Cortical Hyperexcitability

The notion that cortical hyperexcitability may have cross-sensory effects on aberrant perception has been previously suggested in both theoretical and empirical observations (Brighina et al., 2015; Convento et al., 2013; Haigh et al., 2023; Romei et al., 2013; Schoenen, 1996; Welch et al., 1990; Yu et al., 2013). These observations make the fascinating prediction that sensory cortices could engage in a form of reciprocal *'sensory cross-talk'*, where the degree of excitability in one sensory cortex has modulating effects on the degree of excitability in another sensory cortex, with the potential to result in increased aberrant sensory phenomena. This sensory cross-talk may partially explain the frequent occurrence of aberrant perceptual experiences in multiple sensory domains simultaneously (Dudley et al., 2023; Li et al., 2024; Toh et al., 2020; Toh et al., 2024).

At a systems level this may reflect ideas posed in the Dysconnection[3] hypothesis, which states that aberrant interactions between brain regions is an underlying pathophysiological factor which predisposes individuals to aberrant experiences (Friston, 1998; Friston, 1999; Friston et al., 2016; Stephan, Baldeweg & Friston, 2006; Stephan, Friston & Frith, 2009). Hyperexcitability at a network-level has previously been associated with aberrant patterns of connectivity between brain regions, particularly in the context of epilepsy (Bear, 1979; Courtiol et al., 2020; Vaudano et al., 2009; Varotto et al., 2012). This

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[3] Note – Dysconnection refers to both hyper and hypo-connection within and between neural systems.

may suggest that aberrant functional and / or structural connectivity within specific neural networks may underlie an association between cortical hyperexcitability and increased sensory cross-talk.

There is evidence that hyperexcitability in cortical areas such as the temporoparietal junction (TPJ) may underlie this sensory cross-talk effect, particularly between visual and auditory domains. This makes intuitive sense given the significant structural and functional connectivity of the TPJ bilaterally with sensory cortices such as the visual and auditory cortices (Braga et al., 2017; Horiguchi, Wandell & Winawer, 2016; Rolls et al., 2023).

Increased neural activity bilaterally at the TPJ has been implicated in audiovisual hallucinations in individuals with a diagnosis of psychosis (Jardri et al., 2013; Silbersweig et al., 1995). Furthermore, both Transcranial Magnetic Stimulation (TMS) and Transcranial Electric Stimulation (tES) studies have shown that inhibitory stimulation protocols known to decrease the underlying excitability levels of the left TPJ can have attenuating effects on hallucination severity across multiple sensory domains (Jardri et al., 2009; Koops et al., 2018; Vercammen et al., 2009; Vercammen et al., 2010). This presents a direct relationship between excitability at the TPJ (and sensory cortex) and the occurrence of aberrant perceptual experiences across sensory domains.

1.7 Cross-modal Correspondence

The principle of sensory cross-talk could be extrapolated from investigations of veridical perceptual processes by Spence and colleagues (Driver & Spence, 1998; Spence & Driver, 2004; Spence, 2011) through ‘cross-modal correspondence’, whereby inputs from one sensory modality can modulate perceptual processing in another. These cross-modal correspondences are particularly pronounced when stimuli share some non-redundant perceptual features which are correspondent across sensory domains such as pitch in the auditory domain, and lightness or brightness in the visual domain - a principle those researchers termed ‘synaesthetic congruence’ (Gallace & Spence, 2006; Parise & Spence, 2008; Parise & Spence, 2009).

In addition, temporal (i.e. time-bound) congruence of stimuli, such as a matched onset and offset of perceptual inputs can strengthen cross-modal associations, this principle is termed ‘temporal congruence’ (Di Stefano & Spence, 2025; Shore, Barnes & Spence, 2006; Spence, 2007). The exact effects of a cross-modal correspondence on associated perceptual experiences are broad, and highly dependent on the specific perceptual features which drive the cross-modal correspondence occurring (for review see Spence, 2011).

A specific form of cross-sensory interaction is the notion of the cross-modal enhancement, where information in one sensory domain can enhance the salience of sensory signals in another domain. One example of this is the sound-induced flash illusion (SIFI). Here, the presentation of two short auditory tones paired with a single visual flash can lead to the illusory perception of a second flash, demonstrating an aberrant salience of an illusory visual signal driven by the paired auditory stimulus (Shams, Kamitani & Shimojo, 2000; 2002). As with other cross-modal correspondences, parietal regions such as the TPJ are implicated in the SIFI. Inhibitory rTMS over the right TPJ has been shown to have deleterious effects on the SIFI (Hamilton et al., 2013; Kamke et al., 2012), again suggesting a relationship between TPJ excitability and aberrant multisensory perception. Specifically, the authors here suggest a role for the TPJ in binding the two perceptual streams of visual and auditory information together under typical circumstances in the SIFI. Subsequently, the inhibitory rTMS is posited to ‘disrupt’ this binding mechanism by attenuating the influence of irrelevant auditory information on critical visual information. This would suggest that the cross-talk observed between visual and auditory streams in the SIFI occurs via a neural binding process where the auditory stream enhances the salience of associated visual signals, and that this enhancement is at least partially mediated by excitability at the TPJ (or more broadly within associated networks).

However, while SIFI does indeed involve multisensory integration, its outcomes are heavily influenced by attentional and decision-making processes, rather than reflecting purely bottom-up perceptual mechanisms. For instance, the illusion’s magnitude can be modulated by expectancy priming where participants instructed to anticipate more flashes are more likely to report illusory percepts (Wang et al., 2019). Therefore, it could be argued that the disruption observed in the above studies represents a disruption in attentional processes necessary for cross-sensory binding to occur, rather than disrupting the binding process directly.

In summary, sensory cross-talk may represent a specific form of cross-modal correspondence where sensory information in one domain has a boosting effect (i.e. enhanced salience) on sensory information in another domain. Sensory cross-talk appears to occur within cortical networks comprised of sensory cortices mediated by activity in parietal regions such as the TPJ. An aberrant degree of sensory cross-talk may occur due to hyperexcitability (and hyperconnection) in these networks, and this may have implications for neurocognitive models of multisensory aberrant experiences. However, the exact underlying mechanism for the occurrence of hyperexcitability is unclear, as is the exact role of parietal regions in mediating sensory cross-talk.

Overview of the Current Study

The present study examined the role of a potential ‘sensory cross-talk’ effect in individuals displaying signs of increased cortical hyperexcitability. Pattern Glare tests assess aberrant visual experiences thought to occur due to atypical processing in visual cortices. However, this does not necessarily mean that cortical hyperexcitability is confined to the boundaries of visual cortex. It is certainly theoretically plausible that, in certain individuals, cortical hyperexcitability may extend across broader brain networks, suggesting it could be more accurately conceptualized, at least in part, as a more domain-general cortical process. In this context, cortical hyperexcitability would not be confined to a singular region, like the visual cortex, but could influence multiple brain regions.

A domain-general form of cortical hyperexcitability could be seen through examples of cross-sensory enhancement, similar to the effects of auditory information on visual information in the SIFI discussed previously. Here one would expect to see irritable auditory information enhance the salience (or intensity) of irritable visual Pattern Glare experiences (AVDs) when presented in concert. This would suggest that the processing of irritable sensory information in the auditory domain can impact the perceptual manifestation of aberrant sensory processing in the visual domain. Again, this represents a specific form of sensory cross-talk leading to enhanced salience of visual information.

Such an enhancement could be indicative of cortical gain control as an underlying mechanism for sensory cross-talk due to the relationship between high-gain states and inability to regulate cortical responses to sensory information (see section 1.2 Cortical Hyperexcitability and Cortical Gain). If both visual and auditory signals are processed under conditions of high-gain (i.e. elevated cortical hyperexcitability), cortical responses to both perceptual streams would both be insufficiently modulated by cortical gain processes and therefore perceived as highly salient. This enhancement of perceptual streams and their integration would be somewhat akin to Spence's notion of synaesthetic congruence (i.e. a shared non-redundant physical property). This cross-sensory correspondence would then lead to a sensory cross-talk effect at the cortical level whereby auditory and visual signals become integrated, which would manifest perceptually as an increased salience (or intensity) of the visual experience (AVDs).

The present study extended the concept of pattern-glare into the multisensory domain by developing a novel multisensory (visual and auditory) version of the pattern-glare test. The visual pattern-glare test has been reported across several previous studies demonstrating effects with neurotypical hallucinators and individuals with migraine and has been examined further with brain-stimulation and EEG (Braithwaite et al., 2013; Braithwaite, Mevorach & Takahashi, 2015; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Fong et al., 2022).

In the current experiment the presentation of these gratings was combined with the presentation of auditory pure tones at various auditory frequencies (some of which are known to be irritative in the auditory domain) to create a mixture of visual-only (baseline) and audiovisual trials. These tones were inconsequential to the AVDs assessed, but allowed for examination of whether these visual processes occurring in typical visual-only Pattern Glare may be exasperated by the co-occurrence of the auditory tones. The goal was to investigate potential multisensory cross-talk effects, where hyperexcitation in auditory cortex may 'cross-talk' into the reported aberrant visual experiences generated by viewing aversive gratings, leading to an enhanced salience (or intensity) of AVDs.

Within visual-only Pattern Glare trials the baseline-corrected ΔAVD score can also be determined as a measure of state-based cortical hyperexcitability (Evans & Stevenson, 2008). Here the participants mean AVD score in response to the high-frequency grating (14 cycles-per-degree) is subtracted from their mean score in response to the medium-frequency grating

(3 cycles-per-degree). As AVD's elicited by the medium and high frequency gratings are known to differently relate to underlying central cortical (medium-frequency) versus more optical (high-frequency) processes respectively (Conlon et al., 2001; Evans & Stevenson, 2008), this score is more conservative than AVD scores alone in measuring cortical hyperexcitability (a form of baseline correction). The association between ΔAVD score and AVD scores in multisensory trials can therefore reveal whether state-based cortical hyperexcitability is an underlying factor of increased predisposition to sensory cross-talk.

In addition, participants completed the trait-based Audiovisual Aberration Scale (AVAS: See Chapter 2). The AVAS is a proxy measure of trait-based cortical hyperexcitability across auditory and visual domains, building on the visual-only equivalent – the Cortical Hyperexcitability Index II (CHi_II; Braithwaite et al., 2015; Fong et al., 2019: See Chapter 2). It measures proxy signs of trait-based cortical hyperexcitability based on the frequency and intensity of aberrant auditory and visual experiences which are known to reflect elevated cortical hyperexcitability. The AVAS can be devolved into distinct clusters (or factors) of aberrant experiences, namely: (i) Heightened Sensory Sensitivity and Discomfort (HSSD), (ii) Migrainesque Visual Aura Symptoms (MVAS), and (iii) Voice Hearing Experiences (VHE). The selective associations of these trait-based factors with predisposition to state-based sensory cross-talk in the Audiovisual Pattern Glare Test was then examined.

It was predicted that adding irritating tones (4 KHz, 8 KHz) to the concurrent presentation of visual gratings will lead to increased intensity of AVDs relative to the visual-only (no tone) and non-irritating tone (0.5 KHz) conditions. This enhancement of AVDs under dual-irritating sensory conditions would reflect a 'sensory cross-talk' between visual and auditory information. In addition, the existence of any cross-talk effect would be further mediated by trait-based measures. This presents a novel method for measuring state-based multisensory hyperexcitability in a laboratory setting. The selective associations between the trait-based factors of the AVAS questionnaire with the degree of state-based sensory cross-talk in the Audiovisual Pattern Glare Test was then examined.

Finally, some exploratory analyses were conducted to examine differences in sensory cross-talk between migraineur sub-groups (migraine-with-aura, migraine-without-aura) and neurotypical controls[4].Migraineurs are of particular interest here as a non-neurotypical population who are predisposed to aberrant perceptual experiences such as hallucinations and distortions (Hadjihkani et al., 2001; Huang et al., 2003; Huang et al., 2011; Rasmussen & Olesen, 1992; Russell & Olesen, 1996), but not the associated aberrant beliefs observed in populations such as individuals with schizophrenia or psychosis which may create response biases(Allen et al., 2010; Freeman & Garety, 2003; Lataster et al., 2006; Verdoux & van Os, 2002; Yung et al., 2009). Migraineurs may therefore serve as a window into the association between cortical hyperexcitability and sensory cross-talk in non-neurotypical populations, supplementing findings in the neurotypical population which form the focus of this chapter.

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[4] Note that a modest sample of individuals with migraine were collected, as such these analyses are treated as exploratory here with the main focus on whole sample analyses.

Methods

2.1 Participants

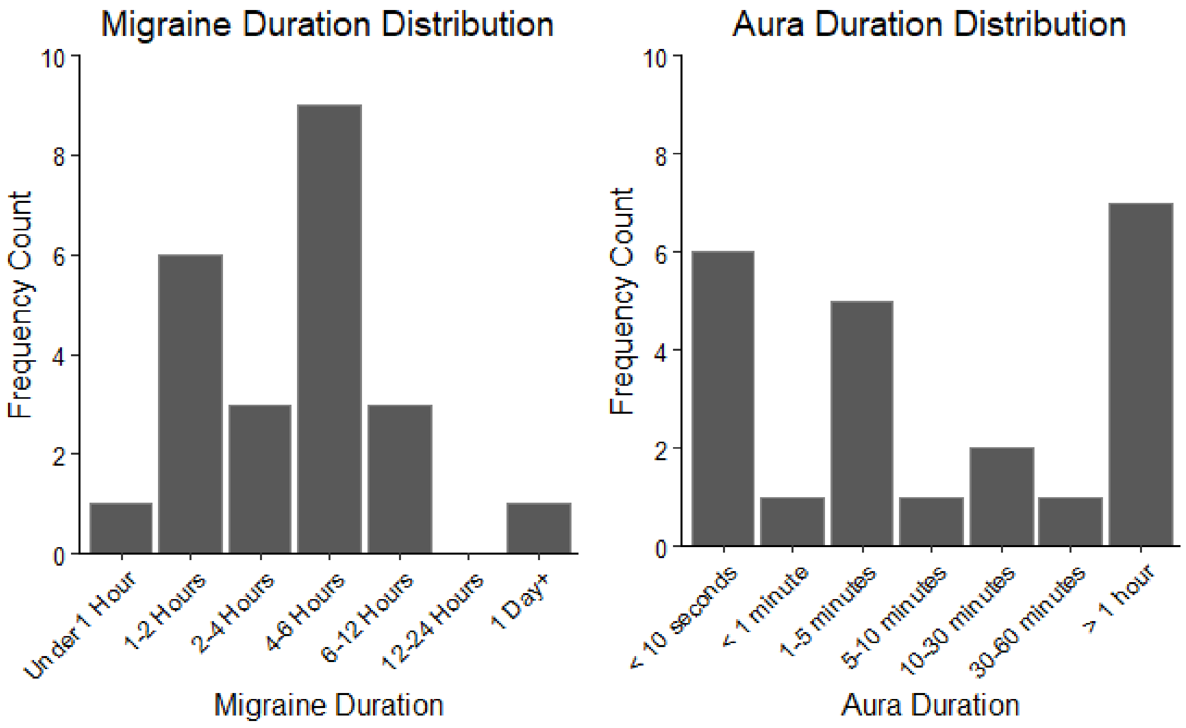
Seventy-three participants (65.75% Female, 34.25% Male) aged 18-37 (*M* = 21.56, *SD* = 3.91) were recruited via Lancaster University's SONA recruitment system. Participants were compensated with a £20 cash payment. All participants had normal or corrected-to-normal visual acuity (minimum 20/25), and no history of hearing loss as confirmed by a Pure Tone Hearing Threshold test following the procedure outlined by the British Society of Audiology (BSA, 2018). Any participants presenting a hearing threshold above 20 dB HL at any tested frequency were excluded prior to data collection but were still compensated for their participation as per Lancaster University ethical guidelines.

Participants completed a brief preliminary questionnaire asking them to declare any relevant psychological or neurological contraindications including: neurosurgery, epilepsy or seizures of unknown origin, migraine, tinnitus or reoccurring noises of unknown origin, hyperacusis (or hypersensitivity to sound), neurological conditions requiring medication, psychiatric conditions requiring medication, ocular conditions (e.g., astigmatisms, colour blindness), or hearing loss (partial or complete). Those who responded 'yes' to any of these items (besides migraine) were excluded from this study prior to data collection.

Those who responded 'yes' to having a history of migraine completed a further measure to gauge the phenotypic characteristics of migraine present in the sample. Twenty-three participants declared themselves as migraineurs: of these, thirteen experienced migraine-with-aura, and ten experienced migraine-without-aura. Distributions for both migraine duration and aura duration are presented in Figure 1.

Figure 1.

Migraine and Aura Durations.



Migraineurs also completed a pre-assessment measure to gauge phenomenological aspects of their migraines. Descriptive statistics for responses to these items are available in Table 1. As can be seen from Table 1, the most frequent Migraine symptoms in this sample were visual, followed by vestibular (vertigo / nausea), and finally auditory.

Table 1.

Associated Migraine Characteristics.

Shortened Pre-screen Item	Mean	Standard Deviation (±)
Sensitivity to light?	66.61	30.67
Visual Discomfort?	59.65	29.67
Vertigo or Nausea?	52.09	36.67
Accompanied by aura?	49.04	39.50
Auditory Discomfort?	29.13	33.53

2.2 Materials

2.2.1 The Multisensory Pattern-Glare Test

The present study developed a novel multi-sensory (visual and auditory) pattern-glare test. The typical visual pattern-glare test involves presenting visual grating patterns which differ in terms of their spatial frequency (see Figure 2 for examples). There is a low-frequency baseline grating (0.5 cycles-per-degree: cpd), the crucial medium-frequency (3 cpd) grating, and a baseline high-frequency (14 cpd)[5] grating. In the current study, on the majority of trials the presentation of the gratings was combined with the presentation of auditory pure tones at various auditory frequencies (some of which have been empirically demonstrated to be irritative in the auditory domain, reflecting cortical hyperexcitability; Ashkenazi et al., 2009; Ashkenazi et al., 2010; Woodhouse & Drummond, 1993). Collectively, this created a mixture of typical visual-only (baseline), and new audiovisual trials. This allowed for statistical comparisons between, (i) more typical visual-only baseline and novel audiovisual trials to

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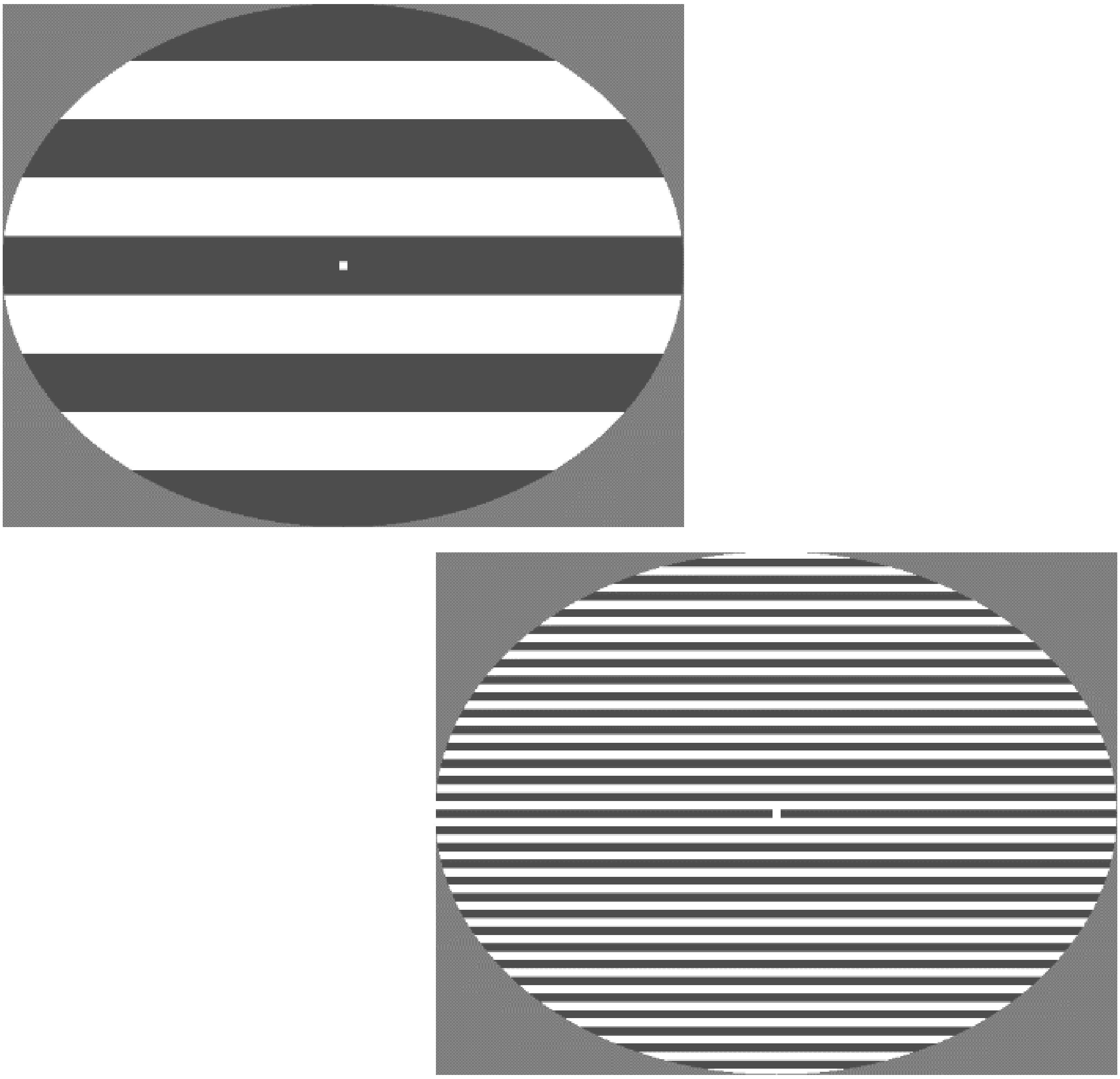
[5] Note – in pattern-glare tasks the baseline gratings should not be thought of as being devoid of potential visual effects, more so that the degree of effects experienced are far greater for the medium-frequency grating which likely reflect more central cortical processes.

examine the presence of cortical hyperexcitability in the auditory domain, (ii) the potential occurrence of a ‘sensory crosstalk’ effect, and (iii) an assessment of whether the crosstalk effect increases with trait-based signs of predisposition to aberrant experience (the AVAS).

Figure 2.

Examples of Low and Medium Frequency Visual Grating Stimuli.



Illustrations of the low-frequency (top) baseline grating and the crucial medium-frequency (bottom) irritative grating. The high-frequency grating is not shown here as it cannot be shown faithfully due to the high spatial frequency which suffers aliasing when rescaled, thus image is not demonstrative of experimental stimulus. Note: The exact cycles-per-degree may vary here due to the rescaling of image here.

Based on published findings from previous studies, three pure tone frequencies were selected[6]. A 0.5 KHz tone was selected as a relatively benign (non-irritating) auditory condition against which the irritating auditory stimuli could be examined. Both 4 and 8 KHz were taken as potentially irritating auditory conditions (Ashkenazi et al., 2009; Ashkenazi et al., 2010; Woodhouse & Drummond, 1993). The no-tone condition acted as a visual baseline measure (e.g., the typical pattern-glare effect) against which the effects of the auditory stimuli were compared (i.e., a standard visual pattern-glare task with no tone).

All visual and audiovisual stimulus configurations (totalling twelve stimulus conditions) were presented ten times each for a total of 120 trials, with thirty second breaks every ten trials and an (optional) extended five-minute break every 30 trials. Stimuli were presented in a pseudo-randomised order so that an exact condition replication (same auditory and visual stimulus) never occurred across two adjacent trials (to counteract potential trial-by-trial carryover effects).

The experiment was conducted in a dimly lit laboratory. The full task took approximately two hours to complete. All preliminary questionnaires were completed online via Qualtrics prior to the in-person study. All visual stimuli had Michelson contrast set to 0.75 cd/m^2 and mean luminance across the three stimuli was 40 cd/m^2. Grating patterns were presented as an ellipse (height × width = 154mm × 198mm) of black and white horizontal lines on a dark grey background (luminance 20 cd/m^2). Gratings were presented at eye-level on a 27” Iiyama G-MASTERGB2788HS-B1 Red Eagle monitor (1920 × 1080 resolution, 144 Hz refresh rate). Participants were fixed in place on an office chair at an 80cm viewing distance to maintain the visual angle (11.0 × 14.1 degrees). Auditory stimuli were presented

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[6] In addition, a small selection of participants were asked to independently rate these tones in terms of their irritating nature. Findings here reflected published literature (See Appendix B).

through Sennheiser HD650 impedance-matched cabled headphones at a fixed volume of 60 dB SPL and were calibrated externally using a Brüel & Kjær Type 4153 Artificial Ear.

Each trial began with a four second blank inter-stimulus interval, followed by a twelve second presentation of a given visual or audiovisual stimulus condition. During that period participants could press the spacebar to hide the visual stimulus if they experienced excessive irritation, and a subsequent spacebar press would return the visual stimulus on screen. This could be repeated as many times as needed during the twelve second viewing period (following the procedure of previous work: Braithwaite et al., 2015; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022). After twelve seconds, participants responded to twenty items pertaining to induced aberrant perceptions / sensations including visceral, hallucinatory, and distortion symptoms associated with the Pattern Glare effect (referred to as Associated Visual Distortions: AVD; see Appendix C for AVD items and descriptions). Responses to these questions were collected on 0-6 Likert scales representing the intensity of the experience (0 = Not at all, 6 = Extremely intense); a zero response was considered as an absence of that experience, with any value greater indicating the relative intensity of a salient AVD. Responses were summed to give an AVD score out of 120 for each trial. Prior to the experiment, participants completed three practise trials with non-irritative checkerboard visual stimuli (vertical and horizontal spatial frequency approximately 0.5 cpd) and no auditory stimulus to practise using the response scales.

Crucially, despite the inclusion of the auditory stimuli, the AVD scale asked participants to rate their visual experiences only. That is to say, all AVD questions were focused on the perceptual effects of the visual PG grating, and not the auditory tones. Participants were explicitly instructed that the auditory stimuli were incidental that they were not rating the tones, and to solely rate their experiences in relation to perceived effects from the presentation of the visual gratings.

Individuals who scored exceptionally highly in the Pattern Glare test (‘extreme responders’) were identified prior to analyses. In line with previous investigations of the Pattern Glare Test (e.g. Fong et al., 2019), the upper limit for ‘typical’ scoring on the low-frequency grating was defined by the 95th percentile, and participants scoring above this benchmark were excluded from all analyses as this is often taken to imply a potentially confounding response bias.

2.2.2 Audiovisual Aberration Scale (AVAS)

The 35-item, 3-factor AVAS questionnaire was examined as a trait-based measure to complement results from the newly devised state-based multisensory Pattern Glare test. The AVAS acted as an indirect trait-based proxy measure for cortical hyperexcitability by measuring the frequency and intensity of symptoms thought to be related to the presence of cortical hyperexcitability.

Factor one, Heightened Sensory Sensitivity and Discomfort (HSSD), is made up of sixteen items reflecting aspects of sensitivity to external visual and auditory stimuli (e.g., ‘Have indoor lights ever seemed so bright that they have become irritating to you?’; ‘Have you ever noticed certain sounds appearing louder or more irritating than usual?’). Factor two, Migrainesque Visual Aura Symptoms (MVAS), is made up of fourteen items which primarily reflect elementary visual hallucinations, somewhat similar to those reported by individuals with Migraine-with-Aura (e.g., ‘Have you ever experienced a transient, partial loss of vision (e.g., an island of blindness) that was also surrounded by angular striped zigzag patterns?’). Factor three, Voice Hearing Experiences (VHE), is made up of five items covering various experiences of perceiving a voice / multiple voices in the absence of an external speaker / speakers, sometimes termed an auditory verbal hallucination (e.g. ‘Have you ever heard a single voice talking aloud when no one else was there?'). For each item scores for frequency (from '0 = Never' to '6 = All the time') and intensity (from '0 = Not at all' to '6 = Extremely intense') were summed to give a score between 0 - 12 for each item, and between 0 - 420 for the overall AVAS questionnaire.

2.3 Analysis

Analyses consisted of pairwise comparisons, Pearson's r correlations, analysis of variance (ANOVA), and linear regression models. These analyses were chosen to assess the propensity of specific irritating audiovisual stimulus conditions to elicit symptoms of Pattern Glare (AVDs) which can be facilitated by sensory crosstalk. In addition, these analyses examined whether these symptoms are prevalent to a heightened degree in individuals who are known to exhibit elevated trait-based signs of cortical hyperexcitability within neurotypical individuals and Migraineurs. Note, sex differences in sensory cross-talk were also explored as a post-hoc rationalisation given recent evidence for significant sex differences in cortical hyperexcitability (Jurkovičová et al., 2024), these are presented as an addendum (see Appendix D). Where appropriate, these analyses were supplemented with additional post-hoc and Bayesian analyses. All ANOVAs were supplemented with Tukey's HSD (Abdi & Williams, 2010) to assess pairwise differences between groups of means, whilst controlling (as far as possible) for type I errors. All frequentist analyses were conducted in R Studio (R version 4.3.0), and Bayesian analyses were conducted using JASP (v 0.16.3).

Where any pairwise comparisons were conducted, the False Discovery Rate (FDR; Benjamini & Hochberg, 1995) was applied. This was intended both to correct for inflated type I error rates and to assess the relative strength of the relationships between each AVAS factor and Pattern Glare. FDR assigns a new critical value (B&H) to each comparison by ranking each *p*-value in ascending order, then applying the equation B&H = (i/k) * Q, where i is the original rank, k is the number of comparisons, and Q is the relevant threshold of significance (here .05). The highest ranked significant *p* value where *p* < B&H is deemed significant, along with all comparisons ranked below where *p* < B&H. Where a comparison is deemed statistically significant but *p* > B&H, that comparison and all subsequent comparisons would be deemed not statistically significant upon adjustment.

Bayesian analyses estimate a Bayes Factor (BF_{10}) value which makes a comparison of whether the data are more in favour of the null or alternative hypothesis. Bayes factors were interpreted in line with Jeffreys' theory of probability (Jeffreys, 1998; see also, Lee & Wagenmakers, 2014). As such, $BF_{10} < 1.0$ would be taken as indicating the probability of the data being in favour of the null hypothesis, and $BF_{10} > 1.0$ taken as indicating the probability of the data being in favour of the alternative hypothesis. Values closer to zero are deemed stronger evidence for the null hypothesis (e.g., 0.01 – 0.10 considered very strong, 0.10 – 0.33 considered substantial) and larger values above 3 are deemed stronger evidence for the alternative hypothesis (3 – 10 considered substantial, 10 – 100 considered strong / very strong, and > 100 considered decisive). Values between 0.33 – 3 are considered insensitive or anecdotal evidence for either hypothesis. These values can additionally be interpreted in terms of a numerical likelihood; for example, a BF_{10} of 10 suggests the data fit 10 times better with the alternative hypothesis than the null hypothesis. Equally, a BF_{10} of 0.1 suggests the data fit 10 times better with the null hypothesis than the alternative hypothesis. For all Bayesian analyses, the Cauchy prior value was set to the default conservative value of 0.707 (Wagenmakers et al., 2018).

Results

Initial outlier identification was conducted by determining the 95th percentile value for mean AVD score in the low frequency (0.5 cycles-per-degree; cpd) visual-only condition, which was determined as 10.03. Two participants' mean scores in the control condition exceeded this value (*M* = 23.7, *M* = 33.7), and hence their responses were omitted from all analyses. This left a final sample of 71 participants (65.75% Female, 34.25% Male) aged 18 – 37 (*M* = 21.56, *SD* = 3.91). As the low frequency grating is intended only as a screening measure, it is subsequently removed from all analyses.

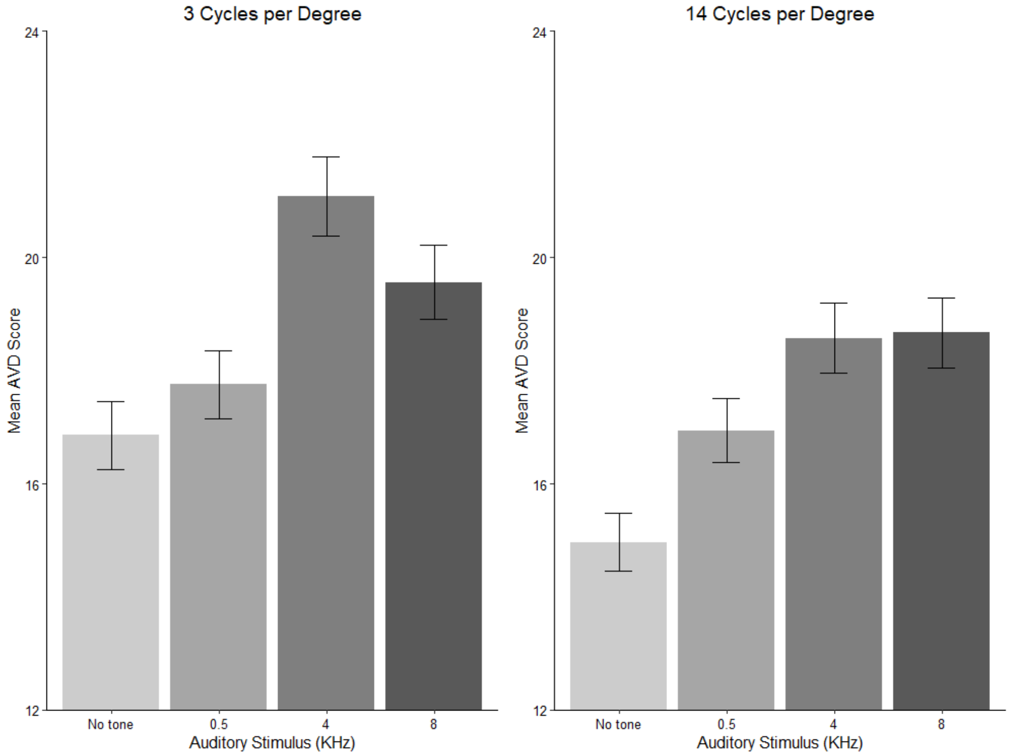
3.1 Multisensory Pattern Glare Effect

3.1.1 AVD Score

Whole sample means for AVD scores in visual only and audiovisual conditions are presented in Figure 3.

Figure 3.

AVD Means and Standard Errors for Whole Sample by Auditory Stimulus.



AVD scores were entered as an outcome variable into a 2 (Visual Stimulus: 3 cpd, 14 cpd) x 4 (Auditory Stimulus: No tone, 0.5 KHz, 4 KHz, 8 KHz) within-subjects ANOVA. This revealed significant main effects of Visual Stimulus $F(1, 5672) = 12.35$, $p < 0.001$, $\eta^2\rho = 0.002$, $BF_{10} = 13.35$, and of Auditory Stimulus $F(3, 5672) = 16.61$, $p < .001$, $\eta^2\rho = 0.009$, $BF_{10} > 1000$. There was no significant effect of the interaction term $F(3, 5672) = 0.88$, $p = .445$, $\eta^2\rho = 0.0005$, $BF_{10} = 0.002$.

Tukey's HSD was used to identify which visual and auditory stimulus conditions differed significantly in the intensity of AVD's reported. For visual stimuli only trials, participants reported significantly more intense AVDs for the medium frequency grating (3 cpd) than the high frequency grating (14 cpd; Diff = 1.52, 95 CI [0.67, 2.37], $p < .001$. This is commensurate with the typical pattern-glare effect. For the effect of auditory stimulus pooled across both visual stimuli (see Table 2), participants reported significantly more intense AVDs in irritating auditory conditions (4 KHz and 8 KHz) relative to the visual only (no tone) condition. Additionally, more intense AVDs were reported in both irritating auditory conditions (4 KHz, 8 KHz) compared with the non-irritating auditory condition (0.5 KHz). There was no significant difference between the visual only (no tone) condition and the non-irritating auditory condition (0.5 KHz) in the reported intensity of AVDs. Although there appeared to be an increased effect for the 4KHz condition over the 8KHz condition in reported AVD intensity (see Figure 3), this failed to be reliable.

Table 2.

Tukey's HSD comparisons for pooled effects of Auditory Stimulus on AVD.

Auditory Stimulus	Difference	- 95 CI	+ 95 CI	*p*
4 KHz – No tone	3.91	2.34	5.49	< .001***
8 KHz – No tone	3.20	1.63	4.78	< .001***
4 KHz – 0.5 KHz	2.48	0.90	4.05	< .001***
8 KHz – 0.5 KHz	1.76	0.19	3.39	.021*
0.5 KHz – No tone	1.44	-0.14	3.01	.088
4 KHz – 8 KHz	0.71	-0.86	2.29	.651

* - Denotes significance: *** = $p < .001$; * = $p < .05$

The above results show that adding an irritating tone to visual PG stimuli significantly increased the subjective intensity of reported AVDs. Importantly, this increase occurred with the specific addition of an irritating tone (4 KHz, 8 KHz) but not a non-irritating tone (0.5

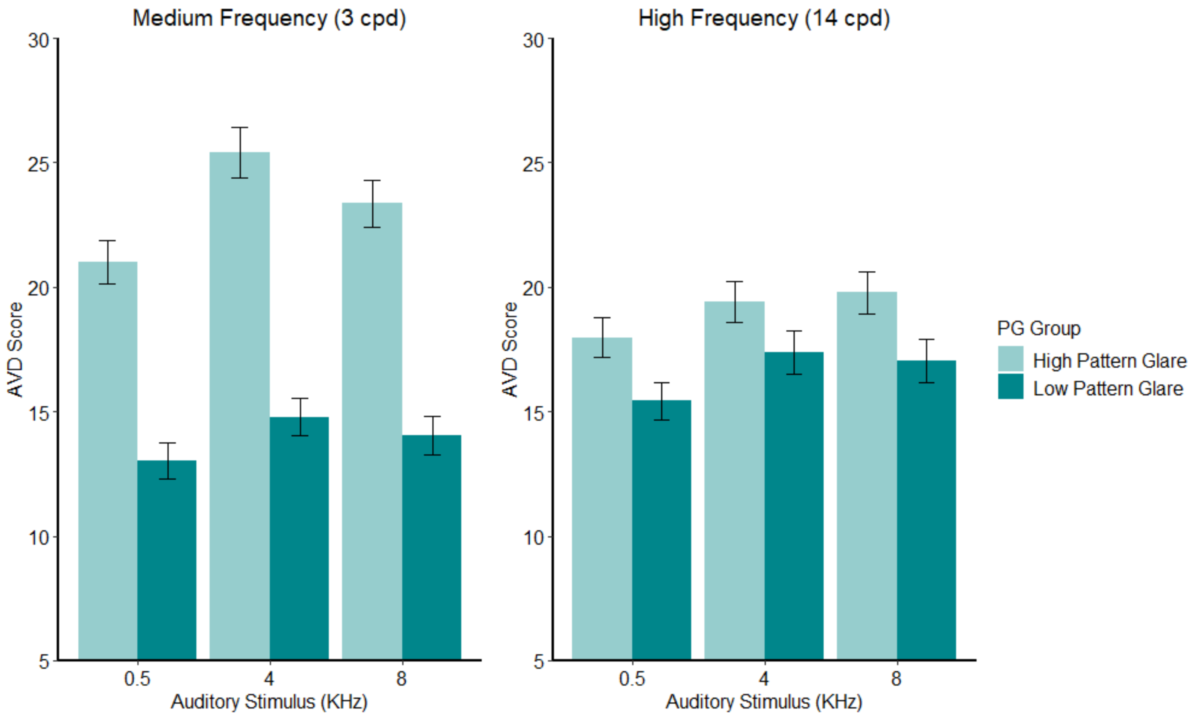
KHz). There was no interaction between visual stimulus and auditory stimulus, suggesting that the addition of an auditory stimulus increases the intensity of AVDs experienced in response to both PG gratings. These findings are in line with the notion of a facilitatory sensory crosstalk effect, where the co-presentation of additional auditory stimuli enhanced the severity of visual AVDs (see Discussion).

3.1.2 Medium frequency – high frequency (ΔAVD)

Whole Sample Analysis. In addition, ΔAVD scores were calculated by subtracting participants' mean AVD score in response to the high-frequency grating (14 cpd) from the medium frequency grating (3 cpd) in visual only (no tone) conditions. This creates a baseline-corrected delta score which is more conservative than analysing AVD scores in the medium frequency alone (Evans & Stevenson, 2008: see also Braithwaite et al., 2013 for a similar approach). Participants were then split into those that displayed elevated PG, relative to those that did not based on whether they presented a positive (High PG) or negative (Low PG) ΔAVD score. This distinction of High PG group versus Low PG group provides a meaningful variable to examine whether the facilitatory effects of auditory tones on PG gratings (i.e. sensory cross-talk) are mediated by individual differences in state-based cortical hyperexcitability. In addition, as AVDs elicited by the medium and high frequency gratings are known to differently relate to underlying central cortical (medium-frequency) versus more optical (high-frequency) processes respectively (Conlon et al., 2001; Evans & Stevenson, 2008), PG group differences in effects of auditory tones on the medium-frequency and high-frequency gratings may also be revealing on the underlying mechanisms by which sensory-crosstalk occurs. PG group differences in AVD scores in audiovisual conditions are presented in Figure 4.

Figure 4.

PG Group Differences in AVD Scores in Audiovisual Conditions.



PG group differences in AVD score were examined via a 3 (Auditory Stimulus, within-subjects; 0.5 KHz, 4 KHz, 8 KHz) × 2 (Visual Stimulus, within-subjects; 3 cpd, 14 cpd) × 2 (Pattern Glare group, between-subjects; High PG, Low PG) mixed ANOVA. This revealed significant main effects of PG Group, F (1, 4248) = 131.62, $p < .001$, $\eta^2\rho = 0.030$, $BF_{10} > 1000$; Auditory Stimulus, F (2, 4248) = 8.56, $p < .001$, $\eta^2\rho = 0.004$, $BF_{10} > 1000$; and Visual Stimulus F (1, 4248) = 7.74, $p = .005$, $\eta^2\rho = 0.002$, $BF_{10} = 13.35$. There was also a significant PG group × Visual Stimulus interaction, F (1, 4248) = 45.22, $p < .001$, $\eta^2\rho = 0.011$, $BF_{10} > 1000$.

Tukey's HSD was used to identify in which auditory conditions the intensity of reported AVDs differed significantly (see Table 3). Significantly more intense AVDs were reported in both irritating auditory conditions (4 KHz and 8 KHz) relative to the non-irritating auditory condition (0.5 KHz). There was no significant difference between the two irritating auditory conditions in reported intensity of AVDs.

Table 3.

Tukey's HSD for effects of Auditory Stimulus on AVD in PG Groups.

Auditory Stimulus	Difference	- 95 CI	+ 95 CI	*p*
4 KHz – 0.5 KHz	2.48	1.03	3.92	< .001***
8 KHz – 0.5 KHz	1.76	0.32	3.21	.012*
4 KHz – 8 KHz	0.71	-2.16	0.73	.480

* - Denotes significance: *** = $p < .001$; * = $p < .05$

The interaction between Visual Stimulus and PG Group was examined further with a mixed ANOVA. AVD Score was entered as outcome variable into a 2 (Visual Stimulus, within-subjects; 3 cpd, 14 cpd) × 2 (PG Group, between subjects; High PG, Low PG) mixed ANOVA. This revealed significant effects of PG Group $F(1, 4256) = 131.19$, $p < .001$, $\eta^2\rho = 0.030$, $BF_{10} > 1000$; and Visual Stimulus $F(1, 4256) = 7.72$, $p = .006$, $\eta^2\rho = 0.002$, $BF_{10} = 1.38$. There was also a significant PG group × Visual Stimulus interaction, $F\ (1, 4256) = 45.08$, $p < .001$, $\eta^2\rho = 0.010$, $BF_{10} > 1000$.

Tukey's HSD was used to examine differences within and between PG groups in response to the medium (3 cpd) and high (14 cpd) frequency grating. Between groups (see Table 4) the High PG group reported significantly more intense AVDs than the Low PG group irrespective of Visual Stimulus. Within groups (see Table 5) the PG group reported more intense AVDs for the medium than the high frequency grating, whilst the no PG group reported more intense AVDs for the high than the medium frequency grating.[7]

Table 4.

Tukey's HSD for between-PG-group comparisons of Visual Stimulus effects.

Visual Stimulus	Direction (PG Group)	Difference	- 95 CI	+ 95 CI	*p*
Medium	High PG > Low PG	9.31	7.45	11.18	< .001***
High	High PG > Low PG	2.43	0.57	4.29	.004**

* - Denotes significance: *** = $p < .001$; ** = $p < .01$

Table 5.

Tukey's HSD for within-PG-group comparisons of Visual Stimulus effects.

PG Group	Direction (Visual Stimulus)	Difference	- 95 CI	+ 95 CI	*p*
High PG	Medium > High	4.21	2.53	5.90	< .001***
Low PG	High > Medium	2.67	0.65	4.70	.004**

* - Denotes significance: *** = $p < .001$; ** = $p < .01$

The above results show that both the High PG and Low PG groups report significantly increased intensity of AVDs with the addition of irritating tones (4 KHz, 8 KHz) versus a non-irritating tone (0.5 KHz) in audiovisual trials. The High PG group reported greater

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[7] It is important to remember that the groups are split based on visual only trials (no tone). Which is then used to examine the multisensory trials (with tones). If these analyses were not in the context of multisensory trials this may form a circular argument. However, the results here show that auditory tones are having prominent effects for different visual stimuli dependent on the visual-only PG group split.

intensity of AVDs for the medium frequency (3 cycles per degree) than the high frequency (14 cycles per degree) grating in multisensory trials, suggesting a greater sensory cross-talk effect for the medium frequency grating in the High PG group. However, the Low PG group reported greater intensity of AVDs in the high frequency (14 cycles per degree) than the irritating medium frequency (3 cycles per degree) grating, suggesting a greater sensory cross-talk effect for the high frequency grating in the Low PG group. This shows similar effects of the auditory tones across the sample, but at different spatial frequencies of the visual grating stimulus dependent on PG Group (see Discussion).

Without Migraineurs. To rule out the possibility that the interaction effect was being driven entirely by Migraine participants in the High PG group reporting more intense AVDs with the medium-frequency grating, all migraineurs were removed from the sample and analyses were repeated. As such, another 3 (Auditory Stimulus, within-subjects; 0.5 KHz, 4 KHz, 8 KHz) × 2 (Visual Stimulus, within-subjects; 3 cpd, 14 cpd) × 2 (Pattern Glare group, between-subjects; High PG, Low PG) mixed ANOVA was conducted. This revealed significant main effects of PG Group, $F\ (1, 2988) = 16.94, p < .001, \eta^2\rho = 0.006, \mathrm{BF}_{10} = 170.93$; and Auditory Stimulus, $F\ (2, 2988) = 6.52, p = .002, \eta^2\rho = 0.004, \mathrm{BF}_{10} = 2.49$. There was also a significant PG group × Visual Stimulus interaction, $F\ (1, 2988) = 21.51, p < .001, \eta^2\rho = 0.007, \mathrm{BF}_{10} > 1000$. There was no significant main effect of Visual Stimulus, $F\ (1, 2988) = 0.34, p = .562, \eta^2\rho = 0.0001, \mathrm{BF}_{10} = 0.05$.

These findings show that the High PG group and Low PG group still reported more intense AVDs in different audiovisual trials after the removal of migraineur participants. This is indicated by the persistence of the interaction between the Visual Stimulus and PG Group variables after removal of migraineurs from the sample.

3.2 Trait-based and State-based Associations - AVAS Factors × AVDs

Medium-Frequency Grating

To assess the association between state-based Pattern Glare effects and trait-based AVAS scores, Pearson's R correlations were calculated between AVD score and the separate factors of the AVAS questionnaire. AVD scores in response to the irritating medium frequency grating (3 cpd) in visual only and audiovisual conditions were correlated with total score on each separate AVAS factor. B&H corrections were applied to correct for multiple comparisons (see Table 6). Interestingly, in all conditions there were significant correlations with Factor 2 (Migrainesque Visual Aura Symptoms, MVAS). All other correlations were not significant ($p > .05$: not shown here).

Table 6.

Correlational analysis for AVD Scores (3 cpd) and AVAS factors.

	Frequentist			Bayesian		
Correlation	*r*	*p*	B&H	BF_{10}	Hypothesis	Support
4 KHz × MVAS	0.40	< .001*	.004	44.38	Alternative	Very Strong
No tone × MVAS	0.38	.001*	.008	26.76	Alternative	Very Strong
0.5 KHz × MVAS	0.36	.002*	.013	15.67	Alternative	Very Strong
8 KHz × MVAS	0.35	.003*	.017	13.18	Alternative	Very Strong

* Denotes significance after correction for multiple comparisons. MVAS – Migrainesque Visual Aura Symptoms. All correlations not featured were not statistically significant ($p < .05$) and Bayes factors suggested substantial or very strong support for the alternative hypothesis ($BF_{10} < 0.33$).

High-Frequency Grating

Additionally, AVD scores in response to the high frequency grating (14 cpd) in visual only and audiovisual conditions were correlated with total score on each individual AVAS factor. B&H corrections were applied to correct for multiple comparisons (see Table 7). For the high frequency grating all correlations were not statistically significant after correcting for multiple comparisons.

Table 7.

Correlational analysis for AVD Scores (14 cpd) and AVAS factors.

	Frequentist			Bayesian		
Correlation	*r*	*p*	B&H	BF_{10}	Hypothesis	Support
No tone × MVAS	0.28	.020	.004	2.09	Alternative	Anecdotal
0.5 KHz × MVAS	0.27	.024	.008	1.77	Alternative	Anecdotal
8 KHz × MVAS	0.23	.057	.013	0.80	Null	Anecdotal
4 KHz × MVAS	0.21	.080	.017	0.66	Null	Anecdotal

MVAS – Migrainesque Visual Aura Symptoms; HSSD – Heightened Sensory Sensitivity and Discomfort; VHE – Voice Hearing Experiences. All correlations not featured were not statistically significant ($p < .05$) and Bayes factors suggested substantial or very strong support for the alternative hypothesis ($BF_{10} < 0.33$).

These results show that an elevated degree of one specific facet of trait-based cortical hyperexcitability (predisposition to visual aura-like hallucinations: MVAS) is associated with more intense AVDs reported in both visual-only and audiovisual conditions. Interestingly, this effect is specific to the crucial medium frequency (3 cpd) grating.

3.3 Moderation Analysis for State-based and Trait-based Associations

Moderation analyses were conducted to check whether migraineurs (particularly Migraineurs-with-Aura) drove the association between the state-based measure of Pattern Glare, and the trait-based factors measured in the AVAS. For this purpose, a regression model was constructed using AVD scores from trials where the medium frequency grating was paired with a 4 KHz tone. The medium frequency grating was selected as the correlational analyses showed a closer relationship between the factors of the AVAS and symptoms of pattern glare elicited by the medium frequency grating (relative to the high frequency grating). This is consistent with the notion that AVDs reported in response to high frequency gratings may reflect more ocular rather than cortical processes (Conlon et al., 2001; Evans & Stevenson, 2008). The 4 KHz tone was selected as, where significant relationships were uncovered between AVAS factors and measures of PG, these were typically more positive in trials with 4 KHz tones. For the predictor variable, participants' score on the MVAS factor of the AVAS questionnaire was used as a predictor variable, as only MVAS showed a significant correlation with AVDs. The model also included migraineur status as a dummy coded variable (Migraine-with-Aura = 1; Other = 0).

Assumption Testing

The assumptions of multivariate normality of each variable was assessed initially using repeated Mardia's tests for skewness and kurtosis and adjusting for multiple comparisons using B&H adjustments (Mardia, 1971; Mardia, 1980; Mardia, Kent & Taylor, 2024). These revealed violations of multivariate normality for both MVAS score (Skewness and Kurtosis) and AVD score (Skewness only), and as such both variables underwent square root transformations (Osborne, 2002) and their multivariate normality was reassessed, again adjusting for multiple comparisons. After transformation, these variables subsequently fit the assumptions of multivariate normality. A summary of the statistics from multivariate normality tests is presented in Table 8.

Table 8.

Multivariate Normality Tests for Regression Model.

Before Transformation					
Variable	Test	Value	*p*	B&H	Sig?
AVDs	Skewness	31.48	< .001	.0125	Yes
AVDs	Kurtosis	5.47	< .001	.0250	Yes
MVAS	Skewness	5.68	.017	.0375	Yes
MVAS	Kurtosis	-0.1	.920	.0500	No
After Transformation					
Variable	Test	Value	*p*	B&H	Sig?
AVDs	Skewness	4.63	.032	.0125	No
MVAS	Kurtosis	-1.59	.110	.0250	No
MVAS	Skewness	0.72	.400	.0375	No
AVDs	Kurtosis	0.24	.810	.0500	No

Model

A multiple regression model was constructed with AVD score (3 cycles-per-degree, 4 KHz tone) as the outcome variable. Both MVAS factor score, and Migraine Status were included as predictor variables (Model: AVDs ~ MVAS * Migraine Status). The overall model was statistically significant $R^2 = 0.207$, $F(3, 67) = 7.08$, $p < .001$. It was found that MVAS factor score significantly predicted AVDs ($\beta = 0.63$, $t = 2.90$, $p = .005$) but Migraine Status did not significantly predict AVDs (β = 2.94, $t = 1.69$, $p = .096$). There was however a significant interaction between MVAS score and Migraine Status (β = -0.58, $t = -2.52$, $p = .014$).

This interaction was explored further by splitting the sample into Migraineurs-with-Aura and other participants (Migraine-without-Aura, Non-Migraineur) and creating two separate simple linear regression models using MVAS Factor score to predict AVDs (Model: AVDs ~ MVAS).

Migraine-with-Aura. For Migraine-with-Aura participants, the overall model was statistically significant $R^2 = 0.335$, $F(1, 12) = 7.54$, $p = .018$. It was found that MVAS Factor score significantly predicted AVDs (β = 0.63, $t = 2.75$, $p = .018$).

Other participants. For Migraine-without-Aura and Non-Migraineur participants, the overall model was not statistically significant $R^2 = -0.012$, $F(1, 55) = 0.33$, $p = .0567$. It was found that MVAS Factor score did not significantly predict AVDs (β = 0.05, $t = 0.58$, $p = .567$).

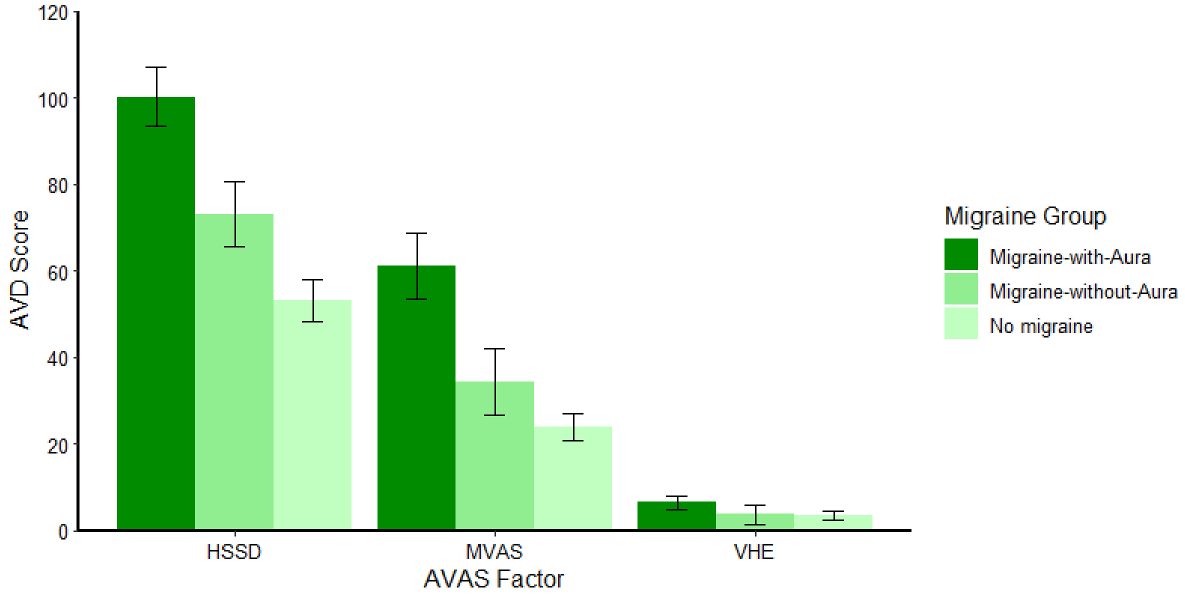
These results suggest that the relationship between trait-based cortical hyperexcitability and AVDs was primarily present in Migraine-with-Aura participants within this sample.

3.4 Migraine and Cortical Hyperexcitability

The role of cortical hyperexcitability in the migraine group was also assessed. Migraineurs-with-Aura (MwA) typically exhibit a greater degree of cortical hyperexcitability than in cases of Migraine-without-Aura (MwoA) (Chen et al., 2011; Palmer et al., 2000; van der Kamp et al., 1996). As a result, it would be expected that any between-group differences which exist between no migraine (Control) and MwA groups, to also exist between MwoA and MwA groups. This suggests effects are more likely to reflect elevations in cortical hyperexcitability, rather than broader pathophysiological aspects of migraine. This pattern can be seen in migraine groups' mean scores on the separate factors of the trait-based AVAS questionnaire (see Figure 5).

Figure 5.

Migraine Group Differences in Mean AVAS Factor Scores.



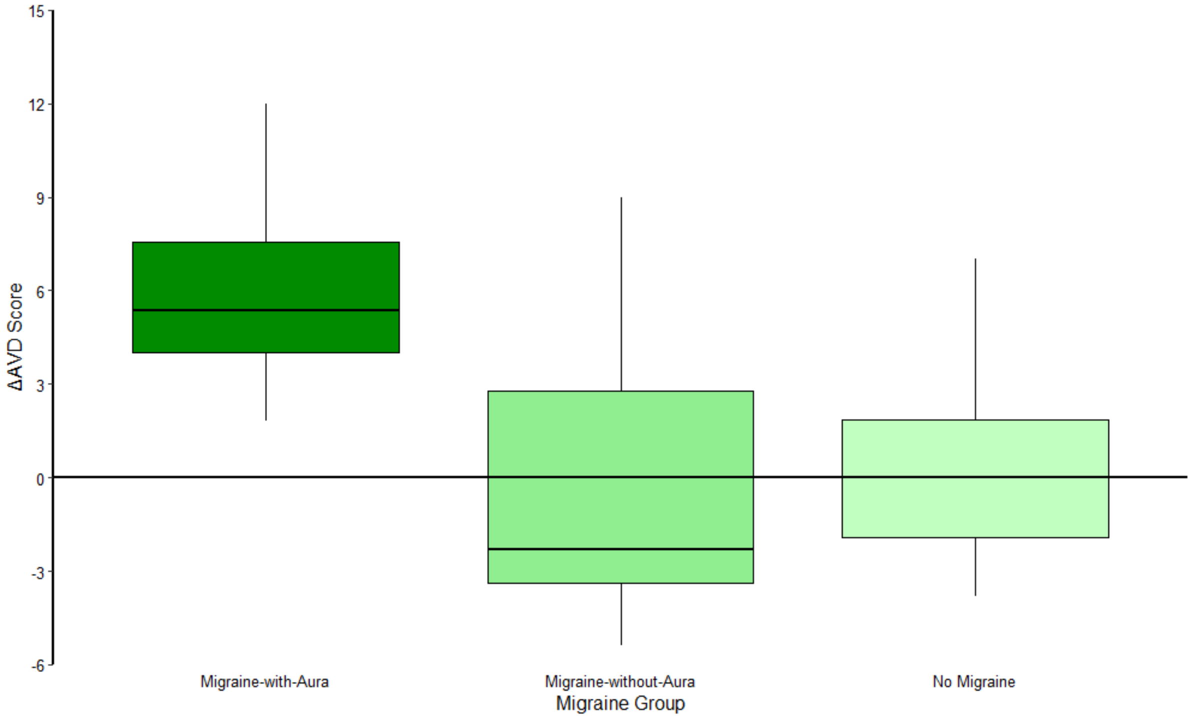
Differences between migraine groups are thought to reflect cortical hyperexcitability and therefore would be most notable in response to the medium frequency (3 cpd) grating, as well as the medium frequency – high frequency (ΔAVD) calculation. Migraineur differences were examined for ΔAVD scores to compare this sample against previous investigations (e.g. Braithwaite, Mevorach & Takahashi, 2015; Fong, Takahashi & Braithwaite, 2019).

3.4.1 Migraine and ΔAVD

A visual illustration of migraineur group differences in ΔAVD scores is presented in Figure 6.

Figure 6.

Migraine Group Differences in ΔAVD Scores.



To examine these group differences, ΔAVD scores were entered as an outcome variable into a one way between-subjects ANOVA with Migraine Group (MwA, MwoA, No migraine) as predictor variable. This revealed a significant effect of Migraine Group F (2, 68) = 11.92, $p < .001$, $\eta^2\rho = 0.260$, $BF_{10} = 656.99$. Post-hoc Tukey's HSD (see Table 9) revealed MwA participants scored significantly higher than both MwoA and No Migraine participants, but that MwoA and No Migraine participants did not differ significantly. The presence of hallucinatory aura was therefore the crucial difference.

Table 9.

Tukey's HSD for migraineur comparisons of ΔAVD scores.

Migraine group	Difference	-95 CI	+95 CI	*p*
MwA - Control	7.39	3.68	11.10	< .001***
MwA - MwoA	7.85	2.17	13.53	< .001***
Control - MwoA	0.46	-4.49	5.41	.973

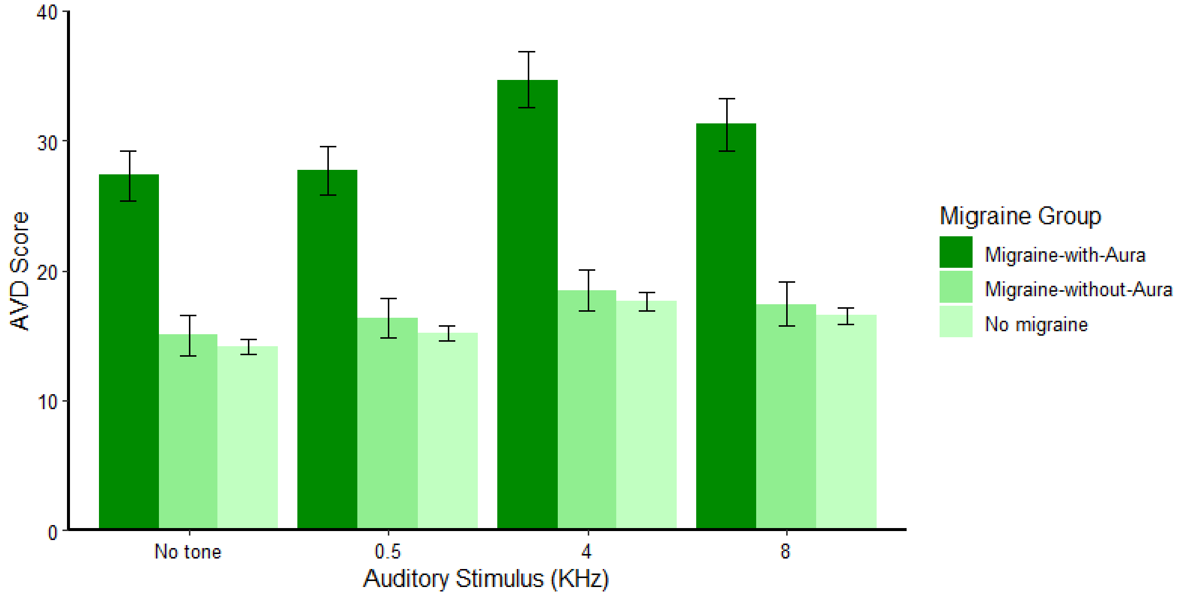
* Denotes significance level. *** = $p < .001$

3.4.2 Migraine and AVDs

A visual illustration of migraineur group differences in mean AVD scores in response to the medium frequency grating (3 cpd) across visual-only and audiovisual conditions is presented in Figure 7.

Figure 7.

Migraine Group Differences in Mean AVD Scores (3 cpd) by Auditory Stimulus.



To examine these group differences further, AVD scores in response to the medium frequency grating were entered as an outcome variable into a 3 (Migraine Status; No migraine, MwoA, MwA) x 4 (auditory stimulus; No tone, 0.5 KHz, 4 KHz, 8 KHz) ANOVA. There was a significant main effect of Migraineur Status $F(2, 2828) = 175.27$, $p < .001$, $\eta^2\rho = 0.110$, $BF_{10} > 1000$; and of Auditory Stimulus $F(3, 2828) = 9.64$, $p < .001$, $\eta^2\rho = 0.010$, $BF_{10} = 188.36$. There was no significant effect of the interaction term $F(6, 2828) = 0.89$, $p = 0.502$, $\eta^2\rho = 0.002$, $BF_{10} = 0.002$.

Post-hoc Tukey's HSD for the effects of Migraineur Status revealed that MwA participants reported significantly more intense AVDs than both the No Migraine and the MwoA group. There was no significant difference between MwoA and control participants in terms of reported intensity of AVDs (see Table 10).

Table 10.

Tukey's HSD for migraineur comparisons of AVD scores, 3 cpd.

Migraine group	Difference	-95 CI	+95 CI	*p*
MwA – No Migraine	14.36	12.55	16.17	< .001***
MwA – MwoA	13.41	10.63	16.18	< .001***
MwoA – No Migraine	0.95	-1.46	3.37	.625

* Denotes significance level. *** = $p < .001$

Post-hoc Tukey's HSD for the effects of Auditory Stimulus revealed that relative to the baseline no-tone condition the non-irritating 0.5 KHz tone did not increase the intensity of AVDs (Diff = 0.90, $p = .720$), but both the irritating 4 KHz (Diff = 5.74, $p < .001$) and 8 KHz (Diff = 4.22, $p = .009$) tones did increase the intensity of AVDs. Then, relative to the non-irritating 0.5 KHz tone, there was a significant increase in the intensity of AVDs for the 4 KHz tone (Diff = 3.32, $p < .001$) but not for the 8 KHz tone (Diff = 1.80, $p = .152$). There was no significant difference between the two irritating (4 and 8 KHz) tones (Diff = 1.52, $p = .289$).

These results show the Migraine-with-Aura group experienced significantly more AVDs than the no migraine group and the Migraine-without-Aura group. All groups reported significant increases in the intensity of AVDS with the addition of an irritating tone to the medium-frequency grating, with the greatest increase occurring with the addition of an irritating 4 KHz tone.

Discussion

The present study examined the role of cortical hyperexcitability in the context of a novel cross-sensory effect mediating aberrant perceptual experiences. Here, the typical visual-only Pattern Glare test was extended into the auditory domain and combined with irritating (4 KHz, 8 KHz) and non-irritating (0.5 KHz) tones that were presented simultaneously with the visual gratings. The underlying motivation was to examine if cortical hyperexcitability remained confined to a unitary sensory domain (i.e., vision), driven only by visual information, or whether there are instances when visual aberrations are mediated / increased by the co-presence of irritating auditory tones.

Findings revealed a sensory cross-talk effect, where the co-presentation of irritating tones elevated the intensity of the reported aberrant visual experiences and this was increased in groups with elevated state-based (High PG vs Low PG) and trait-based (AVAS, Migraine-with-Aura vs No Migraine) cortical hyperexcitability. Selective factors of the AVAS measure, a trait-based proxy measure of trait-based cortical hyperexcitability, were found to correlate significantly with Pattern Glare measured under both unisensory (no tone) and cross-sensory (4 KHz tone) conditions. Together, these findings lend support to the idea that, at least in part, cortical hyperexcitability may extend beyond the boundaries of a given unitary sense with implications for either independent sensory processing, or processes involved in the integration of them (see also Haigh et al. 2023; Li et al., 2024; Toh et al., 2024).

4.1 Multisensory Pattern Glare

In visual only trials, the results replicated typical findings from previous research on Pattern Glare (Braithwaite, Mevorach & Takahashi, 2015; Evans & Stevenson, 2008; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022; Wilkins et al., 1984; Wilkins, 1995). Specifically, individuals displaying elevated state and trait-based cortical hyperexcitability reported elevated intensity of AVDs for the medium-frequency grating, whilst those indicating (relatively) attenuated state and trait-based cortical hyperexcitability reported elevated intensity of AVDs for the high-frequency grating.

In multisensory trials, the aberrant visual experiences associated with Pattern Glare (AVDs) were reported as being significantly more intense when paired with irritating tones (4 KHz, 8 KHz) than when gratings were presented alone (no tone). Importantly, there was no significant increase in the intensity of AVD's when gratings were paired with a non-irritating tone (0.5 KHz) than when gratings were presented alone (no tone).

PG Group Differences

Notably, those in the High PG group reported greater sensory cross-talk in response to tones paired with the medium-frequency grating. This makes intuitive sense, as AVDs in response to the medium-frequency grating are known to be more centrally cortically mediated and the PG group are more hyperexcitable at the cortical level as has been demonstrated previously across behavioural and neuroimaging studies (Braithwaite et al., 2015; Evans & Stevenson, 2008; Fong et al., 2020; Fong et al., 2022; Haigh, Cooper & Wilkins, 2015; Haigh et al., 2012; Huang et al., 2003; Huang et al., 2011; Wilkins, 1995). So, if sensory cross-talk occurs at the cortical level, it would predominantly be these AVDs (medium-frequency grating) which become more intense when the irritating tones are added, rather than AVD's which are arguably more associated with pre-cortical / ocular processes (high-frequency grating). In addition, this effect would only be seen in participants who exhibit elevated signs of elevated state-based cortical hyperexcitability (the High PG group), as this would reflect the underlying neural mechanism operating in a high-gain state.

For the Low PG group (who do not present signs of elevated state-based cortical hyperexcitability), one would not expect to see greater sensory cross-talk for the medium-frequency grating than for the high-frequency grating, and this was observed in the data. This is because they do not have the same underlying predisposition to cortically mediated aberrant experiences, as the underlying neural architecture would be operating under conditions of typical gain (see coming discussion on cortical gain). Therefore, if the cortical response to the visual grating is insufficiently salient on its own, any cross-sensory enhancement from the auditory tone would be minimal. This suggests a fundamental underlying difference in state-based cortical hyperexcitability, possibly reflective of differing states of cortical gain control, which makes the PG group more susceptible to sensory cross-talk at the cortical level than the No PG group.

Crucially, the interaction between PG group and grating type remained significant even after excluding migraineurs, confirming that the observed cross-modal effects are not reducible simply to migraine status. Neurotypical High and Low PG groups continued to show distinct sensitivity to specific grating frequencies, reinforcing the robustness of the effect. Although the main effect of grating frequency was no longer significant, this overall attenuation is expected: migraineurs, especially those with aura, showed heightened AVDs in response to the medium-frequency grating, which merely inflated group means in the full sample. Their removal naturally reduced the overall main effect size (Evans & Stevenson, 2008) but did not eliminate the core findings (interaction).

4.2 Trait-based and State-based Associations

Correlational analyses supported a fractionated view of cortical hyperexcitability (see also Braithwaite et al., 2015; Fong, Takahashi & Braithwaite, 2019; for similar findings). The intensity ratings for visual aberrations in response to the medium-frequency grating were significantly correlated with the Migrainesque Visual Aura Symptoms (MVAS) factor of the AVAS across visual only and audiovisual trials. This mirrors previous findings with the CHi_II measure, where only the subscale made up primarily of visual hallucinations was correlated positively with Pattern Glare intensity (Fong, Takahashi & Braithwaite, 2019) and is associated with the efficacy of brain-stimulation (Joshi et al., 2024). This supports the notion that both the facilitatory sensory cross-talk effect observed in the Multisensory Pattern Glare task and the aberrant perceptual experiences measured by the MVAS subscale of the AVAS questionnaire measure concepts which are likely centrally cortically mediated.

Moderation analysis revealed that Migraineurs-with-Aura appeared to drive the association with trait-based measures. Again, given that both AVDs and the MVAS subscale are thought to measure concepts which are predominantly centrally cortically mediated, it is unsurprising that in Migraineurs-with-Aura the association between these two measures is closer than in other participants, as Migraineurs-with-Aura typically display the most elevated signs of cortical hyperexcitability (Chen et al., 2011; Cucchiara et al., 2015; Fong et al., 2020; Evans & Stevenson, 2008; Palmer et al., 2000).

That the model failed to be significant for all other participants when pooled (migraine-without-aura, no migraine) may be indicative of the fractionation of state-based and trait-based factors underlying predisposition to aberrant experiences (Ffytche, 2008; Kühn & Gallinat, 2012; Mo et al., 2024; Zmigrod et al., 2016). This may suggest that these long-range connections associated with trait-based factors create an additional susceptibility to cortical hyperexcitability and hence a heightened degree of sensory cross-talk, whilst in other participants sensory cross-talk may be mediated predominantly by localised state-based mechanisms. That is not to suggest a difference in mechanism between the migraine-with-aura group and other participants, rather that this greater trait-based cortical hyperexcitability may exacerbate the localised state-based mechanisms underlying sensory cross-talk across both Migraine and neurotypical participants[8]. Under a cortical gain framework, this could be explained by high-gain states in frontal and / or subcortical areas which feed back into sensory cortical areas via long-range connections which exacerbate the localised high-gain state, creating relatively higher gain states in these individuals with migraine-with-aura. This therefore supports the idea that there is not a one-to-one relationship between state-based and trait-based factors in the visual (Braithwaite et al., 2015; Ffytche, 2008; Fong et al., 2019) and auditory (Kühn & Gallinat, 2012; Mo et al., 2024; Zmigrod et al., 2016) domains, extending it to cross-sensory interactions in aberrant perceptual experiences.

4.3 Exploratory Migraine Group Differences

Migraineurs-with-Aura reported significantly greater intensity of AVDs than Migraineurs-without-Aura and non-migraineur controls across both visual only and audiovisual trials. This is consistent with the view that the presence of aura reflects an elevated degree of cortical hyperexcitability which may itself be dissociable from the pathophysiology of migraine. This is supported by broader findings which evidence the link between underlying cortical hyperexcitability and the existence of migraine aura (Chen et al., 2011; Cucchiara et al., 2015; Chronicle et al., 2006; Mulleners et al., 2001; Palmer et al., 2000). Finding elevated cross-sensory enhancement in Migraine-with-Aura, but not in Migraine-without-Aura, extends this idea beyond the visual domain thus supporting the notion that elevated cortical hyperexcitability acts as factor of predisposition to multisensory aberrant perceptual experiences.

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[8] Note that PG group differences (i.e. state-based cortical hyperexcitability differences) remained significant after Migraineurs were excluded, suggesting continuity of state-based mechanism across Migraine and neurotypical groups.

While the migraine groups were modest in terms of sample size, which may raise concerns about statistical sensitivity, these concerns can be alleviated to some degree by the Bayesian analyses. Specifically, Bayes factors allowed us to distinguish between genuine null results and data that are simply insensitive to the effects of interest (Kass & Raftery, 1995; Quintana & Williams, 2018; Schönbrodt et al., 2017). Where Bayes factors are inconclusive (i.e. $BF_{10} \approx 1$), this suggests a lack of statistical sensitivity due to a failure to accumulate meaningful evidence for either the null or alternative hypothesis (Dienes, 2014; Kass & Raffery, 1995; Lee & Wagenmakers, 2014; Wagenmakers & Love et al., 2018; Wagenmakers & Marsman et al., 2018). Here we observed decisive evidence (i.e. $BF_{10} > 100$) for the alternative hypothesis when migraine status was included as an independent variable in all relevant statistical models. This suggests that the data are not insensitive to differences between the migraine subgroups. As such, Bayesian inference offers a robust framework for interpreting the present findings in relation to migraine subgroups under conditions of modest sample size.

4.4 Theoretical Implications

Collectively, the present findings support a sensory cross-talk enhancement effect in which irritating auditory information intensified the experience of aberrant visual distortions (AVDs). Crucially, this effect was not observed with the presentation of non-irritative tones, and occurred in a frequency-dependent manner, with stronger amplification at 4-8 kHz tone frequencies known to elicit discomfort and reflect hyperexcitability in the auditory domain (Ashkenazi et al., 2009; Ashkenazi et al., 2010; Woodhouse & Drummond, 1993). As such, this pattern cannot be explained by generalised experimental factors (e.g. overall arousal, attentional distraction, task complexity, or perceptual load) as cross-sensory effects were frequency specific and mediated by both trait-based and state-based cortical hyperexcitability. Instead, these effects point to a cross-modal enhancement mechanism, wherein activity in one sensory modality enhanced the perceptual salience or intensity in another under conditions of heightened cortical responsivity.

The current findings resonate well with foundational behavioural research on multisensory integration. Work by Spence and colleagues (Driver & Spence, 1998; Spence & Driver, 2004; Spence, 2011) has shown that inputs from one sensory modality can modulate perceptual processing in another, even when features from the two sensory inputs may not intuitively lead to such an association. These cross-sensory enhancements are particularly pronounced when stimuli share some basic perceptual features such as pitch, lightness, or brightness - a principle those researchers termed *'synaesthetic congruency'* (Gallace & Spence, 2006; Parise & Spence, 2008; Parise & Spence, 2009). In this study, the simultaneous and congruent presentation of perceptually irritating auditory and visual stimuli appears to facilitate the formation of strong cross-sensory associations, resulting in enhanced sensory cross-talk and the elevated perception of intense AVDs.

Notably, the observed enhancement was elevated in sympathy with signs of both state-based and trait-based cortical hyperexcitability which suggests that hyperexcitability itself may well operate either through: (i) concurrent dysregulation in multiple localized sensory regions, or (ii) as a broader, domain-general property of cortical processing. Either scenario implies that hyperexcitability is not necessarily confined to a single modality or cortical area but could extend beyond the boundaries of a unitary discrete sensory system (Aurora & Wilkinson, 2007; Coppola et al., 2007; Petrusic et al., 2018; Silvestro et al., 2022; Welch et al., 1990).

The suggestion that cortical hyperexcitability may extend beyond unitary sensory domains necessitates a neural mechanism by which sensory cross-talk may occur. In line with work on excitation / inhibition control in cortical hyperexcitability (Aurora & Wilkinson, 2007; Coppola et al., 2007; Palmer et al., 2000), the occurrence of facilitatory sensory cross-talk may point towards dysregulation of gain control processes, which may extend beyond isolated sensory networks across multiple sensory channels (Adams, Popovich & Staines, 2017). This aligns with suggestions that increased sensory sensitivity underlying hallucination proneness may reflect a broader failure to appropriately constrain excitability and suppress irrelevant or redundant input (Aurora & Wilkinson, 2007; Hugdahl, 2009; Jardri et al., 2016; Tass, 1995; Welch et al., 1990).

Such interactions are consistent with broader frameworks of multisensory integration that propose mutually facilitatory effects between sensory systems, especially when inputs are aversive or near perceptual threshold, or are presented in concert (Cappe & Thut et al., 2009; Choi, Lee & Lee, 2018; Murray et al., 2016; Stein & Stanford, 2008). In these frameworks, input from one modality can increase the gain or reliability of concurrent input in another (see discussion on cortical gain and sensory cross-talk), particularly when the sensory system is operating in a high-gain or unstable state, as it would be if cortical hyperexcitability were present. Consequently, the present findings suggest that in individuals with elevated cortical hyperexcitability, such cross-modal interactions may become maladaptive resulting in exaggerated or distorted perceptual experiences.

Cortical Gain and Sensory Cross-talk

The present findings also mesh well with cortical gain frameworks. In computational terms, cortical gain determines the amplitude (or intensity) of neural response relative to the salience or reliability of incoming sensory evidence, acting as a dynamic neural filter for signal-to-noise optimisation (Aston-Jones & Cohen, 2005; Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001). Under typical conditions cortical gain control operates to regulate the responsiveness of sensory neurons, enhancing the representation of salient inputs while suppressing irrelevant noise (Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001).

Critically, gain is not a singular, unitary process but can be expressed at multiple localised / global spatial scales. Local gain modulation is typically mediated through intracortical interactions involving inhibitory interneuron networks, short-range recurrent connections, and layer-specific feedback projections, which together shape the precision and selectivity, of sensory representations (Ferguson & Cardin, 2020; Friston et al., 2015; Harris & Mrsic-Flogel, 2013; Piëch et al., 2013; Pinotsis et al., 2014). In contrast, more global gain mechanisms are orchestrated by diffuse neuromodulatory systems, such as noradrenergic and dopaminergic pathways, that broadcast modulatory signals across wide cortical networks, reflecting global arousal and salience (Aston-jones & Bloom, 1981; Foote, Aston-jones & Bloom, 1980; Happel, 2016; Kroener et al., 2009; Sara, 2009). Thalamocortical circuits further contribute to global gain regulation, enabling coordination and gating of sensory throughput between cortical regions (Colonnese & Phillips, 2018; Hindriks & van Putten, 2013; Kostopoulos, 2001; Sherman, 2017).

In hyperexcitable systems, such as in migraine-with-aura and neurotypical individuals with elevated cortical hyperexcitability, this regulation is likely compromised (McColl & Wilkinson, 2000). When a patterned visual stimulus (e.g., an irritative grating) is presented, the visual cortex begins to respond. In individuals with normal gain control, local inhibitory networks act to dampen this response, stabilising the perceptual experience. However, in hyperexcitable individuals, this dampening is inefficient: initial visual responses are exaggerated, and local inhibition fails to suppress them effectively. As a result, the stimulus starts to overwhelm visual neurons, leading to perceptual instability and the emergence of associated visual distortions (AVDs; Wilkins, 1995).

In sensory cross-talk this imbalance is further exacerbated by the concurrent presentation of an irritative auditory tone. In the presence of dysfunctional gain control, the auditory input may inadvertently increase gain across nearby or convergent cortical areas, either through non-specific neuromodulatory pathways (e.g., cholinergic or noradrenergic systems; Ferguson & Cardin, 2020; Kunnath et al., 2023; Zikopoulos & Barbas, 2007) or through shared multisensory hubs such as the temporoparietal junction (Cappe, Rouiller & Barone, 2009; Matsuhashi et al., 2004). This causes an endogenous amplification in visual cortical responsivity, even though the auditory signal is irrelevant to the task. Instead of remaining confined to the auditory stream, the signal may act as a cross-modal amplifier, further potentiating the already dysregulated visual response. The outcome is a maladaptive increase of excitation across modalities, producing heightened perceptual salience, increased subjective discomfort, and more pronounced AVDs. This failure of selective gain allocation, amplifying all salient inputs regardless of modality or relevance, is a core signature of sensory systems operating in a high-gain state (Hillyard, Vogel & Luck, 1998; Le Masson et al., 2002; Scolari & Serences, 2009; Woolley et al., 2005).

This gain-based interpretation is further supported by the modality and frequency specific nature of the observed effects. That is, only those visual and auditory stimuli known to be irritative produced reliable cross-modal amplification. This suggests not just a generalised increase in excitability, but a selective misallocation of gain across sensory channels, consistent with theories proposing that multisensory integration is weighted according to the reliability and salience of available inputs (Angelaki, Gu & DeAngelis, 2009; Deneve & Pouget, 2004; Fetsch et al., 2012; Morgan, DeAngelis & Angelaki, 2008; Rohe & Noppeney, 2015). In high-gain states, the nervous system may over-weight bottom-up sensory signals, leading to failures in sensory gating, increased cross-modal interference, and aberrant perceptual fusion. This is particularly relevant in migraine and populations of neurotypical hallucinators, where cortical responsiveness is elevated and inhibitory mechanisms are compromised (Coppola et al., 2007; de Tommaso et al., 2014; Haigh et al., 2023). The current findings may therefore reflect an instability in gain regulation, in which trait predisposition interacts with stimulus characteristics to produce maladaptive cross-sensory amplification.

Within this framework, the observed cross-sensory amplification could reflect a general principle of sensory enhancement, in which auditory input dynamically alters the salience of concurrent visual processing. However, in individuals with elevated cortical hyperexcitability, these normally adaptive mechanisms may become maladaptive, leading to excessive perceptual gain and reduced filtering between modalities. The result is a form of sensory cross-talk that reflects an exaggerated instantiation of typical multisensory integration, consistent with evidence that cross-modal gain modulation and temporal co-activation play central roles in shaping multisensory experience (Murray et al., 2016; Rohe & Noppeney, 2015; Welch & Warren, 1980). These findings situate the present effects within a broader literature on cross-modal perception, while highlighting how trait-level differences in gain control processes can give rise to amplified, and potentially destabilising, multisensory interactions.

Multisensory Neural Mechanisms of Cortical Gain

Whilst the neural mechanisms remain to be fully elucidated, prior imaging work with hyperexcitable individuals (with migraine-with-aura) has shown alterations in both functional connectivity and structural integrity of thalamocortical networks (Coppola et al., 2021; Tu et al., 2019; Valenzuela-Fuenzalida et al., 2021), which are known to play a critical role in multisensory gating (Castro-Alamancos, 2004; McCormick & Bal 1994) and integration (Cappe & Morel et al., 2009; Cappe, Rouiller & Barone, 2009). These thalamocortical changes are notably absent in migraine-without-aura (Granziera et al., 2013) and heightened in cases of multisensory aura relative to unisensory aura (Coppola et al., 2021), mirroring the present finding that cross-modal amplification is greater in individuals with increased sensory sensitivity, and further increased where this sensory sensitivity may exist in more than one brain region / network.

Sensory thalamocortical networks are crucial for gating the relay of information between sensory cortices. Specifically, cortical feedback to thalamic nuclei such as the thalamic reticular nucleus can have facilitatory or inhibitory effects on sensory thalamic bursts, which then have potent feedback effects on levels of neural activity within sensory neural networks (Rauschecker, 1998; Sherman, 2001; Swadlow & Gusev, 2001). As such, thalamic nuclei have the capacity to receive inputs from various sensory neural networks and feedback to these networks to modulate (gait) neuronal activity (Ward, 2013).

In vitro investigations suggest that functional connectivity of thalamic nuclei to areas of sensory cortical circuits is modulated by the level of gain within these networks (Le Masson et al., 2002; Mease et al., 2016). Under conditions of high gain, sensory cortical and thalamic areas are relatively functionally disconnected (Le Masson et al., 2002; Ward, 2013). Conversely, conditions of low gain increase functional connectivity between thalamic nuclei and sensory cortical networks (Le Masson et al., 2022; Ward, 2013). This disconnection in high gain corticothalamic networks leads to a failure of thalamic nuclei to gait activity in sensory cortical networks (Le Masson et al., 2022). As such, high gain within thalamocortical networks is associated with conditions of thalamocortical disconnection which may allow for greater sensory cross-talk to emerge. Presently these ideas are extrapolated from in vitro models of corticothalamic loops, but demonstrating these effects in vivo represents a promising next step in understanding the relationship between cortical gain and aberrant multisensory experiences.

Collectively, these findings suggest that the cross-modal amplification observed here may reflect a systems-level instability, in which local cortical gain and long-range connectivity jointly contribute to aberrant multisensory integration in trait-susceptible individuals. Examining the relationship between cross-sensory aberrant experiences and thalamocortical connectivity poses a pertinent framework for future investigations.

In addition, cortical gain within neighbouring multisensory areas such as the TPJ could be seen as critical to gaiting the binding of perceptual streams to allow cross-modal interactions to occur, as demonstrated with the SIFI (Hamilton et al., 2013; Kamke et al., 2012). In SIFI, event-related responses at the TPJ typically occur later than in visual and auditory cortex, suggesting a later role in binding streams after initial localised processing (Mishra, Martinez & Hillyard, 2008). Therefore, under high-gain states in relevant sensory cortices the TPJ would likely receive both visual and auditory signals which are low in perceptual precision and therefore unstable in their representations of sensory information (Hillyard, Vogel & Luck, 1998; Hénaff et al., 2020; Scolari & Serences, 2009; Woolley et al., 2005), meaning there is limited sensory evidence to resolve the ‘binding problem’. This is exacerbated further by high gain states within the TPJ itself which mean inhibitory mechanisms are insufficient to filter out irrelevant background information where the two streams converge (Ferguson & Cardin, 2020; Greenhouse, 2022; Hasselmo et al., 1997).

Applied to the present findings, auditory signals from the auditory tone would be irrelevant to the perceptual representation of the visual grating. However, under high gain states these auditory signals may be insufficiently filtered out from visual signals leading to aberrant binding of the two streams, and hence could increase the output (i.e. firing rate) of neuronal populations within the TPJ which feed back into the visual cortex. As discussed earlier, high gain states are characterised by significant increases in output of a neuronal population for a given input, whilst in low gain states the output perturbation would be relatively modest for the same input (Carandini & Heeger, 2012; Ferguson & Cardin, 2020). So, in lower gain states this cross-modal amplification of output back to the visual cortex would be relatively small and stabilised rapidly, leading to very little cross-modal amplification. However, in high gain states this cross-modal amplification would occur rapidly, and inhibitory mechanisms would fail to stabilise the output of the TPJ back to the visual cortex, leading to decreased stability of visual representation and hence increased likelihood of perceptual aberration. High gain states could therefore be associated with sensory cross-talk at a more localised level in the sensory cortices as discussed, as well as more broadly within cortical networks previously associated with multisensory aberrant experiences.

Together, these considerations suggest that cross-modal sensory amplification may reflect an interaction between local cortical gain dynamics and large-scale gating dysfunction, producing heightened perceptual salience and reduced filtering of irrelevant input. The present findings do not distinguish between gain dysregulation occurring locally (e.g. within visual or auditory cortex), or more globally via functional or structural connections within corticothalamic loops. Investigating how such trait-based sensory dysregulation maps onto thalamocortical connectivity remains a promising direction for future research.

4.5 Limitations and Future Research

Although the current study did not measure or manipulate neural processing directly, the present findings mesh well with the broader literature that has examined cortical hyperexcitability via more direct neuroscientific methods (Braithwaite, Mevorach & Takahashi, 2015; Fong et al., 2020; Fong et al., 2022; Joshi et al., 2024; Jurkovičová et al., 2024). Consequently, both the core of the trait-based measure used here (the original CHi_II developed into the AVAS) and the computer-based pattern-glare task, have considerable broader empirical support.

To further examine the association between cortical hyperexcitability and sensory cross-talk, future studies may wish to use neuroimaging and / or brain stimulation techniques to directly measure or manipulate neural excitability. EEG studies of electrophysiological activity during visual-only Pattern Glare show an association between impaired perceptual learning and intensity of AVDs (Fong et al., 2020; Fong et al., 2022), thought to represent a failure of 'gaiting' neural responses to visual information. For the present paradigm, an equivalent cross-sensory gating mechanisms could be demonstrated with markers of impaired cross-sensory gating such as attenuated cross-sensory P50 suppression (Magnée et al., 2009), or desynchronisation of alpha and / or gamma oscillations (see Misselhorn, Friese & Engel, 2019; Misselhorn et al., 2019).

In addition, brain stimulation studies have demonstrated that anodal tDCS over the visual cortex can increase susceptibility to Pattern Glare in those showing elevated signs of cortical hyperexcitability (Braithwaite, Mevorach & Takahashi, 2015). This provides a direct relationship between neuronal excitability in the visual cortex and the intensity of aberrant experiences (AVDs) in the visual only Pattern Glare test. Demonstrating an equivalent effect by modulating the observed cross-sensory enhancement effect using neuromodulation techniques presents a challenge, as it is unclear whether this cross-sensory enhancement occurs locally within auditory / visual cortices, or across a more distributed network of modality-specific and multisensory cortical areas. There is therefore a lack of an obvious candidate stimulation site to modulate sensory cross-talk. A logical first step in investigating this question would be to modulate neuronal excitability in relevant multisensory integration hubs and observe downstream effects on sensory network excitability during multisensory Pattern Glare, either directly via concurrent EEG, or indirectly through effects on AVDs. A likely candidate for this would be posterior parietal areas such as the temporoparietal junction (TPJ), which have been demonstrated to be more active during multisensory than unisensory hallucinations (Jardri et al., 2013; Silbersweig et al., 1995).

The present findings with migraineurs were exploratory; primarily, these findings show that individuals displaying elevated cortical hyperexcitability (whether migraineurs or neurotypical individuals) show a greater predisposition to sensory cross-talk than individuals displaying relatively attenuated cortical hyperexcitability. However, it is a fascinating finding that migraineurs (and particularly those with aura) present within the sample show such an elevated degree of sensory cross-talk relative to neurotypical participants. An important extension of the current work would be to examine effects with a targeted and larger group of migraineurs, thus facilitating a detailed breakdown not just of migraine type (aura versus without aura) but extending further in aura classifications (visual, auditory, multisensory, etc). This would facilitate a detailed examination of how specific aberrations may reflect particular neural processes and / or particular neural networks aiding a more comprehensive understanding between neural processes and the consequences for consciousness.

Furthermore, it should be noted that our migraine sample was collected through participants self-reporting their migraine status. Although the present migraine findings should be viewed tentatively, the findings are in direct line with previous work on the distinctions between migraine with aura and those without aura, though now extended into the multisensory domain (Fong et al., 2019; Fong et al., 2020; Fong et al., 2022). Therefore, the present findings are commensurate with the known predictions from previous migraine studies on what the aura itself reflects (increased cortical hyperexcitability). In addition, further support can be taken from previous investigations demonstrating elevated rates of predisposition to multisensory hallucinations in Migraineurs relative to non-clinical samples (Li et al., 2024; Toh et al., 2020; Toh et al., 2024). Future studies may wish to strengthen these findings with greater samples of both migraine-with-aura and migraine-without-aura participants, as well as confirming migraine diagnosis with tools such as the ICHD-3 (IHS, 2018).

4.6 Conclusion

The present study examined the existence of a novel multi-sensory crosstalk effect mediated by elevated degrees of cortical hyperexcitability. Aberrant visual experiences elicited by irritative visual gratings (producing pattern-glare experiences) were enhanced by the co-presentation of irritative auditory stimuli. These findings support the notion of a cross-modal facilitatory effect which is mediated by elevated cortical hyperexcitability. It was hypothesised that these effects likely reflect a cortical gain factor underlying the increased sensory cross-talk enhancement. In addition, this sensory cross-talk effects showed associations with selective factors of the AVAS trait-based measure of cortical hyperexcitability across both auditory and visual domains. This supports the notion of a complex relationship between state-based and trait-based cortical hyperexcitability across multiple sensory domains, building on previous findings in the visual domain (Braithwaite et al., 2015; Fong et al., 2019; Fong et al., 2020). Collectively, these findings suggest that cortical hyperexcitability may be present in more than one cortical network (e.g., perhaps more domain-general) mediating predisposition to aberrant perceptual experiences. As such these findings are commensurate with both cross-modal correspondence and cortical gain control mechanisms as a neurocognitive explanatory framework. Future investigations may seek to further investigate whether this cross-sensory enhancement occurs within localised or more distributed neural networks using the multisensory Pattern Glare paradigm alongside neuroimaging and brain stimulation techniques.

Chapter 4

A Novel Multisensory Method for Investigating Aberrant Multisensory Experiences in the Laboratory Examined Under the Hodotopic Framework

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Abstract

The complex interplay between state- and trait-based factors of predisposition to anomalous visual experiences of differing complexity has been outlined in the Hodotopic framework as an interaction between topological (localised, state-based) and hodological (diffuse, trait-based) aberrations. The present investigation sought to examine the hodotopic framework across multisensory domains. Here we developed dynamic visual stimuli, where Pattern Glare gratings reverse in contrast at certain frequencies (which are sometimes neuronally irritating) and added irritating auditory stimuli (frequency-modulated tones). Subsequently, we examine phenomenology of aberrant perceptions (hallucinatory vs distortions) and the multisensory processes underlying them. Phase reversals were presented (creating a perceptual 'flicker') at 3Hz, 10Hz, and 15Hz. Specific trials paired these with simultaneous frequency-modulated tones to create audiovisual stimulation. Participants completed the Audiovisual Aberration Scale (AVAS) as a trait-based measure of cortical hyperexcitability. Results show: (i) adding specific flicker frequencies increased the intensity of aberrant experiences versus typical static gratings; (ii) a significant multisensory effect emerged whereby the intensity of reported hallucinations, but not distortions, increased further with simultaneous audiovisual stimulation. Finally, we examined the relationship between aberrant experiences and specific factors of the AVAS. Here results show the occurrence of aberrant visual experiences in visual only trials showed a selective association with the Migrainesque Visual Aura Symptoms factor of the AVAS, however cross-sensory enhancement of these experiences was associated with all three factors of the AVAS. This fractionated relationship between state-based and trait-based factors may support a hodotopic interpretation of aberrant experiences elicited across sensory domains. Findings are discussed in terms of the integration of cortical gain control and cross-modal correspondence frameworks.

Introduction

1.1 Cortical Hyperexcitability

Anomalous perceptual experiences, including; altered sensory sensitivity, distorted sensory perception, and hallucinations, are associated with aberrant patterns of neurophysiological activity in the cerebral cortex, collectively referred to as cortical hyperexcitability (Chronicle, Pearson & Mulleners, 2006; Mulleners et al., 2001; Palmer et al., 2000; van der Kamp, et al., 1996; Wilkins, 1995).

There are two separate but related concepts pertaining to cortical hyperexcitability. These are (i) state-based hyperexcitability and, (ii) trait-based hyperexcitability (Braithwaite et al., 2015a; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Joshi et al., 2024; see also Chapter 2 and Chapter 3). Here trait-based cortical hyperexcitability refers to the stable latent background level relating to predisposition to aberrant experiences over time, whilst state-based cortical hyperexcitability refers to the current 'state' of the system at any given point in time and specific occurrences of aberrant perceptual experience.

Investigations of neural factors underlying predisposition to aberrant perceptual experiences across both auditory and visual domains have shown that the relationship between state-based and trait-based factors is not always a one-to-one association. In the auditory domain, trait susceptibility to hallucinations has been associated with heightened activity in auditory processing areas, whilst the hallucination state has been associated more so with heightened activity in speech production regions (Kühn & Gallinat, 2012; Mo et al., 2024; Zmigrod et al., 2016). Similarly, trait susceptibility to visual hallucinations is often associated with aberrant cortico-cortical and cortico-subcortical connections of the visual cortex (Collerton et al., 2005; Erskine et al., 2019; Ford et al., 2015; van Ommen et al., 2023), whilst the hallucination state is associated with more local hyperexcitability within the visual cortex (Abraham & Duffy, 2001; Bressloff et al., 2002; Ffytche, 2008). While these contributions are distinct, they converge, with network-level abnormalities modulating the expression of local cortical instabilities. This highlights that considering both state-based and trait-based factors in tandem is critical to gaining a fuller understanding of factors underlying predisposition to aberrant perceptual experiences.

1.2 Cortical Gain and Precision Weighted Predictive Coding

Cortical hyperexcitability is increasingly associated with aberrations in cortical gain control - a neural process for the moderation of the amplitude of cortical responses relative to salience of incoming sensory information (Aston-Jones & Cohen, 2005; Carandini & Heeger, 2012; for extensive discussion see Chapters 1 and 3). Cortical gain is typically defined as the slope of a neuron's input-output function; high gain states within neuronal populations are characterised by a rapid increase in response (i.e. firing rate) for a change in input, whilst low gain states are characterised by modest perturbations in response for the same change in input (Carandini & Heeger, 2012; Ferguson & Cardin, 2020). Cortical gain control is thought to enact processes such as sensory gating at the neuronal level, *i.e.* enhancing salient signals whilst suppressing irrelevant signals to maximise the clarity of sensory information in neural representations, acting as a dynamic filter for neural signal-to-noise ratio (Grunwald et al., 2003; Vogels & Abbott, 2009).

Cortical gain control has also been incorporated into the predictive coding framework, which states that perception occurs through a Bayesian process of active inference whereby incoming (sensory) information is shaped by prior expectations around external events (or 'priors'; Bastos et al., 2012; Corlett, Frith & Fletcher, 2009; Corlett et al., 2019; Friston, 2005; Powers, Kelley & Corlett, 2017; Powers, Mathys & Corlett, 2017; Rao & Ballard, 1999; Sterzer et al., 2018). Where there is a mismatch between sensory evidence and priors this creates a ‘prediction error’, however not all prediction errors are treated equally; the salience of prediction errors is weighted dependent on the relative degree of confidence associated with priors and sensory information (Kanai et al., 2015; Powers, Mathys & Corlett, 2017). Where sensory signals are highly uncertain and prediction error signals are weighted as highly salient, priors dominate in shaping perceptual representations, creating greater predisposition to the perception of non-veridical sensory information (i.e. aberrant perceptual experiences; Kanai et al., 2015; Millidge, Seth & Buckley, 2021; Powers, Mathys & Corlett, 2017). Cortical gain control is thought to be the biological mechanism by which these prediction error signals are weighted for precision (Barrett & Simmons, 2015; Bastos et al., 2012; Feldman & Friston, 2010; Kanai et al., 2015).

Within this framework, aberrant cortical gain control provides a mechanistic explanation for why some individuals are more susceptible to aberrant visual perceptions. Hyperexcitability enhances the effective gain applied to incoming signals, amplifying prediction error responses. Crucially, this locally generated hyperexcitability in visual areas can be misinterpreted as a genuine signal and, when afforded undue precision, is erroneously prioritised in perceptual inference. As a consequence, prediction-errors derived from noise or instability become integrated into the perceptual construction, biasing the system towards over-weighting priors and increasing the likelihood of non-veridical experiences. This convergence of hyperexcitability, aberrant gain modulation, and predictive coding offers a principled account of how both state-dependent cortical instability and trait-level susceptibility can manifest as heightened proneness to hallucination-like experiences.

1.3 Multisensory Cortical Hyperexcitability

Cortical hyperexcitability is increasingly viewed as a central theme and is not confined to a single sensory domain (Welch et al., 1990; Schoenen, 1996). This is highlighted further by findings suggesting that, across clinical and neurotypical populations, most individuals who report aberrant perceptual experiences report such symptoms in multiple sensory domains (Dudley et al., 2018; Dudley et al., 2023a; Dudley et al., 2023b; Li et al., 2024; Toh et al., 2020; Toh et al., 2024; Rogers et al., 2023). The predominance of multisensory aberrant experiences may suggest reciprocal roles of sensory signals in different perceptual domains as modulators of cross-sensory cortical gain processes. This would suggest a form of sensory cross-talk between sensory channels may occur, leading to an aberrant integration of sensory information across perceptual domains under conditions of cortical hyperexcitability (see Chapter 3; Jardri et al., 2013; Silbersweig et al., 1995).

Sensory cross-talk can be viewed within a precision-weighted predictive coding framework, mediated by cortical gain control mechanisms (Barrett & Simmons, 2015; Bastos et al., 2012; Carandini & Heeger, 2012; Feldman & Friston, 2010; Kanai et al., 2015). Under hyperexcitable conditions, concurrent sensory inputs are encoded with unstable or degraded precision, reducing the quality of evidence available to resolve the binding problem (deciding which signals across modalities should be integrated at a given moment: Spence, 2011). In states where precision is well calibrated, binding can exploit higher-order statistical regularities across sensory systems (e.g., temporal, spatial, phonetic, or semantic features: Körding et al., 2007; Noppeney, 2021; Sato et al., 2007; Shams & Beierholm, 2010). By contrast, when perceptual uncertainty prevails, spurious fluctuations may be misclassified as meaningful signals and afforded undue precision. This mis-weighting generates cross-sensory prediction errors that intrude into perceptual inference highlighting susceptibility to illusory or hallucination-like experiences.

However, the exact underlying neural systems associated with this cross-talk process are unclear. The multisensory neocortex hypothesis (Ghazanfar & Schroeder, 2006) would suggest that cortical regions typically thought of as unisensory (*i.e.* visual cortex, auditory cortex) are directly subject to sensory cross-talk effects. This account aligns with a more cortical-wide and diffuse failure of gain control (under situations of hyperexcitability), leading to indiscriminate amplification of cross-modal inputs which ultimately detracts from the successful filtering of sensory signals (Ghazanfar & Schroeder, 2006; Tye et al., 2024). Equally, elevated neural activity in cortical areas associated with multisensory integration such as the temporoparietal junction (TPJ) have been implicated in the occurrence of multisensory hallucinations in comparison to individuals experiencing unisensory hallucinations (Jardri et al., 2013; Silbersweig et al., 1995), suggesting sensory cross-talk (binding) occurs in broader neural networks beyond sensory cortices. Regardless of the exact underlying neural mechanism, both hypotheses support the possibility of sensory cross-talk between sensory domains, implicating cortical hyperexcitability and / or cortical gain control as an underlying mechanism.

In summary, there is evidence that in individuals displaying elevated signs of cortical hyperexcitability, sensory systems may engage in a form of enhanced sensory cross-talk. Cortical gain control mechanisms under the precision-weighted predictive coding framework may provide a tentative explanatory framework for why sensory cross-talk is enhanced in hyperexcitable individuals.

1.4 Pattern Glare

A useful and well-established paradigm for investigating aberrant visual experiences associated with cortical hyperexcitability is the visual Pattern Glare (PG) test. In this task, participants view static square-wave gratings of various spatial frequencies, some of which are visually aversive and can overwhelm visual neurons. Exposure to these gratings can produce a range of aberrant visual distortions (AVDs), including shimmering, flicker, bending lines and coloured fringes, all of which are collectively referred to as 'pattern-glare experiences' (Braithwaite et al., 2013; Evans & Stevenson, 2008; Wilkins, 1995). These gratings consist of: i) a low frequency control grating at 0.5 cycles-per-degree (cpd), ii) the crucial medium frequency grating at 3 cpd, iii) a high frequency control grating at 14 cpd. Across clinical, neurological, and neurotypical populations, an elevated degree of state-based cortical hyperexcitability is associated with elevated reporting of AVDs (and hence more 'glare' induced by the grating pattern) in response to the aversive medium frequency grating (Braithwaite, Mevorach & Takahashi, 2015; Braithwaite et al., 2015b; Evans & Stevenson, 2008; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022; Haigh et al., 2012; Harle & Evans, 2004; Huang et al., 2003; O'Hare & Hibbard, 2011; Wilkins, 1995). Under a precision-weighted predictive coding framework, this could be explained as a failure to regulate the neural response to this highly potent visual grating due to conditions of cortical hyperexcitability, leading to an unstable perceptual representation and the emergence of AVDs under low perceptual stability (McColl & Wilkinson, 2000).

More recently, findings around PG have extended into multisensory domains. Haigh et al. (2023) reported that individuals experiencing higher levels of visual Pattern Glare also rated high-frequency auditory pure tones as more irritating than individuals reporting a lower degree of visual Pattern Glare, suggesting aberrant neural responses may extend across sensory domains. However, there are important limitations to this study that restrict the strength of its conclusions. Most critically, auditory and visual stimuli were presented and rated separately (not simultaneously), meaning the study could not address whether the aberrant sensory responses actually interact across modalities dynamically at the same time.

As such the findings speak only to the parallel hypersensitivities rather than to genuine real-time cross-sensory binding. By contrast, Chapter 3 demonstrated a true cross-sensory enhancement effect when high-frequency auditory tones were paired with the critical irritating medium frequency Pattern Glare gratings, participants with elevated state-based cortical hyperexcitability reported significantly stronger aberrant visual distortions (AVDs) than under visual presentation alone. This provides more direct evidence for an enhanced sensory cross-talk effect, indicating that high cortical gain states are associated with an aberrant form of cross-sensory binding in which the precision of sensory signals is compromised.

Traditional Pattern Glare does, however, have its limitations as a tool to quantify sensory cross-talk. The AVDs used to index PG are largely restricted to perceptual distortions and sensory irritation with little emphasis on hallucination-like-phenomena. While these outcomes can all be considered forms of aberrant perceptual experience, they do not necessarily reflect the same underlying mechanisms. Rather, they may sit along a continuum of complexity, with irritation, distortions, and hallucinations reflecting subtly different underlying processes (Ffytche, 2008; Silverstein & Lai, 2021). Evidence for such a continuum has been developed in the visual domain under the hodotopic framework, which suggests that different state-based and trait-based factors may create predisposition to aberrant perceptual experiences of differing complexity (from irritation, to distortions, to hallucinations: Ffytche et al., 1998; Catani & Ffytche, 2005; Ffytche, 2008; Silverstein & Lai, 2021).

1.5 The Hodotopic Framework: Connective and Localised Contributions

The hodotopic framework builds on early ideas of a perception-hallucination continuum, stating hallucinations lie on a continuum of complexity of aberration with veridical perception[9] (Fischer, 1969; Fischer, 1970; Fischer, 1971). Broadly, the hodotopic framework proposes that the hallucination state arises through *topological* (or localised 'within-system') abnormalities in neural activity, whilst the hallucination trait itself reflects *hodological* (connectivity 'between-system') abnormalities (Ffytche et al., 1998; Catani & Ffytche, 2005; Ffytche, 2008).

Ffytche (2008) used light-flicker induced hallucinations (see later discussion) in a combined EEG-fMRI study to examine localised and connective factors of predisposition to visual hallucinations. The occurrence of visual hallucinations was associated with a relative decrease in functional connectivity between pre-cortical regions and occipitotemporal regions of the visual cortex. In addition, a paradoxical increase in localized excitability phase coherence was observed across broad areas of the visual cortex (V2 to V5). This likely represents a shift from tonic firing (reliable transmission of sensory signals) to burst mode (unreliable transmission of sensory signals), a characteristic shift in firing patterns of thalamic nuclei in high-gain states (demonstrated in vitro: Le Masson et al., 2002; Mease et al., 2016). This suggests that a trait tendency towards high-gain states in corticothalamic circuits within mid to late visual cortex can subsequently create a state predisposition to cortical hyperexcitability and associated aberrant perceptions / hallucinations. Consistent with this, Ffytche (2008) reported no significant changes in phase coherence within primary visual cortex (V1), instead implicating later visual regions. Silverstein and Lai (2021) subsequently

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[9] This continuum has been strengthened by the addition of other aberrant perceptual experiences such as heightened sensory sensitivity and perceptual distortions as intermediate stages between veridical perception and hallucinations, showing a clear progression in complexity of experience along the continuum (Braithwaite et al., 2015; Fong et al., 2019; Silverstein & Lai, 2021).

extended the framework, proposing that similar patterns of aberrant local and connective processes in V1 and its corticothalamic loops may underlie predisposition to lower-level perceptual aberrations, such as visual distortions[10].

It is important to emphasise that these mechanisms are best understood as points along a continuum rather than as distinct models (Silverstein & Lai, 2021). Nonetheless, the implication is that different forms of aberrant perceptual experience, ranging from distortions to hallucinations, may reflect subtle variations in underlying neural mechanisms. This, in turn, suggests that the influence of sensory cross-talk may not be uniform across the continuum, raising the question of whether the cross-sensory enhancement effect observed in Chapter 3 generalises equally to distortions and hallucinations, or whether it interacts differentially with their respective candidate mechanisms.

Under the multisensory neocortex hypothesis, individual neurons are not thought to serve domain-specific roles in sensory processing (Ghazanfar & Schroeder, 2006; Tye et al., 2024). This implies that localised aberrations in cortical gain processes could mediate sensory cross-talk in both early visual cortex contributing to distortions and irritation, and in later visual regions contributing more so to hallucinations. At the same time, intermediate multisensory hubs such as the temporoparietal junction (TPJ), different state-based and trait-based factors shape cross-sensory interactions across the perception-hallucination continuum. In support of this, Wu et al. (2016) used diffusion spectrum imaging to map TPJ connectivity with the visual cortex revealing inferior pathways linked to earlier visual regions and superior pathways linked to later ones. This suggests that distinct trait-level connectivity patterns could differentially mediate cross-sensory influences in aberrant perceptual experiences of

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[10] This summarises the key hodotopic differences, although other predictions were made, e.g. for hallucinations, early visual pathways are de-emphasised, instead emphasising the role of neurotransmitters such as acetylcholine and dopamine in higher-order cognitive networks such as the basal forebrain and striatum (Silvertsein & Lai, 2021).

varying complexity. Accordingly, demonstrating a cross-sensory enhancement effect with a paradigm that elicits hallucinations would represent an important extension of the work presented in Chapter 3.

1.6 Flicker Hallucinations

Rhythmic photic stimulation, or repetitive flicker of a light source, has long been known to induce visual hallucinations (Purkinje, 1819; Walter, 1954). This principle has been utilised by Ffytche (2008) in developing the hodotopic framework, and has since been employed in numerous investigations (e.g., Allefeld et al., 2011; Amaya & Schmidt et al., 2023; Amaya & Behrens et al., 2023; Amaya, Nierhaus & Schmidt, 2025; Bartossek, Kemmerer & Schmidt, 2021; Becker et al., 2009; Billock & Tsou, 2007; Pearson et al., 2016; Shenyan et al., 2024). Participants typically report elementary hallucinations sometimes referred to as Purkinje or Klüver forms, consisting of geometric patterns with characteristics of colour, motion, depth, and texture (Billock & Tsou, 2007; 2012). More complex hallucinations, such as faces, objects, or landscapes are also reported (Shenyan et al., 2024). Visual flicker is therefore a robust paradigm for inducing a broad range of visual hallucinatory experiences.

Hallucinations are most salient at flicker rates between 10-20 Hz, particularly within the alpha band (8 – 13 Hz; Amaya et al., 2023; Bartossek, Kemmerer & Schmidt, 2021; Billock & Tsou, 2012; Amaya & Schmidt et al., 2023; Amaya & Behrens et al., 2023). This effect reflects entrainment of neural activity in the visual cortex, whereby oscillations in the alpha range become phase-locked (synchronised) to the rate of visual flicker (Adrian & Matthews, 1934; Amaya & Behrens et al., 2023; Becker et al., 2009; Herrmann, 2001; Schwartzman et al., 2019). Alpha oscillations are widely implicated in gating visual cortical responses by functionally inhibiting irrelevant inputs and enhancing excitability in regions associated with processing anticipated sensory information (Foxe & Snyder, 2011; Jensen & Mazaheri, 2010; van Diepen, Foxe & Mazaheri, 2019). Although their precise role in gating remains debated, one account proposes a top-down gain control mechanism, whereby alpha modulates the overall firing rate of visual neurons (Fries, 2005; Fries, 2009; Saleem et al., 2017; Shin et al., 2023; Singer, 1999).

Two principal mechanisms have been proposed by which sensory cross-talk could modulate this mechanism (Engel & Senkowski, 2024; Lakatos, Gross & Thut, 2019). First, cross-sensory entrainment may occur where oscillations in auditory and visual systems phase-synchronise, leading to mutual enhancement of oscillatory power (Crosse, Butler & Lalor, 2015; Power et al., 2012; Simon & Wallace, 2017). Second, multiple concurrent processes may contribute: (i) phase-resetting, whereby stimulus onset shifts the phase of oscillations across modalities (Diedrich, Schomburg & Colonius, 2012; Kayser, Petkov & Logothetis, 2008; Mercier et al., 2013; Mercier et al., 2015; Senkowski et al., 2005; Thorne et al., 2011), leading to (ii) functional coupling of intrinsic neural oscillations, in which parameters such as phase and amplitude become synchronised between sensory systems (Cooke et al., 2019; Galindo-Leon et al., 2019; Ohki et al., 2016; Ohki et al., 2020). These mechanisms, demonstrated in audiovisual interactions, provide biologically plausible pathways for cross-sensory enhancement of flicker-induced hallucinations (for summary see Engel & Senkowski, 2024; Lakatos, Gross & Thut, 2019).

To summarise, within a precision-weighted predictive coding framework, both distortions in Pattern Glare and visual hallucinations induced by visual flicker can be understood as arising when thalamic outputs become decoupled from cortical representations, generating low-precision sensory signals. Under high-gain conditions, these signals are assigned disproportionately low weight relative to priors, leading perceptual inference to be dominated by prior expectations. However, the state-based and trait-based factors underlying hallucinations differ somewhat from those underlying distortions, as suggested by the hodotopic framework (Ffytche et al., 1998; Ffytche & Catani, 2005; Ffytche, 2008; Silverstein & Lai, 2021). Thus, visual flicker offers a valuable paradigm for testing whether the cross-sensory enhancement effect observed in Chapter 3 generalises across categories of aberrant perceptual experience along the perception-hallucination continuum, and whether the factors mediating sensory cross-talk differ across this continuum. These questions are the primary motivation for the following investigation.

Overview of the Current Study

The present study examined whether audiovisual cross-sensory enhancement of aberrant perceptual experiences extends across the perception-hallucination continuum, and whether common state-and trait-based mechanisms underlie sensory cross-talk along this continuum. To address this, the cross-sensory enhancement effect (observed in Chapter 3) was examined using the Pattern Glare task, which primarily indexes visual distortions and visceral symptoms of irritation. The hodotopic framework (Ffytche et al., 1998; Catani & Ffytche, 2005; Ffytche, 2008; Silverstein & Lai, 2021) proposes that aberrant perceptual experiences of differing complexity reflect subtle variations in the neural mechanisms that are modulated by state and trait-based factors. Extending this view, the cross-sensory enhancement of aberrant perceptual experiences may likewise be mediated by distinct combinations of state- and trait-based influences across the continuum from distortions to hallucinations.

To test this, a rhythmic dynamic phase-reversal was introduced to the visual Pattern Glare gratings whereby each phase (the dark stripe or the light stripe in the grating) alternated dichotomously between luminance polarities. This visual stimulus was selected over pure light flicker to maintain the spatial properties of the gratings which are associated with experiences of distortions and visual irritation, allowing for comparison between different types of aberrant perceptual experiences of varying complexity within the same paradigm. By incorporating rhythmic reversals, the task becomes more comparable to photic light flicker stimulation, which reliably induces elementary hallucinations through visual cortical entrainment (Allefeld et al., 2011; Amaya & Schmidt et al., 2023; Amaya & Behrens et al., 2023; Amaya, Nierhaus & Schmidt, 2025; Bartossek, Kemmerer & Schmidt, 2021; Becker et al., 2009; Billock & Tsou, 2007; Pearson et al., 2016; Shenyan et al., 2024).

Three rates of phase reversal were selected: one outside the critical frequency range for typical light-flicker photic-induced hallucinations (3 Hz), and two inside the critical frequency range for typical light flicker-induced hallucinations (10 Hz, and 15 Hz). Pattern Glare was assessed through modified AVD questions consisting of the original items reflecting (primarily) distortions and some irritation symptoms, and now new additional items reflecting elementary visual hallucinations. These new items were devised in-line with phenomenological reports of photic flicker-induced hallucinations (e.g. Allefeld et al., 2011; Amaya & Schmidt et al., 2023; Amaya & Behrens et al., 2023; Amaya, Nierhaus & Schmidt, 2025; Becker et al., 2009; Billock & Tsou, 2007; 2012; Shenyan et al., 2024). Collectively, these AVD items could then be split into three subcategories of hallucinations, distortions, and irritation, in line with perception-hallucination continuum (Ffytche, 2008; Fischer, 1969; Fischer, 1970; Fischer, 1971; Silverstein & Lai, 2021). The degree of hallucinations, distortions, and irritation reported across different combinations of reversal rate and spatial frequency (critical irritating medium frequency, non-irritating high frequency) were examined in relation to state-based / trait-based factors underlying the occurrence of each, respectively.

To examine cross-sensory enhancement, phase-reversal gratings of specific frequencies were paired with frequency specific auditory stimuli on 50% of trials. The auditory stimuli were selected to match (as far as possible) perceptual characteristics of the flickered Pattern Glare gratings to maximise the cross-modal correspondence between auditory and visual streams and therefore maximise sensory cross-talk (Spence & Driver, 2004; Spence, 2011; see also Chapter 3 introduction). Here an irritating carrier frequency (4 kHz) was frequency modulated[11] at a matched frequency to the rate of visual flicker in a given visual stimulus (*i.e.*, 3 Hz frequency modulation with 3 Hz reversal, 10 Hz frequency modulation with 10 Hz reversal, 15 Hz frequency modulation with 15 Hz reversal) for both the medium frequency and high frequency visual grating. The prediction was that pairing

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[11] Frequency modulation refers to variations in the instantaneous frequency of an auditory waveform around a central carrier frequency whilst maintaining a constant amplitude. For example, a 4000 Hz carrier frequency with a modulation index of 10% would vary constantly between 3600 and 4400 Hz (± 10%, or 400 Hz).

these frequency-modulated tones with flickered Pattern Glare gratings would lead to a greater intensity of AVDs reported, indicating a cross-sensory enhancement.

Finally, participants completed the trait-based Audiovisual Aberration Scale (AVAS: see Chapter 2). The AVAS is a proxy measure of trait-based cortical hyperexcitability across auditory and visual domains, building on the visual-only equivalent, the Cortical Hyperexcitability Index II (CHi_II; Braithwaite et al., 2015; Fong et al., 2019: See Chapter 2). The AVAS measures proxy signs of trait-based cortical hyperexcitability based on the frequency and intensity of aberrant auditory and visual experiences which are known to reflect signs of elevated cortical hyperexcitability.

The AVAS can be devolved into distinct clusters (or factors) of aberrant experiences, namely: (i) Heightened Sensory Sensitivity and Discomfort (HSSD), (ii) Migrainesque Visual Aura Symptoms (MVAS)[12], and (iii) Voice Hearing Experiences (VHE). The selective associations of these trait-based factors with predisposition to sensory cross-talk was demonstrated in Chapter 3, and similar analyses were conducted in the present study, again examining the associations of these factors with sensory cross-talk enhancements.

As photic flicker is primarily associated with the induction of hallucinations (Billock & Tsou, 2007; 2012), it was predicted that adding dynamic phase reversals to Pattern Glare gratings within the critical flicker range (10 Hz, 15 Hz) would selectively increase the intensity of hallucinatory experiences. This effect was expected to be specific to the irritating medium-frequency grating. In addition, given the elevated prevalence of aberrant multisensory experiences reported in both clinical and neurotypical populations (Dudley et al., 2018; Dudley et al., 2023a; Dudley et al., 2023b; Li et al., 2024; Toh et al., 2020; Toh et al., 2024; Rogers et al., 2023) it was further predicted that audiovisual cross-sensory

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[12] Note that distortion items fell on this item of the AVAS (see Chapter 2), therefore distortions, hallucinations, and irritation were all also equally examined by the trait-based measure.

enhancement would manifest across all three subcategories of AVDs; hallucinations, distortions and irritation. Finally, due to the fractionated relationship between state-based and trait-based factors of predisposition to aberrant experiences (Fong, Takahashi & Braithwaite, 2019; Kühn & Gallinat, 2012; Mo et al., 2024; Zmigrod et al., 2016) it was predicted that selective factors of the AVAS measure would show associations with the sensory cross-talk effect, and that there would be differences in the factors associated with sensory cross-talk for hallucinations, distortions, and irritation respectively.

Methods

2.1 Participants

Sixty-two participants (66.13% Female, 30.65% Male, 3.23% Other / Prefer Not to Say) aged 18 - 44 (*M* = 20.03, *SD* = 4.47) were recruited via Lancaster University's SONA recruitment system. Participants were compensated with course credits and / or entry into a prize draw for one of three £50 cash prizes. All participants had normal or corrected-to-normal visual acuity (minimum 20/25), and clinically normal hearing confirmed by a Pure Tone Audiometry test following the procedure outlined by the British Society of Audiology (BSA, 2018). Participants also completed a pre-screen questionnaire to confirm they had no history of any neurological or psychological conditions which may affect perception and / or response tendencies in this study, including epilepsy or seizures, hearing loss, sight loss, optical conditions (astigmatism, colour blindness etc.), tinnitus, neurological and / or psychological conditions, and having undergone neurosurgery (including eye or ear surgery). All participants were also required to complete the ICHD-3 Migraine Diagnosis Questionnaire to confirm non-migraineur status.

2.2 Materials

2.2.1 The Computerised Pattern Glare Test

Braithwaite et al. (2013a; 2013b) developed a computerised adaptation of the earlier paper-based Pattern Glare (PG) test (Wilkins et al., 1984; Wilkins, 1995). In both versions participants are presented with square-wave visual grating patterns which vary in spatial frequency, some of which are known to be visually irritating and can create the perception of associated visual distortions and elementary hallucinations (AVDs; Braithwaite et al., 2013a, 2013b; Braithwaite et al., 2015; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022;

Jurkovičová et al., 2024). Grating patterns are presented as follows; a baseline low-frequency (0.5 cycles-per-degree; cpd), the crucial irritating medium-frequency (3 cpd), and another baseline high-frequency grating (14 cpd)[13]. These computerised Pattern Glare stimuli were presented to participants (five presentations per stimulus type, fifteen visual-only trials) in a pseudo-randomised order so that the same spatial frequency never occurred in consecutive trials. Examples of these stimuli are presented in Figure 1.

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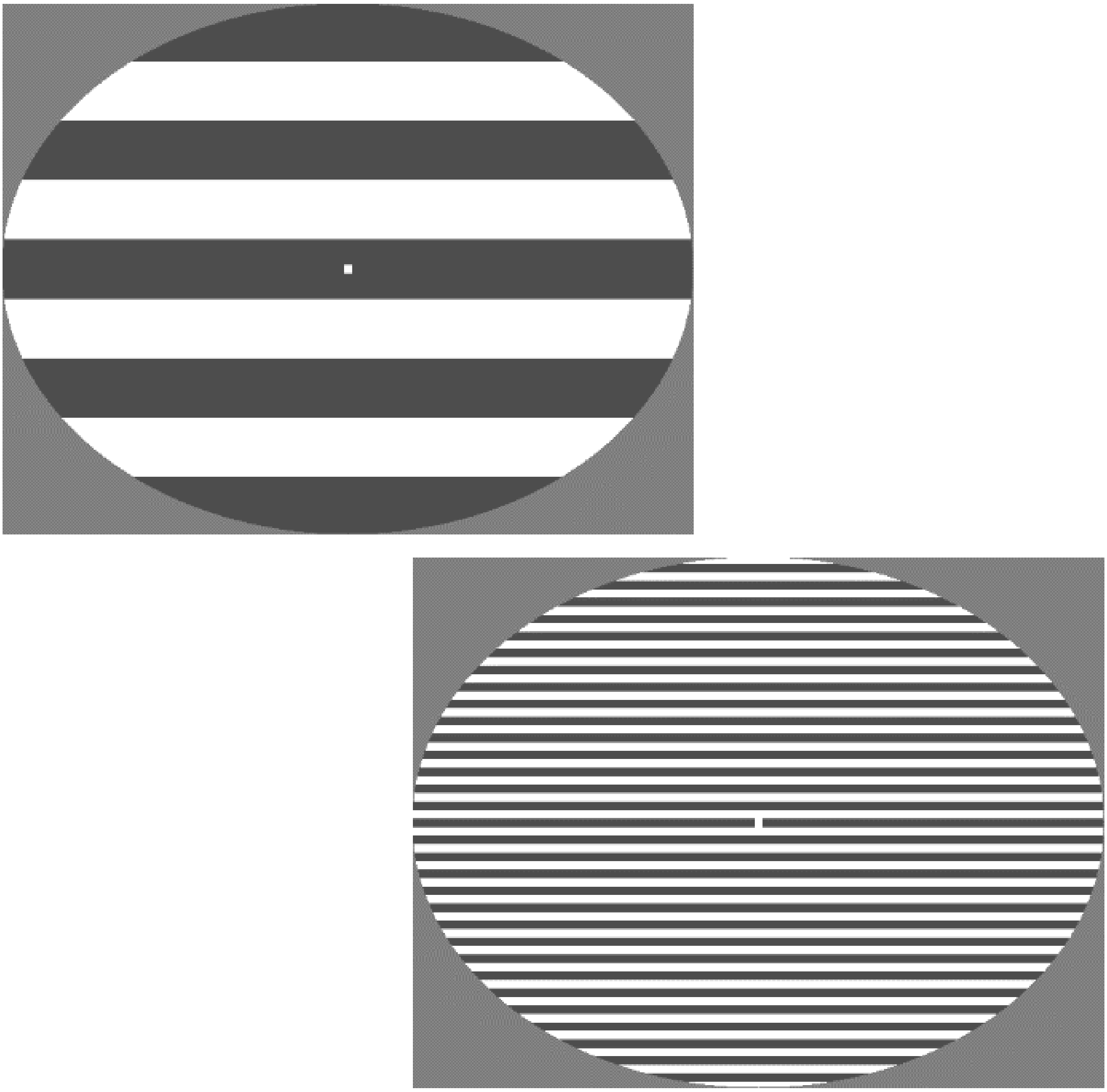
[13] Note – in pattern-glare tasks the baseline gratings should not be thought of as being devoid of potential visual effects, more so that the degree of effects experienced are far greater for the medium-frequency grating which likely reflect more central cortical processes.

Figure 1.

Examples of Low and Medium Frequency Visual Grating Stimuli



Illustrations of the low-frequency (top) baseline grating and the crucial medium-frequency (bottom) irritative grating. High-frequency grating is not demonstrated here as the high spatial frequency suffers aliasing when rescaled, thus image is not demonstrative of experimental stimulus. Note: The exact cycles-per-degree may vary here due to the rescaling of images.

2.2.2 Contrast Reversal Pattern Glare

Visual Stimuli. A visual phase-reversal effect was introduced to Pattern Glare gratings through rhythmic contrast reversals whereby each individual phase in the grating (line) alternates dichotomously between dark and light stripes. Gratings were reversed at three temporal frequencies: 3 Hz (control frequency), 10 Hz (slower critical frequency), and 15 Hz (faster critical frequency). Ten and 15 Hz were selected as critical frequencies, as studies on photic light flicker within ranges 10 – 20 Hz typically elicit most salient hallucinations (Amaya & Behrens et al., 2023; Amaya & Schmidt et al., 2023; Billock & Tsou, 2012). Three Hz was selected as a low-frequency control outside this window, which has not been shown to reliably induce visual hallucinations in photic stimulation (Amaya & Behrens et al., 2023; Amaya & Schmidt et al., 2023).

Two contrast-reversed images were created for each PG grating to create visual reversals when presented in rapid succession on-screen. The low spatial-frequency grating (0.5 cpd) was omitted given its primary role as a screening tool for response bias in traditional Pattern Glare, meaning both the visual medium-frequency (3 cpd) and visual high-frequency (14 cpd) grating were presented with contrast reversals. The viewing duration (trial-length) for each reversed grating was set at 12 seconds, in line with previous computerised pattern-glare studies using static gratings (e.g. Braithwaite et al., 2013a; 2013b; Braithwaite, Mevorach & Takahashi, 2015; Fong, Takahashi & Braithwaite, 2019). Visual stimulus files imitated the original computerised PG stimuli with a Michelson contrast of 0.75 cd/m^2 and configuration within a 154mm × 198mm ellipse within a 1920 × 1080-pixel grey background image (luminance 20 cd/m^2). All stimuli were presented via PsychoPy on an Iiyama G-MASTERGB2788HSU-B1 Red Eagle monitor (set to 120 Hz refresh rate). Reversal rates from the resulting output were calibrated externally with an mBBTK v2 submillisecond TTL event marker to ensure that what the experimental programme was asking for was faithfully represented on the screen.

Auditory Stimuli. To create audiovisual trials, in 50% of reversed trials, visual stimuli were combined with frequency modulated auditory tones. These tones consisted of a carrier tone at an irritating frequency which has previously been shown to amplify the intensity of AVDs on co-presentation with PG gratings, reflecting a cross-sensory enhancement due to the association between the two irritating stimuli (see Chapter 3). In all audiovisual trials tones were modulated at a matched frequency to the frequency of visual reversal in the grating (3 Hz, 10 Hz, or 15 Hz respectively). The modulation index for all tones was set at 10% for all stimuli. All auditory stimulus files were created in MATLAB and presented through Sennheiser HD650 impedance-matched cable headphones. Stimuli were presented at an average volume of 60 dB SPL and were calibrated externally using a Brüel & Kjær Type 4153 Artificial Ear.

The resulting Contrast Reversal PG task therefore consisted of 12 stimulus combinations: the two spatial frequencies of visual PG gratings (medium-frequency, high-frequency) each at three rates of visual reversal (3 Hz, 10 Hz, 15 Hz) all presented in the two sensory conditions (visual only, audiovisual). To reduce the potential for trial-by-trial carryover effects, stimuli were presented in a pseudo-randomised order to ensure that the same spatial and temporal frequency combination never occurred on consecutive trials. Stimuli were presented across five blocks of stimuli (twelve trials per block, one per stimulus combination - sixty trials total) with a five-minute rest period between blocks[14].

Associated Visual Distortion Scale. Aberrant experiences in Pattern Glare are typically measured by the Associated Visual Distortions (AVDs) scale (Braithwaite et al.,

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[14] A smaller number of trials and increased length of breaks between blocks relative to typical Pattern Glare was introduced to account for increased likelihood of participant fatigue with more potent stimuli used here.

2013a, 2013b; Braithwaite, Mevorach & Takahashi, 2015; Fong, Braithwaite & Takahashi, 2019; Fong et al., 2020; Fong et al., 2022). AVDs are a list of nineteen pre-defined experiences of visual irritation, visual distortions, and elementary visual hallucinations, each of which is rated for its intensity from 0 (not at all) to 6 (extremely intense) on each presentation of a PG grating. However, AVDs are predominantly made up of visual distortions and visceral experiences of discomfort. Given the broad phenomenology of hallucinations reported across photic visual flicker paradigms (e.g. Allefeld et al., 2011; Amaya & Behrens et al., 2023; Amaya & Schmidt et al., 2023; Bartossek, Kemmerer & Schmidt, 2021; Billock & Tsou, 2007; Ffytche, 2008; Shenyan et al., 2024), new items were created based on these previous findings. In addition, several AVD items were removed given the use of dynamic stimuli (i.e., items pertaining to illusory movement as the stimuli were now themselves dynamic). This movement inherent in the stimuli may be difficult to distinguish from illusory sensations of movement which are described in the original AVD questionnaire, namely items like ‘Flickering’ and ‘Jitter’.

The development of new items for hallucinations was guided by previous investigations of photic stimulation hallucinations. As well as examining participants’ total AVD scores, AVDs were split into three subcategories of hallucinations (*n* = 7), distortions (*n* = 4), and irritation (*n* = 8). These three subcategories represent different components of the continuum of aberrant experiences (Ffytche, 2008; Fischer, 1969; Fischer, 1970; Fischer, 1971; Silverstein & Lai, 2021). An overview of additional new and altered AVD items is presented in Table 1.

Table 1.

New and Altered AVD Items and Descriptions

Experience	Description
Floating	The entire grating pattern itself may appear to move around a central point. This may be movement in the x,y coordinates, or appearing to float off the screen. This does not relate to movement of the lines within the grating
Spirals	The observer perceives curved lines around a centre point or central axis. These may curve in a clockwise or counterclockwise motion, or appear to ripple / wave.
Radials	The observer perceives a series of straight lines originating from a central point. These might sometimes be described as star-like or cross-like patterns.
Honeycomb	The observer perceives an arrangement of small, dark geometric shapes, such as diamonds or hexagons, which cover or partially cover the surface of the grating.
Kaleidoscopic	The observer perceives complex formations of colourful geometric shapes. These may appear to go through several transformations, such as rotating or changing in colour.
Faces	The observer perceives a human-like face, or features of a human-like face such as eyes and a mouth, during presentation of the grating.
Other	You will have the opportunity to report any additional unusual experiences which may occur. These may be visual experiences, or any other relevant experiences you notice. Please try to provide a single word or short description which accurately characterises your experience.

Note: These are in addition to other AVDs. For descriptions of all other AVDs see Appendix E.

2.2.3 Audiovisual Aberration Scale

The Audiovisual Aberration Scale (AVAS) is a recently devised 35-item proxy measure of trait-based cortical hyperexcitability in the auditory and visual domains (see Chapter 2), building on the foundations of the visual-only Cortical Hyperexcitability Index (CHi_II; Braithwaite et al., 2015; Fong et al., 2019). The AVAS presents a series of brief statements referring to a relevant perceptual experience, and participants respond on two 0 – 6 Likert scales to indicate the relative frequency (0 = Not at all, 6 = All the time) and intensity (0 = Not at all, 6 = Extremely intense) of each experience, giving a total score /12 for each item and /420 for the overall questionnaire. The factor structure of the AVAS means that it can be examined in terms of separate subcomponents which make up trait-based cortical hyperexcitability as an overall concept.

2.3 Procedure

All participants gave informed consent and completed eligibility and AVAS questionnaires online via Qualtrics prior to the in-person testing session. All pre-screen responses were re-confirmed verbally in the laboratory to ensure participant suitability. Pure Tone Audiometry testing and the ICHD-3 Migraine Diagnosis Questionnaire were then administered. Participants were seated comfortably in an office chair at a distance of 80cm from the testing screen. A chin-rest was used to maintain a constant viewing distance throughout the testing procedure. Prior to testing a fixation cross was displayed in the centre of the screen and participants guided the instructor in adjusting the height on the chin-rest to ensure their eyes were level with the cross. Participants were given chance to familiarise themselves with the full list of AVDs and definitions before testing commenced and were allowed to refer back to the list at any time during the experiment.

Participants read through a brief instruction screen which instructed them to ensure their eyes are open and focused on the centre of the gratings at all times during presentation, and to inform the experimenter if they experienced excessive visual irritation during the task.

Three practise trials allowed participants to familiarise themselves with the controls and response procedure using black and white checkerboard patterns (0.5 cpd vertically and horizontally) to prevent habituation to experimental stimuli. Both static and reversal trials were presented in a pseudorandomised order. Each trial consisted of a brief fixation cross, relevant stimulus presentation, and the AVD scale. After the full procedure, participants were invited to briefly provide drawings of some additional AVDs they verbally reported during the task with the free response option, and were then thoroughly debriefed. Participation typically lasted 1.5 hours.

2.4 Analysis

Statistical Analysis

Analysis consisted of pairwise comparisons, Pearson's r correlations, and analysis of variance (ANOVA) models. ANOVAs were chosen to first assess the propensity of specific combinations of PG gratings at specific rates of visual reversal to elicit aberrant perceptual experiences (AVDs). These experiences were then broken down into subcategories of hallucinations, distortions, and irritation, again allowing examination of whether subcategories across the continuum of aberrant perceptual experiences were reported in response to the same stimulus combinations. Following this, t-tests were chosen to examine the effects of additive auditory stimuli on the elicited symptoms of Pattern Glare (i.e. sensory cross-talk enhancements) by comparing visual-only and audiovisual conditions for each PG grating at each rate of reversal. Again, AVDs were also broken down into subcategories of hallucinations, distortions, and irritation to examine whether these subcategories differed in their propensity for mediation by sensory cross-talk. Finally, correlations were chosen to examine the relationship between state-based (AVDs and subcategories) and trait-based (factors of the AVAS questionnaire) factors of cortical hyperexcitability. Where appropriate, these analyses were supplemented with additional Post-hoc and Bayesian analyses. All ANOVAs were supplemented with Tukey's HSD (Abdi & Williams, 2010) to assess pairwise differences between groups of means, whilst controlling (as far as possible) for type I errors. All analyses were conducted in R Studio (R version 4.3.0).

Where multiple related comparisons were conducted, the False Discovery Rate (FDR; Benjamini & Hochberg, 1995) was applied. This was intended both to correct for inflated type I error rates and to assess the relative strength of the relationships between each AVAS factor and Pattern Glare. FDR assigns a new critical value (B&H) to each comparison by ranking each *p*-value in ascending order, then applying the equation B&H = (i/k) * Q, where i is the original rank, k is the number of comparisons, and Q is the relevant threshold of significance (here .05). The highest ranked significant *p* value where *p* < B&H is deemed significant, along with all comparisons ranked below where *p* < B&H. Where a comparison is deemed statistically significant but *p* > B&H, that comparison and all subsequent comparisons would be deemed not statistically significant upon adjustment.

Bayesian analyses estimate a Bayes Factor (BF_{10}) value which makes a comparison of whether the data are more in favour of the null or alternative hypothesis. Bayes factors were interpreted in line with Jeffreys' theory of probability (Jeffreys, 1998; see also, Lee & Wagenmakers, 2014). As such, $BF_{10} < 1.0$ would be taken as indicating the probability of the data being in favour of the null hypothesis, and $BF_{10} > 1.0$ taken as indicating the probability of the data being in favour of the alternative hypothesis. Values closer to zero are deemed stronger evidence for the null hypothesis (e.g., 0.01 – 0.10 considered very strong, 0.10 – 0.33 considered substantial) and larger values above 3 are deemed stronger evidence for the alternative hypothesis (3 – 10 considered substantial, 10 – 100 considered strong / very strong, and > 100 considered decisive). Values between 0.33 – 3 are considered insensitive or anecdotal evidence for either hypothesis. These values can additionally be interpreted in terms of a numerical likelihood; for example, a BF_{10} of 10 suggests the data fit 10 times better with the alternative hypothesis than the null hypothesis. Equally, a BF_{10} of 0.1 suggests the data fit 10 times better with the null hypothesis than the alternative hypothesis. For all Bayesian analyses, the Cauchy prior value was set to the default conservative value of 0.707 (Wagenmakers et al., 2018).

Free Responses

Free responses were not formally analysed, rather they were examined for their frequency and thematic content. First responses were prepared for frequency analysis to establish the most frequent additional AVDs reported by participants across trials. To examine frequency, responses were first stripped of content not relevant to the aberrant experiences being reported. Here they were stripped of stop words, whitespace, punctuation, and capitalisation using the ‘tm’ package in Rstudio, as well as selected words specific to the paradigm which did not add meaning to participants’ reports (e.g. ‘saw’, ‘grating’, ‘hallucination’). After stripping, frequency counts were established for individual response words across all trials. Response words with a report frequency < 3 were excluded in-line with similar free response data collection methods for examinations of hallucinations (Shenyan et al., 2024).

After preparation, responses were primarily categorised as ‘simple’ or ‘complex’ forms of aberrant experiences based on the typical division between simple form constants (e.g. colours, geometric shapes) and complex imagery (e.g. people, animals, scenes; Siegel, 1977; Sacks, 2012, p. 10). Response words indicating aspects of movement or dynamic hallucinations were also examined for their frequency given evidence that specific stimulus properties may selectively elicit experiences with aspects of movement (Amaya et al., 2023;

Shenyan et al., 2024). Finally, any other non-visual aberrant experiences were also examined. In addition to establishing raw frequencies of response words, word clouds indicating relative word frequency for response words by PG stimulus were created using the ‘wordcloud2’ package in R studio. Examination of verbal free responses was supplemented with some visual examples of participants’ drawings of their hallucinations.

Results

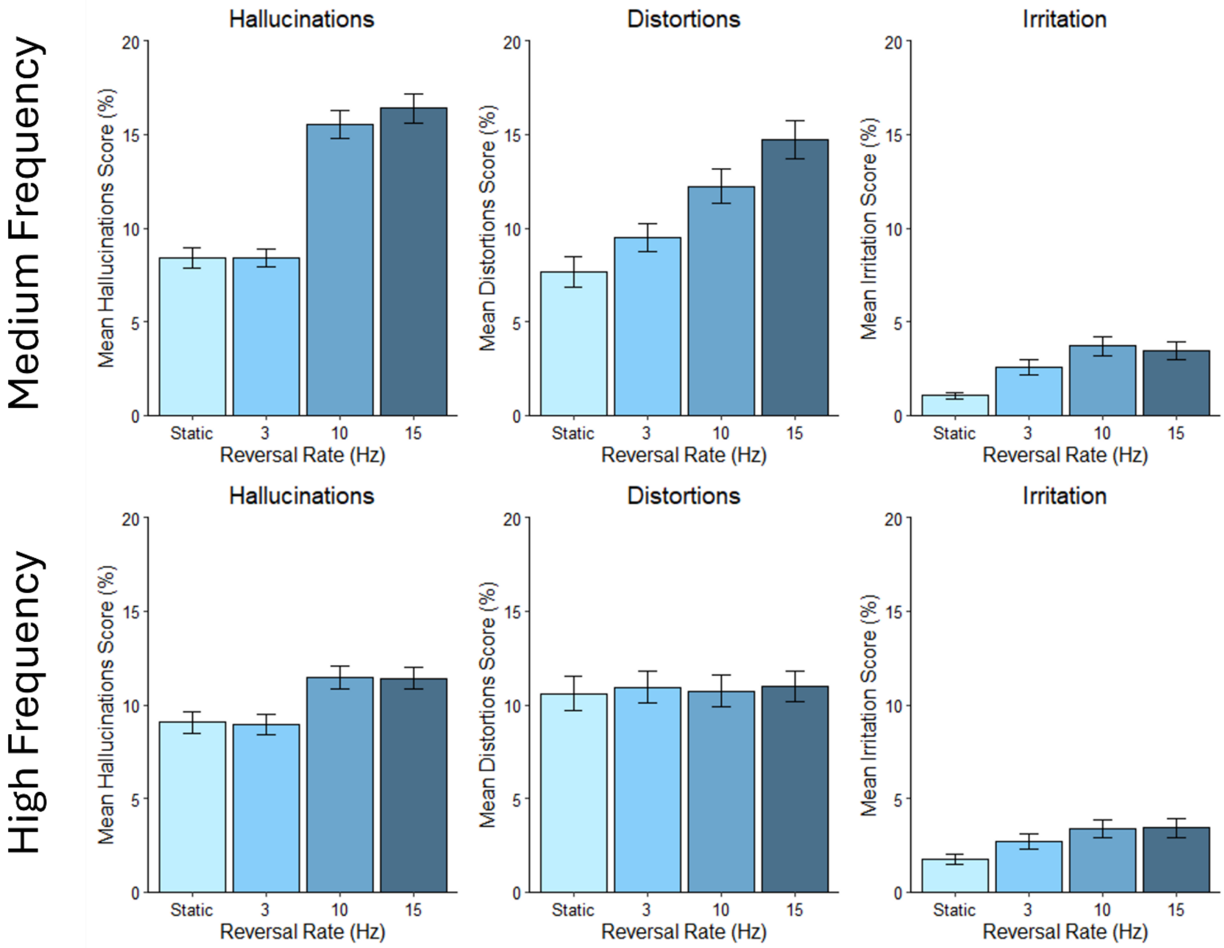
Initial outlier identification was conducted by determining the 95th percentile value for mean AVD score in the low frequency (0.5 cycles-per-degree) condition within the static Pattern Glare gratings, which was determined as 7.81. One participant's mean score in the control condition exceeded this value, and hence their responses were omitted from all analyses. This left a final sample of 61 participants (65.57% Female, 31.15% Male, 1.64% Non-binary / Third Gender, 1.64% Prefer not to say) aged 18 – 44 (*M* = 20.02, *SD* = 4.51).

3.1 Visual-Only Trials

The AVD response scale was fractionated into three subcategories of: hallucinations, distortions, and irritation. Descriptive statistics for the reported intensity of hallucinations, distortions, and irritation symptoms are presented in Figure 2.

Figure 2.

Intensity of Fractionated AVDs in Visual Trials



AVD scores are expressed here as a percentage of maximum score for each subcategory for visual comparison between categories

Hallucinations. A 2 (Visual Frequency, within-participants; Medium, High) × 4 (Reversal Rate, within-participants; Static, 3 Hz, 10 Hz, 15 Hz) ANOVA with interaction effect was calculated with hallucination intensity scores as the outcome variable. This revealed significant main effects of Visual Frequency ($F(1, 2310) = 22.72$, $\eta_p^2 = 0.010$, $p < .001$, $BF_{10} > 1000$), and of Reversal Rate ($F(3, 2310) = 42.88$, $\eta_p^2 = 0.053$, $p < .001$, $BF_{10} > 1000$), as well as a significant interaction between Visual Frequency and Reversal Rate (*F*(3,

2310) = 11.48, $\eta_p^2 = 0.015$, $p < .001$, $BF_{10} > 1000$). Tukey's HSD was used to determine at which reversal rates participants reported the most intense hallucinations for each grating. For the medium frequency, participants reported significantly more intense hallucinations at the two irritating rates of reversal (10 Hz, 15 Hz) as compared to the non-irritating rate of reversal (3 Hz) and the static grating, but no significant difference was found between the non-irritating rate of reversal and static grating. For the high frequency, there was no significant effect of rate of reversal on the intensity of hallucinations participants reported. A summary of these results is presented in Table 3.

Table 3.

Tukey's HSD for Effects of Reversal Rate and Visual Frequency on Hallucinations

Grating Type	Reversal Rate (Hz)	Difference	- 95 CI	+ 95 CI	*p*
Medium Frequency	Static - 3	0.01	-1.81	1.84	1.00
	10 - Static	4.71	2.89	6.54	< .001***
	15 - Static	5.27	3.44	7.10	< .001***
	10 - 3	4.72	3.00	6.45	< .001***
	15 - 3	5.28	3.56	7.00	< .001***
	15 - 10	0.56	-1.16	2.28	.977

* Denotes significance - *** = $p < .001$; ** = $p < .01$; * = $p < .05$. All comparisons for the high frequency grating were not statistically significant (all $p > .05$; not shown here).

Distortions. A 2 (Visual Frequency, within-participants; Medium, High) × 4 (Reversal Rate, within-participants; Static, 3 Hz, 10 Hz, 15 Hz) ANOVA with interaction term was conducted with distortion intensity scores as the outcome variable. This revealed a significant main effect of reversal rate ($F(3, 2310) = 6.45$, $\eta_p^2 = 0.008$, $p < .001$, $BF_{10} = 10.10$) and a significant interaction between reversal rate and visual frequency ($F(3, 2310) = 5.62$, $\eta_p^2 = 0.007$, $p < .001$, $BF_{10} = 4.10$). There was no significant main effect of visual frequency ($F(1, 2310) = 0.38$, $\eta_p^2 < 0.0001$, $p = .536$, $BF_{10} = 0.06$). Tukey's HSD was used to determine at which reversal rates participants reported the most intense distortions for each grating. For the medium frequency, participants reported significantly more intense distortions at only one irritating rate of reversal (15 Hz) as compared to the non-irritating rate of reversal (3 Hz) and the static grating. No significant difference was found between the two irritating rates of reversal (10 Hz, 15 Hz), nor between the static grating and non-irritating rate of reversal (3 Hz). For the high frequency grating, there was no significant effect of rate of reversal on the intensity of distortions participants reported. A summary of these results is presented in Table 4.

Table 4.

Tukey's HSD for Effects of Reversal Rate and Visual Frequency on Distortions

Grating Type	Reversal Rate (Hz)	Difference	- 95 CI	+ 95 CI	*p*
Medium Frequency	3 – Static	0.33	-0.37	1.03	.842
	10 - Static	0.82	0.12	1.52	.009**
	15 - Static	1.27	0.57	1.97	< .001***
	10 – 3	0.49	-0.17	1.15	.314
	15 – 3	0.94	0.28	1.60	< .001***
	15 – 10	0.45	-0.21	1.10	.446

* Denotes significance - *** = $p < .001$; ** = $p < .01$; * = $p < .05$. All comparisons for the high frequency grating were not statistically significant (all $p > .05$; not shown here).

Irritation. A 2 (Visual Frequency, within-participants; Medium, High) × 4 (Reversal Rate, within-participants; Static, 3 Hz, 10 Hz, 15 Hz) ANOVA with interaction term was conducted with irritation intensity scores as the outcome variable. This revealed a significant main effect of reversal rate ($F(3, 2310) = 9.24$, $\eta_p^2 = 0.012$, $p < .001$, $BF_{10} = 611.21$). There was no significant effect of visual frequency ($F(1, 2310) = 0.10$, $\eta_p^2 < 0.0001$, $p = .755$, $BF_{10} = 0.05$) and no significant interaction between Reversal Rate and Visual Frequency ($F(3, 2310) = 0.44$, $\eta_p^2 = 0.001$, $p = .726$, $BF_{10} = 0.13$). Tukey's HSD was used to determine at which reversal rates participants reported the most intense irritation. Compared to the static grating, participants reported significantly more irritation in response to the non-irritating rate of reversal (3 Hz; Diff = 0.59, 95CI [-0.22, 1.65], $p = .037$) as well as the two irritating rates of 10 Hz (Diff = 1.27, 95CI [0.33, 2.21], $p < .001$) and 15 Hz (Diff = 1.15, 95CI [0.21, 2.09], $p < .001$). No significant differences were found for comparisons between the non-irritating rate of reversal (3 Hz) and irritating rates of reversal (10 Hz, 15 Hz), or between the two irritating rates of reversal themselves (all $p > .05$). To summarise, all rates of reversal increased the intensity of irritation reported by participants, but there was no differentiation between irritating (10 Hz, 15 Hz) and non-irritating rates of reversal, and no differentiation between the medium frequency and high frequency grating.

Together, these findings show that the three subcategories of the AVD subscale are not all equally subject to enhanced salience when irritating rates of reversal are added to PG gratings. Both hallucinations and distortions were reported as significantly more intense when irritating rates of reversal (10 Hz and 15 Hz for hallucinations; but 15 Hz only for distortions) were paired with an irritating grating (medium frequency). This is demonstrated by the interaction observed between grating type and reversal rate for both hallucinations and distortions. Irritation however showed a non-specific effect where reported intensity increased with irritating and non-irritating (3 Hz) rates of reversal, and for both the irritating and non-irritating (high frequency) grating. This is demonstrated by the significant main effect of reversal rate only.

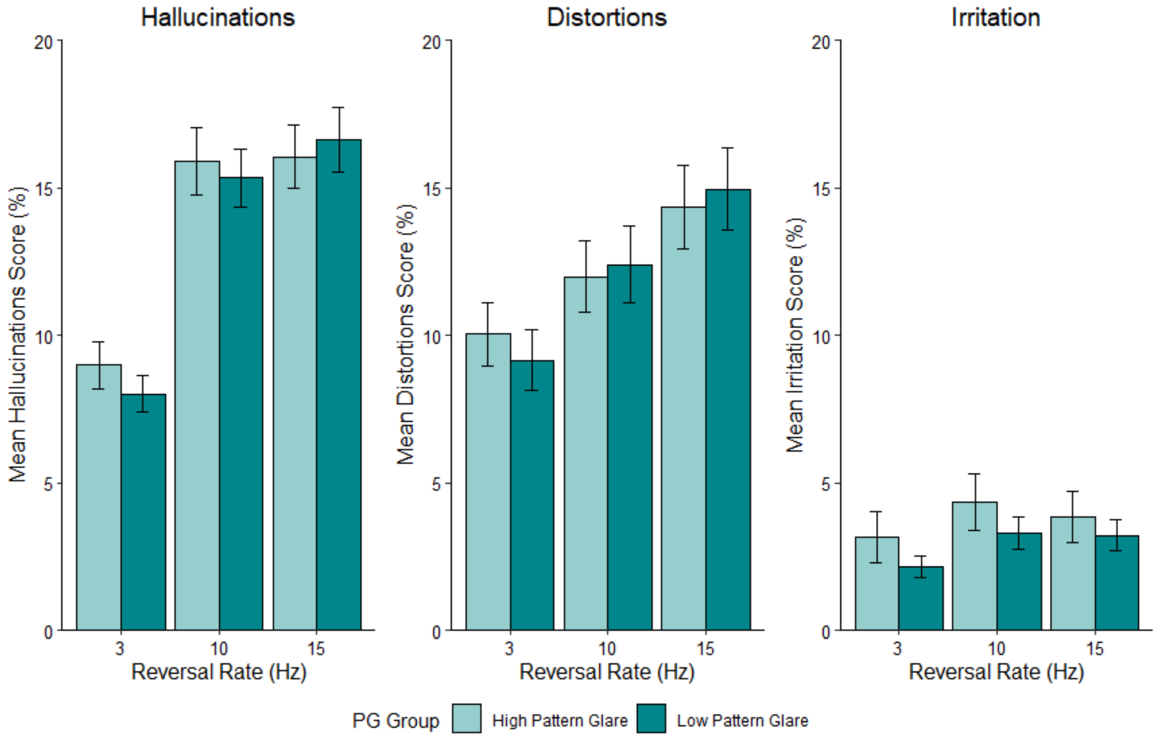
Medium Frequency – High Frequency (ΔAVD)

In addition, ΔAVD scores were calculated by subtracting participants' mean AVD score in response to the high frequency grating (14 cpd) from the medium frequency grating (3 cpd) in visual only (no tone) conditions. This creates a baseline-corrected delta score which represents a quantitative behavioural measure of state-based cortical hyperexcitability (for similar approach see Braithwaite et al., 2015; Evans & Stevenson, 2008; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022).

Participants were then split into those that displayed signs of elevated state-based cortical hyperexcitability, relative to those that did not based on whether they presented a positive (High PG) or negative (Low PG) ΔAVD score. As earlier analyses indicated that varying rates of reversal for the high-frequency grating had no effect on the intensity of AVDs reported, the high frequency grating was excluded from the dependent variable for these analyses. Descriptive statistics for the reported intensity of hallucinations, distortions, and irritation symptoms in High PG and Low PG groups are presented separately in Figure 3.

Figure 3.

Intensity of Fractionated AVDs in High and Low PG Groups



AVD scores are expressed here as a percentage of maximum score for each subcategory for visual comparison between categories

PG Group differences in hallucinations, distortions, and irritation were examined via a 4 (Reversal Rate, within-participants; 3 Hz, 10 Hz, 15 Hz**)** × 2 (PG Group, between-participants; High PG, Low PG) mixed MANOVA with intensity scores for hallucinations, distortions, and irritation included separately as dependent variables. This revealed a significant effect of Reversal Rate[15] F (2, 909) = 15.08, $p < .001$, Wilk's $\lambda = 0.906$, $\eta_p^2 = 0.05$. There was no significant effect of PG Group (F (1, 909) = 0.96, $p = 0.409$, Wilk's $\lambda = 0.997$,

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[15] Post-hoc examination of these effects is not included as this would amount to a repetition of earlier analyses.

$\eta_p^2 = 0.003$) and no significant interaction between Reversal Rate and PG Group (F (2, 909) = 0.16, $p = 0.156$, Wilk's $\lambda = 0.999$, $\eta_p^2 = 0.001$).

These results demonstrate that the reported intensity of AVDs elicited by reversed Pattern Glare gratings is not significantly different between the Low PG and High PG groups (based on state-based responses to the static medium-frequency). This differs from previous findings in relation to static Pattern Glare (e.g. Braithwaite et al., 2015; Fong et al., 2019; see also Chapter 3) which demonstrate an association between state-based cortical hyperexcitability and the intensity of AVDs. This may suggest differences in the state-based characteristics associated with elevated Pattern Glare and AVDs elicited by rhythmic visual reversal respectively (see Discussion).

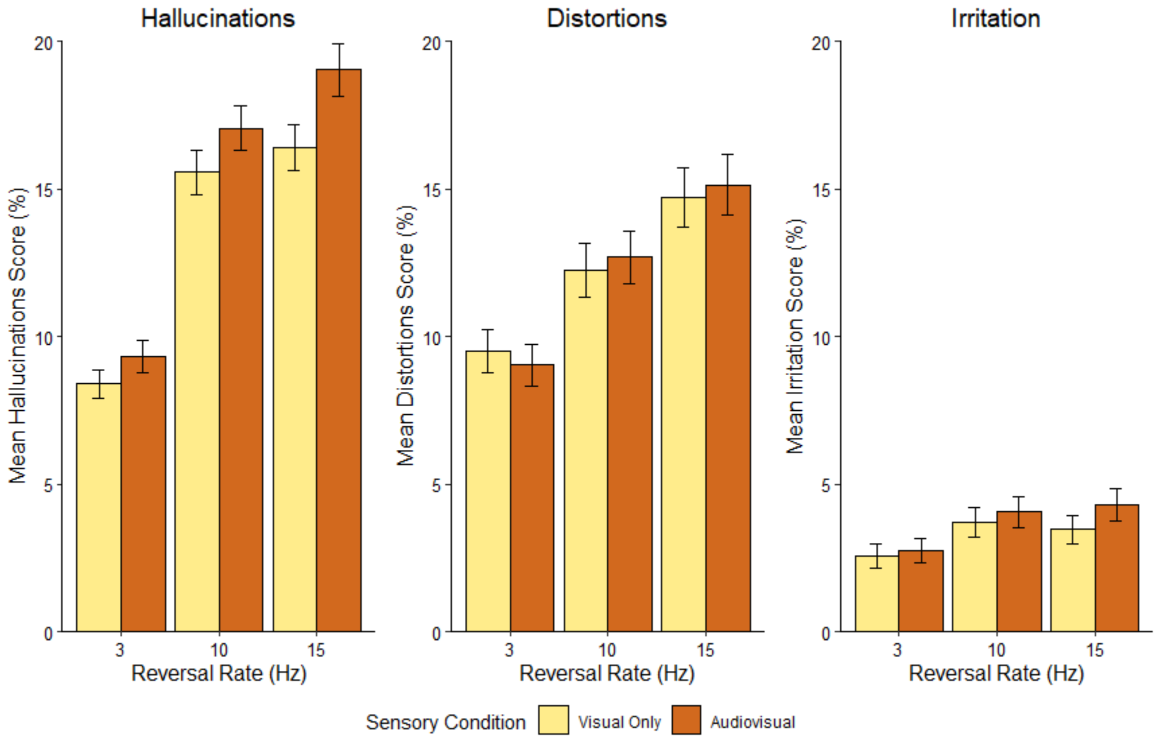
3.2 Multisensory Trials

The following analyses examined the sensory cross-talk effect (i.e. enhanced intensity of AVDs) from co-presented auditory frequency-modulated tones on reversal-induced AVDs. Here the static condition was excluded from the reversal rate variable, as there was no multisensory condition to compare against. In addition, as earlier analyses failed to reliably demonstrate an effect of reversal rate on the intensity of AVDs related to the non-irritating (high frequency) grating, the high frequency grating was also dropped from these analyses.

The AVD response scale was split into the three discussed subcategories of hallucinations, distortions, and irritation. This allowed for examination of whether sensory cross-talk had similar facilitatory effects in increasing the intensity of AVDs from across the continuum of aberrant experiences (Johns & van Os. 2001; van Os, 2003; van Os et al., 2009). Descriptive statistics for reported intensity of hallucinations, distortions, and irritation in visual only and audiovisual trials are presented separately in Figure 4.

Figure 4.

Intensity of Fractionated AVDs in Visual Only and Audiovisual Trials, Medium Frequency Grating



AVD scores are expressed here as a percentage of maximum score for each subcategory for visual comparison between categories

Nine paired samples t-tests were conducted for each of the three categories of AVDs (hallucinations, distortions, irritation) at each of the three rates of reversal (3 Hz, 10 Hz, 15Hz), each comparing between visual only and audiovisual trials. Benjamini-Hochberg adjustments were made for multiple comparisons. Frequentist analyses were also complimented with Bayes factors which were calculated for each comparison. A summary of these analyses is presented in Table 5.

Table 5.

Effect of Sound on Intensity of Fractionated AVDs, Medium Frequency Grating

		Frequentist					Bayesian		
AVD	Reversal	*t*	*d*	*P*	B&H	Sig?	BF_{10}	Hypothesis	Support
Hallucinations	15 Hz	5.20	0.30	< .001	.0056	Yes	> 1000	Alternative	Decisive
Irritation	15 Hz	4.37	0.25	< .001	.0111	Yes	632.18	Alternative	Decisive
Hallucinations	10 Hz	3.15	0.18	.001	.0167	Yes	8.17	Alternative	Substantial
Hallucinations	3 Hz	2.29	0.13	.023	.0222	No	0.84	Null	Anecdotal

Note – for all comparisons presented participants' mean AVD scores were significantly greater for audiovisual trials than visual only trials (i.e. all audiovisual > visual only). All comparisons not presented were not statistically significant under frequentist statistics ($p > .05$) and received substantial or very strong support for the null hypothesis from Bayesian statistics ($BF_{10} < 0.33$).

Hallucinations. Both frequentist and Bayesian statistics suggest participants reported significantly more intense hallucinations in audiovisual trials than in visual only trials at the two irritating rates of reversal (15 Hz, 10Hz). This is consistent with the auditory cross-sensory enhancement effect. Within these two comparisons, Bayes factors suggest decisive support for this difference at 15 Hz ($BF_{10} > 1000$), and substantial support at 10 Hz ($BF_{10} = 8.17$). After correction for multiple comparisons both frequentist and Bayesian statistics suggest no significant difference between visual only and audiovisual trials at the non-irritating rate of reversal (3 Hz).

Distortions. Both frequentist and Bayesian statistics suggest no significant difference in the reported intensity of distortions between visual only and audiovisual trials across all rates of reversal. Bayesian statistics suggested very strong evidence for the absence of this significant difference at all rates of reversal.

Irritation. Both frequentist and Bayesian statistics suggest participants reported significantly more intense irritation in audiovisual trials than visual only trials for one irritating rate of reversal (15 Hz). There was no significant difference between visual only and audiovisual trials for the other irritating rate of reversal (10 Hz) and for the non-irritating rate of reversal (3 Hz).

Together these findings suggest that the sensory cross-talk enhancement effect, whereby adding simultaneous irritating auditory stimulation to reversed Pattern Glare gratings increases the reported intensity of AVDs relative to visual-only trials, is not equivalent for hallucinations, distortions, and irritation. Rather, sensory cross-talk in concert with reversed Pattern Glare gratings was predominantly present for hallucinations, and somewhat for irritation. This effect was specific to reversal rates in the critical frequency range (10 Hz and 15 Hz).

3.3 Trait-based Associations – Visual Only Trials

To examine the relationship between AVDs elicited from reversed Pattern Glare gratings and trait-based cortical hyperexcitability, Pearson's r correlations were calculated between AVD scores in visual only trials and the three factors of the AVAS measure (HSSD, Heightened Sensory Sensitivity and Discomfort; MVAS, Migrainesque Visual Aura Symptoms; VHE, Voice Hearing Experiences).

Medium Frequency Grating.

Pearson's r correlations were calculated between AVD scores in visual-only trials at each reversal rate (3 Hz, 10 Hz, 15 Hz) for the medium frequency grating and each factor of the

AVAS (Heightened Sensory Sensitivity and Discomfort, HSSD; Migrainesque Visual Aura Symptoms, MVAS; Voice Hearing Experiences, VHE). Initially correlations were conducted using overall AVD score to determine at which flicker rates AVDs show associations with selective MVAS factors to reduce the alpha rate when AVDs are broken down into three subcategories of hallucinations, distortions, and irritation.

This created nine correlations which were controlled with Benjamini-Hochberg adjustments and supplemented with an analysis of the Bayes factors. Results revealed a significant relationship between the reported intensity of AVDs at 10 Hz reversal and factor two (MVAS) only. All other correlations were statistically insignificant after B&H corrections were applied (*p* > B&H, or *p* > .05; see Appendix F). To explore this relationship further, AVD score was split into the three discussed subcategories of hallucinations, distortions, and irritation. Three further Pearson's R correlations were therefore conducted for each of these scores in response to the medium-frequency grating at 10 Hz reversal, and the MVAS factor of the AVAS measure. A summary of these analyses is presented in Table 6.

Table 6.

Fractionated AVDs × MVAS Factor of the AVAS Measure for Visual Only Trials, Medium Frequency Grating at 10 Hz Reversal

	Frequentist				Bayesian		
AVD Type	*r*	*P*	B&H	Sig?	BF_{10}	Hypothesis	Support
Hallucinations	.35	.006	.0167	Yes	9.42	Alternative	Substantial
Distortions	.33	.009	.0333	Yes	6.47	Alternative	Substantial
Irritation	.10	.459	.0500	No	0.37	Null	Anecdotal

Results revealed significant correlations with substantial support from Bayes factors for intensity of both hallucinations and distortions. No significant correlation was found with irritation score. This suggests that although predisposition to aura-like hallucinations (MVAS) is associated with greater intensity of aberrant perceptual experiences for reversed Pattern Glare gratings, this is limited to hallucinations and distortions, and not irritation.

High Frequency Grating.

Pearson's r correlations were then calculated between AVD scores in visual only trials at each reversal rate (3 Hz, 10 Hz, 15 Hz) for the high frequency grating, and each factor of the AVAS (Heightened Sensory Sensitivity and Discomfort, HSSD; Migrainesque Visual Aura Symptoms, MVAS; Voice Hearing Experiences, VHE). This created nine correlations which were controlled with Benjamini-Hochberg adjustments and supplemented with Bayes Factors. Results revealed no significant relationships between the reported intensity of AVDs and the factors of the AVAS questionnaire - all correlations were statistically insignificant after B&H corrections were applied (all $p >$ B&H).

Together these findings suggest that a greater intensity of AVDs in response to reversed PG gratings is associated with elevated trait-based cortical hyperexcitability. Specifically, a greater intensity of hallucinations and distortions at one irritating rate of reversal (10 Hz) is associated with greater predisposition to aura-like hallucinations (MVAS). This association was specific to the irritating medium-frequency grating and was not observed for the non-irritating high frequency grating.

3.4 Trait-based Associations – Sensory Cross-talk

In addition to visual-only trials, correlations were calculated between the factors of the AVAS measure and the intensity of AVDs reported in audiovisual trials. This allowed for examination of trait-based factors associated with greater enhancement of AVDs from sensory cross-talk. This may help to suggest whether both the occurrence of AVDs and their cross-sensory enhancement occur via the same mechanisms, or whether additional trait-based factors are associated with this cross-sensory enhancement.

Correlations were first calculated between the three factors of the AVAS (HSSD, MVAS, VHE) and AVD scores in audiovisual trials across the three rates of reversal for the medium frequency grating. Again, correlations were initially conducted with overall AVD score to determine relevant AVAS factors and flicker rates to reduce the number of comparisons when breaking down AVDs into the three subcategories of hallucinations, distortions, and irritation. This created nine further correlations which were controlled with Benjamini-Hochberg adjustments and supplemented with Bayes factor analysis. A summary of analyses are reported in Table 9.

Results revealed significant correlations with support from Bayes factors between the reported intensity of AVDs at both irritating rates of reversal (10 Hz, 15 Hz) and all three factors of the AVAS questionnaire (for detailed summary see Appendix G). Notably, no significant correlations were found between any factor of the AVAS questionnaire and the intensity of AVDs reported at the non-irritating rate of reversal (3 Hz; all $p > .05$).

To explore this relationship further AVDs were again split into the three subcategories of hallucinations, distortions, and irritation. Pearson's R correlations were then calculated between each of the three AVAS factors (HSSD, MVAS, VHE) and these three subcategories of AVDs. All correlations were conducted for the medium frequency grating in audiovisual trials at 15 Hz reversal[16]. This created nine correlations which were controlled with Benjamini-Hochberg adjustments and supplemented with Bayes factors. A summary of analyses is reported in Table 7.

Table 7.

Fractionated AVDs × MVAS Factor of the AVAS Measure for Audiovisual Trials, Medium Frequency Grating at 15 Hz Reversal

		Frequentist				Bayesian		
AVAS Factor	AVD Type	*R*	*p*	B&H	Sig?	BF_{10}	Hypothesis	Support
MVAS	Hallucinations	.40	.001	.0056	Yes	32.55	Alternative	Substantial
MVAS	Distortions	.37	.003	.0111	Yes	16.78	Alternative	Substantial
VHE	Distortions	.35	.006	.0167	Yes	8.93	Alternative	Substantial
VHE	Hallucinations	.33	.009	.0222	Yes	6.87	Alternative	Substantial
HSSD	Hallucinations	.30	.019	.0278	Yes	3.64	Alternative	Substantial
HSSD	Distortions	.29	.026	.0333	Yes	2.86	Alternative	Anecdotal

MVAS = Migrainesque Visual Aura Symptoms; VHE = Voice Hearing Symptoms; HSSD = Heightened Sensory Sensitivity and Discomfort. All comparisons not presented (for irritation score) were not statistically significant under frequentist statistics ($p > .05$).

For both hallucinations and distortions significant correlations were observed with all three factors of the AVAS measure. Notably, intensity of irritation did not demonstrate any significant correlations with any factor of the AVAS measure. This suggests that the cross-sensory enhancement of hallucinations, distortions, and irritation are not mediated by the

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[16] Note that both 10 Hz reversal and 15 Hz reversal in audiovisual trials showed significant correlations with all three factors of the AVAS. As such both 10 Hz and 15 Hz reversal could be correlated here, however only one reversal rate (15 Hz) was selected to reduce the number of comparisons and control the Type I error rate.

same trait-based factors. Cross-sensory enhancement of hallucinations and distortions appear to be mediated by similar trait-based factors (as measured by the factors of the AVAS), however for irritation scores in audiovisual trials there were no significant correlations with any factor of the AVAS.

Together these results suggest that all three factors of trait-based cortical hyperexcitability measured by the AVAS are associated with predisposition to this cross-sensory enhancement of AVDs in reversed Pattern Glare gratings. This is in contrast with previous findings which indicate that predisposition to migraine aura-type hallucinations (measured by MVAS factor) only is associated with cross-sensory enhancement of AVDs (see Chapter 3). Given that significant correlations were observed for both hallucinations and distortions, whereas traditional Pattern Glare focuses primarily on distortions, this may further indicate differences in the trait-based factors associated with predisposition to cross-sensory enhancement of different types of aberrant perceptual experiences (see General Discussion).

3.5 Free Response Data

As an addendum to the quantitative analysis presented, a thematic analysis of the contents of other reported aberrant experiences was conducted. This was conducted given the broad phenomenology of aberrant experiences reported in previous visual flicker paradigms (e.g. Allefeld et al., 2011; Amaya et al., 2023; Bartossek, Kemmerer & Schmidt, 2021; Billock & Tsou, 2007; Ffytche, 2008; Shenyan et al., 2024), which could not feasibly be covered in their entirety by AVD items; this is particularly true for more complex hallucinations, which were represented only by the ‘Faces’ item in the AVD response scale. Participants were also invited to provide hand-drawn examples of some of the additional AVDs they reported to supplement their verbal responses. Free responses were recorded in a total of 573 (13.05%) trials across the entire investigation. These responses came from 39 (63.93%) participants, demonstrating that most participants used the free response option to report some form of additional anomalous experience during the experiment. Raw counts for the number of free responses provided by stimulus type are presented in Table 8[17].

Table 8.

Free Response Raw Counts by Stimulus Type, Medium Frequency Grating

	Reversal Rate		
Sensory Condition	3 Hz	10 Hz	15 Hz
Visual only	45	54	40
Audiovisual	51	43	39
			Total: 272

As most participants deemed it necessary to report additional aberrant experiences beyond those covered in the AVD subscale, an exploratory thematic analysis was conducted to examine their contents. Free responses were therefore used to create an exploratory word cloud and examine the frequency of individual words within free responses to the medium frequency grating, as well as their thematic contents.

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[17] Methodology here differs somewhat from typical photic flicker paradigms as participants were prompted to report aberrant experiences more broadly, not just hallucinations, so elevated scores at 3 Hz reversal does not necessarily reflect an unusual response pattern of reporting hallucinations outside the critical frequency range.

Thematic Analysis

After removal of relevant stop words, frequency counts were calculated for the occurrence of individual words within participant free responses. Four hundred and nineteen unique free response words were used in response to the medium frequency grating with individual frequencies ranging from 1 – 59 (*M* = 2.57, *SD* = 4.35). After removal of free responses with a frequency < 3 (Shenyan et al., 2024), this left 63 unique free response words (frequency *M* = 7.63, *SD* = 8.46). An exploratory word cloud plot indicating relative frequencies of these free response words is presented in Figure 5.

Figure 5.

Free Response Word Cloud – Medium-Frequency

Simple hallucinations consisted largely of shapes and geometric patterns such as lines or stripes, rings, and jagged patterns. Many of these were reported alongside the typical pattern glare colours of red, green, blue, and yellow, as well as additional colours such as purple, pink, and orange. Complex hallucinations were less frequent. The most reported were natural scenes and images such as mountains and flames. Participants also reported seeing examples of text – those being a mixture of letters and numbers, with letters being more frequent. Additionally, there were a small number of reports of seeing human body parts (ears, eyes, mouths). Several descriptions of dynamic aspects were present in participant reports such as moving, flashing, rotating, and changing images, as well as images appearing to move closer. Finally, a selection of other aberrant experiences were reported including feelings of euphoria and the presence of aberrant experiences of sound, namely a ringing sound. A summary of the most frequently reported free response words for the medium-frequency grating is presented in Table 9.

Table 9.

Frequency of Most Reported Free Responses, Medium-Frequency

Simple Hallucinations		Complex Hallucinations		Dynamic Hallucinations		Other Experiences	
Description	Frequency	Description	Frequency	Description	Frequency	Description	Frequency
Lines / stripes	78	Mountains	8	Moving	16	Euphoria	5
Patterns	25	Flames	6	Flashing	8	Sound	3
Shapes	20	Letters	6	Closer	6	Ringing	3
Jagged	9	Numbers	3	Changing	5		
Rings	6	Ears	5	Rotating	4		

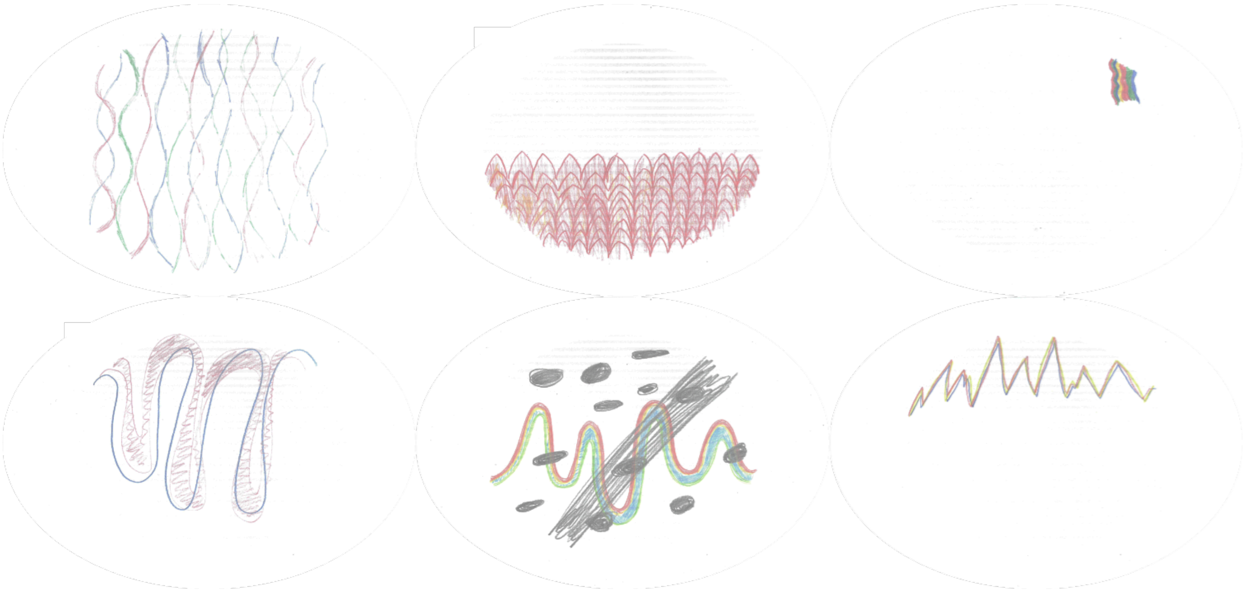
Drawn Responses

A selection of hand-drawn examples of additional reported anomalous experiences are also provided below. Drawn responses largely consisted of simple and complex hallucinations, but some examples of dynamic hallucinations were also provided. Participants broadly expressed difficulty in providing hand-drawn depictions of dynamic hallucinations but could not provide drawn depictions of 'other' experiences at all.

Simple Hallucinations. Depictions of simple hallucinations are presented in Figure 6. As indicated in verbal responses, these largely consisted of coloured geometric shapes and patterns.

Figure 6.

Drawn Examples of Simple Hallucinations

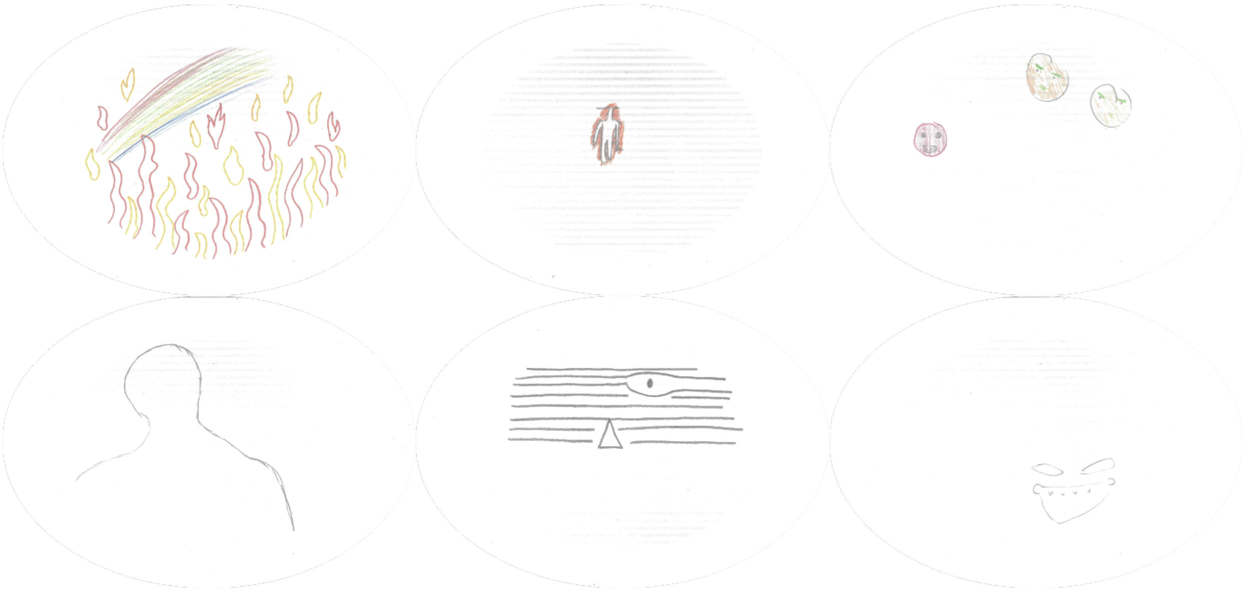


Participants' given descriptions of drawn hallucinations are provided from left to right as follows. Top row: *Helixes, Rings, Chromatic pattern*. Bottom row: *Serpentine, Rainbow, Jagged colours*.

Complex Hallucinations. Depictions of complex hallucinations are presented in Figure 7. These largely consisted of various images of human figures, facial features, and more abstract faces. Participants typically selected to provide images of human figures rather than natural scenes due to feeling these experiences were more profound and unexpected.

Figure 7.

Drawn Examples of Complex Hallucinations

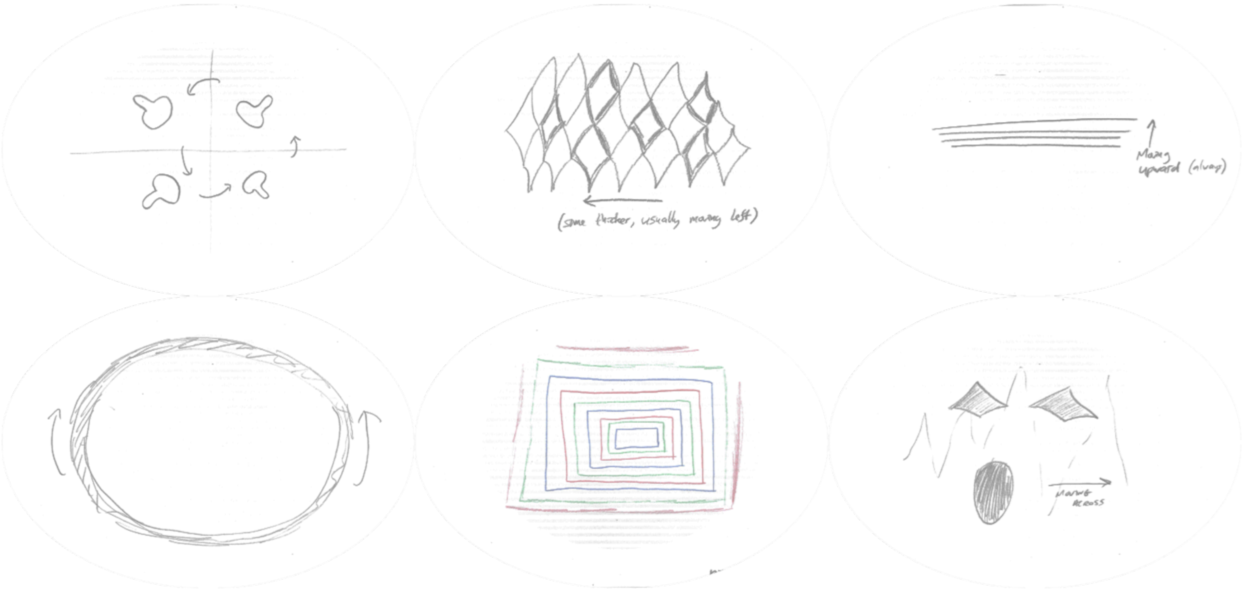


Participants' given descriptions of drawn hallucinations are provided from left to right as follows. Top row: *Flames, Burning man, Elves*. Bottom row: *Human silhouette, Eye and nose, Devil*.

Dynamic Hallucinations. Depictions of dynamic hallucinations are presented in Figure 8. Participants often chose to depict dynamic aspects with arrows and written labels of the nature and direction of movement.

Figure 8.

Drawn Examples of Dynamic Hallucinations



Participants' given descriptions of drawn hallucinations are provided from left to right as follows. Top row: *Rotating shapes, Moving diamonds, Lines moving upwards*. Bottom row: *Rotating rings, Tunnel getting closer, Shifting face*.

These responses indicate that as well as typical AVDs, participants reported a wide range of other visual and non-visual anomalous experiences when viewing reversed Pattern Glare gratings. These ranged from simple hallucinations of geometric shapes and patterns to more complex hallucinations such as natural scenes and human figures, and many reported dynamic hallucinations. As well as visual experiences, participants reported a small number of non-visual (auditory, affective) experiences. These reports are in line with previous findings on rhythmic photopic flicker which demonstrate a wide range of reported anomalous experiences (e.g. Allefeld et al., 2011; Amaya et al., 2023; Bartossek, Kemmerer & Schmidt, 2021; Billock & Tsou, 2007; Shenyan et al., 2024) and suggest that in some cases these experiences can extend beyond the visual domain.

Discussion

The present study examined the role of cortical hyperexcitability as a contributing factor of predisposition to aberrant perceptual experiences across the perception-hallucination continuum, as well as their cross-sensory enhancement effects. Here a rhythmic phase reversal was introduced to Pattern Glare gratings to elicit visual hallucinations alongside typical distortions and irritation. This was further extended into the auditory domain by pairing visual stimuli with concurrent irritative frequency modulated auditory tones. In addition, participants completed the AVAS, a trait-based proxy measure of cortical hyperexcitability. The underlying motivation was to examine whether similar state-based and trait-based factors mediate predisposition to different types of aberrant perceptual experiences across the perception-hallucination continuum, as well as their cross-sensory enhancement.

Findings from visual-only trials revealed a selective enhancement of hallucinations and distortions, but not irritation, with the introduction of rhythmic phase reversals at the two critical frequencies[18] of 10 and 15 Hz. State-trait associations suggested that this effect was associated with one specific factor of trait-based hyperexcitability; predisposition to aura-like hallucinations (MVAS; Migrainesque Visual Aura Symptoms).

Additional findings from audiovisual trials revealed selective enhancements of hallucinations, and to a lesser extent irritation, with concurrent presentation of auditory tones. Here however, state-trait associations suggested that intensity of both hallucinations and distortions elicited under audiovisual conditions were associated with elevated scores on all three factors of trait-based hyperexcitability. Together these findings support suggestions from the hodotopic framework that different state-based and trait-based factors influence susceptibility to aberrant experiences across the perception-hallucination continuum (Ffytche,

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[18] Critical frequencies determined by the 10 – 20 Hz band associated with most salient hallucinations in photic flicker studies (see Billock & Tsou, 2007; 2012).

2008; Silverstein & Lai, 2021) and extend this idea into multisensory domains with their cross-sensory enhancement effects.

4.1 State-based Factors

Visual only trials demonstrated that adding rhythmic phase reversals at 10 Hz and 15 Hz significantly enhanced the intensity of hallucinations, and distortions, relative to both 3 Hz reversals and static Pattern Glare gratings. This meshes with findings from photic stimulation research showing that visual flicker in the 10 – 20 Hz range reliably elicits salient visual hallucinations (Amaya et al., 2023; Bartossek, Kemmerer & Schmidt, 2021; Billock & Tsou, 2012; Amaya & Schmidt et al., 2023; Amaya & Behrens et al., 2023). The joint amplification of hallucinations and distortions indicates that the effect is not strictly specific to hallucinations and can extend to other forms of aberrant experience when the methodology allows for these experiences to be examined. This convergence suggests overlapping state-based mechanisms underlying susceptibility to aberrant experiences across the perception-hallucination continuum, a position consistent with the hodotopic framework (Ffytche, 2008; Silverstein & Lai, 2021).

In audiovisual trials a selective form of cross-sensory enhancement was observed whereby hallucinations and irritation, but not distortions, were enhanced by the co-presentation of frequency modulated tones with reversed gratings at critical frequencies. This extends findings from Chapter 3 suggesting that aberrant experiences are subject to sensory cross-talk enhancements, whereby concurrent processes across multisensory domains can modulate the salience of aberrant perceptual experiences.

PG Group Differences

Interestingly there were no significant differences between PG Groups in the intensity of hallucinations, distortions, or irritation. At first glance this might suggest a limited role for group-level differences in state-based cortical hyperexcitability. However, this interpretation is overly simplistic. The critical reversal frequencies (10 and 15 Hz) enhanced hallucinations and distortions only in conjunction with the medium-frequency grating, which is established as the most provocative stimulus in pattern glare paradigms and consistently differentiates individuals high in state-based cortical hyperexcitability (Braithwaite, Mevorach & Takahashi, 2015; Braithwaite et al., 2015b; Evans & Stevenson, 2008; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022; Haigh et al., 2012; Harle & Evans, 2004; Huang et al., 2003; Wilkins, 1995). Accordingly, the absence of overall PG group differences should not be interpreted as evidence against state-based hyperexcitability, but rather as an indication that its influence emerges most clearly under conditions that maximally drive the visual system.

Consequently, these findings may reflect something of a ceiling effect on state-based excitability. Rhythmic phase reversals are highly potent, likely driving the visual cortex into a heightened excitability state beyond that induced by more traditional static pattern-glare gratings. In addition to the inherently irritating spatial frequency of the medium-frequency grating, the reversal rates used (10–15 Hz) fall within the range of visual flicker that have been associated with heightened functional connectivity within visual cortex and a decoupling of cortical activity from thalamic nuclei – patterns suggestive of aberrant gain control mechanisms (Amaya & Behrens, 2023; Amaya & Schmidt, 2023; Amaya et al., 2025; Bartossek, Kemmerer, & Schmidt, 2021; Billock & Tsou, 2012). Under these conditions, excitability may spread broadly across the visual cortex while inhibitory gain control mechanisms lose their capacity to constrain and filter neural activity.

For individuals typically lower in state-based hyperexcitability (lower gain state and low PG group), inhibitory processes would normally dampen excessive responses to visual stimuli. However, under reversed-grating conditions, thalamic decoupling may undermine this control, effectively ‘levelling’ responses between low and high-PG participants. This provides a plausible explanation for why individuals differing in baseline state-based excitability were not separable, at least in terms of state-based intensity of AVDs reported here.

4.2 Trait-based Factors

In visual only trials correlational analyses reinforced a fractionated view of cortical hyperexcitability (see Chapter 3, also Braithwaite et al., 2015; Fong, Takahashi & Braithwaite, 2019; Joshi et al., 2024 for similar findings). The intensity ratings for hallucinations and distortions, but not irritation, were significantly correlated with the Migrainesque Visual Aura Symptoms (MVAS) factor of the AVAS. This mirrors findings from Chapter 3 across both visual only and audiovisual trials, as well as previous findings with the CHi_II measure where only the subscale made up primarily of visual hallucinations was correlated positively with Pattern Glare intensity (Fong, Takahashi & Braithwaite, 2019) and is associated with the efficacy of brain-stimulation (Joshi et al., 2024). This further supports the notion that both the hallucinations and distortions reported in response to reversed Pattern Glare gratings, and the aberrant perceptual experiences measured by the MVAS factor, are likely cortically mediated. This also supports the hodotopic framework in suggesting some degree of overlap in trait-based factors mediating predisposition to both hallucinations and visual distortions.

It is a noteworthy finding that trait-based cortical hyperexcitability (AVAS) showed a reliable association with predisposition to state-based AVDs, but no significant differences were observed between individuals high and low in state-based cortical hyperexcitability (ΔAVD groups). This highlights the sensitivity of trait-based measures in capturing the broader range of latent factors underlying the concept of cortical hyperexcitability (Braithwaite et al., 2015; Fong et al., 2019). State-based measures such as AVDs reflect a select number of aberrant experiences in a given moment and therefore may not capture aberrant experiences as comprehensively as trait-based measures. Here examining state-based hyperexcitability with the AVD subscale may limit the sensitivity of the measure relative to the AVAS, particularly considering the breadth of additional '*AVDs*' reported by participants in this the present investigation (see free response section). However, for consistency with traditional PG, the use of the AVD subscale was essential in the present study, hence this does not represent a weakness of the present paradigm per se. Rather it highlights a strength of the AVAS with its sensitivity in capturing a broad range of aberrant experiences associated with cortical hyperexcitability over a longer period with both frequency and intensity scores.

Audiovisual trials revealed a more distributed pattern of trait-state associations. At 15Hz all three AVAS factors of heightened sensory sensitivity and discomfort (HSSD), predisposition to aura-like hallucinations (MVAS), and voice-hearing experiences (VHE), correlated significantly with the intensity of both hallucinations and distortions. This differs from the findings in Chapter 3 where cross-sensory enhancement was associated with the MVAS factor only, and suggests that more complex, dynamic audiovisual stimuli may recruit a broader set of trait-based predispositions.

A less straightforward finding was that distortions, which did not themselves show a statistically significant cross-sensory enhancement in audiovisual trials, nevertheless correlated with all three AVAS factors. This might suggest that distortion-related experiences may not form a unitary category but instead reflect a set of partially distinct neural processes. For example, motion-related distortions (e.g. floating) are thought to involve late visual cortex areas such as V5/MT (Beckers & Zeki, 1995; Lee et al., 2000) whereas contour-based distortions (e.g., illusory stripes, bending of lines, and shadowy shapes) are more closely associated with early visual cortex such as V1 (Lee et al., 1998; Lee et al., 2000). This raises the possibility of a functional division between distortions that are preferentially mediated more by later or earlier areas of the visual cortex, which may in turn determine their propensity for cross-sensory enhancement. As motion distortions were largely removed due to the addition of phase-reversals, the present methodology may not be sufficiently sensitive to reveal these cross-sensory effects across these subtypes.

4.3 Free Responses

Alongside pre-defined AVD rating, participants provided a range of free-response descriptions of a variety of aberrant perceptual experiences. These were predominately elementary / simple hallucinations, with occasional reports of complex hallucinations, and often included motion-like qualities (e.g., drifting, or undulating forms). This profile closely matches prior reports of photic flicker-induced hallucinations, where participants predominantly report Klüverian geometric hallucinations with dynamic qualities, alongside less common more complex imagery (Billock & Tsou, 2007; 2012; Shenyan et al., 2024). This demonstrates that the phase reversed Pattern Glare gratings used in the present study can indeed reliably elicit a broad range of hallucinatory experiences, providing a promising methodology for future neurocognitive examinations of both state-based and trait-based predispositions to aberrant perceptual experiences.

4.4 Theoretical Implications

Collectively the present findings support a continuum perspective on aberrant perceptual experiences, whereby symptoms of differing complexity emerge from overlapping but not identical neural mechanisms. This interpretation aligns with the hodotopic framework, which distinguishes between topological (localised) changes in neural activity and hodological (connectivity-based) aberrations as mechanisms underlying experiences of varying complexity (and at different points along the continuum: Ffytche, 2008; Silverstein & Lai, 2021). Importantly, the current findings extend this framework into the multisensory domain, by demonstrating that cross-sensory enhancements selectively amplifies aberrant visual experiences of varying complexity, even in neurotypical populations. This suggests that cross-sensory enhancement effects (observed in Chapter 3) may occur at multiple points along the perception-hallucination continuum, albeit potentially via distinct underlying mechanisms.

Crucially, the enhancement of hallucinations and distortions with phase-reversals was specific to the medium-frequency grating, long established as the most potent stimulus in pattern glare paradigms and reliably associated with elevated AVD reporting under conditions of cortical hyperexcitability (Braithwaite, Mevorach & Takahashi, 2015; Braithwaite et al., 2015b; Evans & Stevenson, 2008; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022; Haigh et al., 2012; Harle & Evans, 2004; Huang et al., 2003; Wilkins, 1995). In addition, the enhancement was specific to the two critical reversal frequencies, 10 and 15Hz, which prior photic-flicker studies have linked to aberrant activity in intermediate visual cortex (V2 – V5: (Ffytche, 2008; Billock & Tsou, 2012; Bartossek, Kemmerer, & Schmidt, 2021). By contrast, no significant increases were observed for the controls reversal rate (3Hz) or for the high-frequency grating, ruling out explanations based on generalised experimental factors such as arousal or perceptual load. Instead, these findings point to an increased salience that is cortically mediated and jointly influenced by both state-based factors (stimulus-driven excitability) and trait-based factors (MVAS).

Furthermore, the cross-sensory enhancement effect observed was restricted to the two critical reversal rates (10 and 15Hz) and was mediated by multiple trait-based factors of cortical hyperexcitability, suggesting that it reflects a cortically mediated mechanism of cross-sensory interaction. These findings are broadly consistent with the cross-modal correspondence framework (Driver & Spence, 1998; Spence & Driver, 2004; Spence, 2011) which proposes that input from one sensory modality can modulate perceptual processing in another when correspondences are established between them.

Two forms of correspondence are particularly relevant here. First, temporal congruence, in which the matched rates of visual reversal in the grating and frequency modulation in the tone, combined with their synchronous onset, promote cross modal binding. Second, a form of affective congruence may have contributed, where the irritating spatial frequency of the grating and the aversive carrier frequency of the tone may function as perceptually correspondent features, akin to synesthetic correspondences (see Chapter 3). Together, these mechanisms could underlie the selective cross-sensory enhancement effect.

Although a comprehensive neurobiological framework for cross-sensory correspondences (and enhancements) is still emerging, the present findings suggests that aberrant cross-sensory effects arise under conditions of elevated state-based cortical hyperexcitability and are further shaped by multiple trait-based predispositions. This pattern implicates underlying aberrations in cortical gain control, a mechanism that ordinarily regulates the neural representation of sensory information, but which can become compromised under conditions of neural instability (McColl & Wilkinson, 2000).

When considering the role of intermediate multisensory regions such as the temporoparietal junction (TPJ), its hodological connections with both early and late visual cortices (Wu et al., 2016) may help explain why distinct AVAS components correlated with cross-sensory enhancement. Different components could reflect sensitivity to different nodes in this network. This view is consistent with the cortical gain frameworks that emphasise gain as a non-unitary process, capable of being regulated at both local (circuit level) and global (neuromodulatory) scales (Aston-jones & Bloom, 1981; Ferguson & Cardin, 2020; Friston et al., 2012; Foote, Aston-jones & Bloom, 1980). The significant correlations of the separate AVAS factors with cross-sensory enhancement may therefore represent distinct contributions to the overall modulation of cortical gain.

Cortical Gain and the Hodotopic Framework

The present findings implicate aberrant cortical gain control processes in the generation of anomalous perceptual experiences. Cortical gain can be defined as the slope of neuronal input-output function, effectively operating as a dynamic filter that optimises the signal-to-noise ratio and calibrates the precision weighting of neural signals (Aston-Jones & Cohen, 2005; Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001). Under typical conditions, gain control enhances informative signals while suppressing irrelevant fluctuations. When gain control becomes aberrant - either excessively high or low - this balance collapses and both meaningful signals and noise may be amplified or suppressed indiscriminately (Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001). Cortical hyperexcitability represents one such state of compromised gain control, where elevated responsively pushes neural populations into unstable operating regimes, leading to degraded or unreliable perceptual representations (McColl & Wilkinson, 2000). In the present study, the selective effects at 10-15Hz reversal frequencies are consistent with this account, as these rates are potent at driving the visual cortex into high-gain states where excitability exceeds inhibitory control, thereby producing unstable perceptions.

The occurrence of hallucinations / distortions is known to relate to hyperexcitability in different localised areas of the visual cortex (Ffytche, 2008; Silverstein & Lai, 2021). In the case of low-complexity distortions this would occur as a localised shift to high-gain states in early areas of the visual cortex (V1), consistent with its role in edge and contour detection (Lee et al., 1998; Lee et al., 2000). Previous investigations of localised and connective factors underlying aberrant perceptual experiences may suggest this reflects an aberration in functional connectivity between pre-cortical and V1 (thalamocortical) networks, and localised aberrations of neural activity at V1 (Silvertsein & Lai, 2021). Here cortical gain processes would fail to effectively filter incoming sensory signals to optimise the signal-to-noise ratio, effectively amplifying both signal and noise, thus lowering the perceptual precision of incoming signals. These low-precision sensory signals in the visual cortex would result in a prediction error (and hence a perceptual aberration; Kanai et al., 2015; Powers, Mathys & Corlett, 2017). As V1 is typically associated with low-level visual processes such as edge detection (Lee et al., 1998; Lee et al., 2000), this ‘unfiltered’ visual signal might manifest as simple distortions of low-level features such as the bending of lines (and similar) in the AVDs reported.

For more complex aberrant perceptual experiences (e.g. hallucinations), shifts in cortical gain control would impact higher visual areas (V2 – V5; Ffytche, 2008) associated with processing visual features such as motion and colour (Beckers & Zeki, 1995; Lee et al., 2000). Here cortical gain processes would again fail to effectively filter signal and noise within incoming sensory signals, creating imprecise sensory signals. However, in later visual areas, poorly filtered sensory signals are more likely to carry low-precision signals in relation to higher-level perceptual features, which in turn manifest as hallucinatory perception of movement and colours, such as the kaleidoscopic AVDs reported.

Previous investigation of photic flicker-induced hallucinations suggests an association between these experiences and high-amplitude alpha oscillations in the late visual cortex (Amaya & Behrens et al., 2023; Amaya & Schmidt et al., 2023; Ffytche, 2008). Although electroencephalographic recordings were not obtained in the present investigation, this association between aberrations of alpha oscillations and the occurrence of aberrant visual experiences has been demonstrated repeatedly for flicker-induced hallucinations (e.g. Amaya et al., 2023; Bartossek, Kemmerer & Schmidt, 2021; Billock & Tsou, 2012; Amaya & Schmidt et al., 2023; Amaya & Behrens et al., 2023; Ffytche, 2008). Alpha oscillations are thought to modulate the excitatory–inhibitory balance of cortical networks, thereby shaping the gain control processes that determine the reliability of sensory signals. It is therefore important to consider how these alpha-band dynamics, likely engaged by 10-15Hz reversals, may have interacted with cortical gain control underlying aberrant perceptual experiences in the present investigation.

In the visual cortex, alpha oscillations are thought to represent cyclical periods of excitatory and inhibitory modulation of neuronal activity, providing a mechanism for gain control to gate sensory signals by modulating cortical excitability (Jensen & Mazaheri, 2010; van Diepen, Foxe & Mazaheri, 2019). Greater oscillatory amplitude reflects more synchronised firing of alpha-generating neurons, suggesting greater homogeneity in the extent to which these neurons facilitate or suppress neuronal representations of sensory information (van Diepen, Foxe & Mazaheri, 2019). Increased alpha power may therefore allow for more uniform action of gain control mechanisms in modulating the precision and salience of sensory representations in the visual cortex. However, under conditions of aberrant gain control, where cortical gain processes fail to optimise the signal-to noise-ratio, this can lead to the amplification of irrelevant noise, creating highly salient but low-precision sensory signals (Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001).

In summary, these findings suggest cortical gain control mechanisms modulate the precision and salience of sensory signals underlying aberrant perceptual experiences, consistent with the precision weighted predictive coding framework (Kanai et al., 2015). The hodotopic framework further suggests that subtle differences in localised and connective processes underlie perceptual aberrations of differing complexity (Ffytche, 2008; Silverstein & Lai, 2021). Accordingly, aberrations in gain control mechanisms may occur in earlier versus later visual cortex depending on the complexity of the aberrant perceptual experience. In addition, such aberrations are likely to vary in sympathy with oscillatory dynamics typically associated with flicker-induced perceptual aberrations, which are analogous to phase-reversals in the present paradigm. The present results would suggest that the MVAS factor of the AVAS measure is associated with a trait tendency for these aberrations in gain control mechanisms to occur across both earlier and later areas of the visual cortex.

Neural Mechanisms for Cross-sensory Enhancement

Crucially, cortical gain control is not a unitary mechanism but operates at multiple levels of neural organisation. At the local circuit level, excitatory-inhibitory interactions and normalisation dynamics regulate responsiveness within specific cortical areas (Ferguson & Cardin, 2020; Harris & Thiele, 2011; Li et al., 2020). At the same time it can be expressed in more global mechanisms, such as diffuse neuromodulatory systems (noradrenergic and dopaminergic pathways) that concurrently influence responsiveness across multiple sensory domains (Aston-jones & Bloom, 1981; Foote, Aston-jones & Bloom, 1980; Happel, 2016; Kroener et al., 2009; Sara, 2009), or through corticothalamic networks that coordinate activity across widespread sensory and multisensory cortical regions (Colonnese & Phillips, 2018; Hindriks & van Putten, 2013; Kostopoulos, 2001; Sherman, 2017). This multilevel organisation implies that in high-gain states, aberrant salience within one sensory modality may have concurrent effects on the salience of sensory signals in another sensory modality, amplifying perceptual instabilities more globally (see Chapter 3). As a result, the synaesthetic and / or temporal congruence in neural representations of auditory and visual signals may enact cross-sensory modulation of gain control mechanisms which underlie the cross-sensory enhancement effect observed.

In cross-sensory interactions, cortical gain may be implemented as a mechanism to resolve the 'binding problem', *i.e.* which sensory signals across differing domains should be integrated at any given time (for overview see Spence, 2011). The binding problem would typically be resolved through the extent of coherence of high-level statistical features across perceptual streams (Körding et al., 2007; Noppeney, 2021; Sato et al., 2007; Shams & Beierholm, 2010) – in this case the matched temporal features and corresponding irritating properties across visual and auditory streams, leading to a binding of highly salient sensory signals (even more so in the presence of hyperexcitability). Gain control acts to attenuate this neural response to preserve perceptual precision of auditory and visual streams (Kanai et al., 2015). However, in high-gain states (e.g. cortical hyperexcitability; McColl & Wilkinson, 2000) this attenuation is weakened. The result is an overly strong low-precision binding of auditory and visual streams in which the addition of the aversive tone amplifies the salience of the visual experience, producing the cross-sensory enhancement of AVDs.

Given the evidence that entrainment of alpha oscillations underlies hallucinations during photopic flicker, it may seem reasonable to attribute the present cross-sensory enhancement effects to a similar mechanism. However, the salience of flicker-induced visual hallucinations is typically maximal when stimulation entrains oscillations within the alpha band (8-13Hz; Amaya & Schmidt et al., 2023; Amaya & Behrens et al., 2023; Bartossek, Kemmerer & Schmidt, 2021; Billock & Tsou, 2012). Yet, in the present investigation sensory cross-talk was observed (and mediated by the same trait-based factors) for both 10 and 15 Hz reversals, with 15 Hz sitting outside the alpha frequency range, and is unlikely to entrain alpha directly.

Alternatively, the observed cross-sensory enhancement could be explained by multi-timescale dynamics in which multiple concurrent processes align intrinsic neural oscillatory activity across sensory domains (Senkowski & Engel, 2024). One candidate mechanism is cross-modal phase-resetting, where the presentation of a stimulus in one sensory domain realigns the phase of ongoing neural oscillations in another. This has been extensively demonstrated in audiovisual interactions (Kayser, Petkov & Logothetis, 2008; Mercier et al., 2013; Mercier et al., 2015; Senkowski et al., 2005; Thorne et al., 2011).

Crucially, phase resetting can occur across the full range of neural oscillations, not only within the alpha band. This makes it a plausible mechanism for cross-sensory enhancement at both 10 Hz and 15 Hz, even though only the former lies within the alpha range. By this account, the same oscillatory processes, and thus the same trait-based predispositions indexed by the AVAS, could mediate susceptibility to cross-sensory enhancement across both frequencies (Daume et al., 2021; Kuroki et al., 2018; Lakatos et al., 2007; Mercier et al., 2015; Senkowski et al., 2005).

Cross-sensory phase resetting is thought to modulate sensitivity of neurons within sensory cortices (Lakatos et al., 2005; Mercier et al., 2013). In the context of alpha activity linked to photic-flicker hallucinations, phase-resetting in the visual and auditory cortex could enhance responsiveness by shifting oscillations into the excitatory phase of their cycle, and away from the inhibitory phase (Busch, Dubois & van Rullen, 2009; Fiebelkorn et al., 2013;

Mathewson et al., 2009). This would align visual and auditory cortices in their excitatory phases, such that maximal salience is simultaneously assigned to auditory and visual signals. The result is a failure of selective cross-modal gain allocation, producing concurrent amplification of both modalities. This view is consistent with evidence that cross-modal gain modulation and temporal co-activation play central roles in shaping multisensory experience (Murray et al., 2016; Rohe & Noppeney, 2015; 2016; Welch & Warren, 1980).

After the initial alignment, temporal correspondence can be maintained through functional coupling, whereby the phase and amplitude of intrinsic oscillations in separate cortical regions become aligned, strengthening functional connectivity. This mechanism has been shown to underlie audiovisual integration (Cooke et al., 2019; Galindo-Leon et al., 2019; Ohki et al., 2016; Ohki et al., 2020). The crucial difference here from cross-sensory entrainment is that such coupling reflects perturbations of intrinsic neural activity in response to cross-sensory inputs rather than patterns of activity directly imposed by external stimulation (Engel et al., 2013). Consequently, both 10 Hz and 15 Hz reversals (and paired tones) could create an alignment of oscillatory activity, including within the alpha band that has been linked to flicker hallucinations in similar paradigms (Amaya & Behrens et al., 2023; Becker et al., 2009; Herrmann, 2001; Schwartzman et al., 2019). The repeated occurrence of highly salient signals, arising from localised high gain states, at regular intervals may explain why synaesthetic and / or temporal congruences are drawn between auditory and visual streams during sensory cross-talk (Spence & Driver, 2004; Spence, 2011). This again could maintain cross-modal gain modulation and temporal co-activation to support sensory cross-talk for the duration of the stimulus presentation (Murray et al., 2016; Rohe & Noppeney, 2015; 2016; Welch & Warren, 1980).

Whilst the present study cannot definitively distinguish between cross-sensory entrainment and multi-timescale dynamics as the mechanism underlying the observed cross-sensory enhancement, the latter provides a more parsimonious account of the effects across both 10 Hz and 15 Hz conditions. These possibilities pose fascinating questions for future research to address.

4.5 Limitations and Future Research

Whilst the present study did not directly measure oscillatory brain activity, the present findings mesh well with the broader literature examining cortical hyperexcitability in relation to both Pattern Glare (Braithwaite, Mevorach & Takahashi, 2015; Fong et al., 2020; Fong et al., 2022; Joshi et al., 2024; Jurkovičová et al., 2024) and photopic flicker hallucinations (Allefeld et al., 2011; Billock & Tsou, 2012; Ffytche, 2008) though now extended into the multisensory domain. In addition, the results relating to the trait-based AVAS questionnaire were also in line with previous examinations showing selective associations of trait-based factors with neuroimaging markers of cortical excitability as well as efficacy of neurostimulation (Fong et al., 2020; Joshi et al., 2024; Jurkovičová et al., 2024). Consequently, both the results attained from the computerised Pattern Glare reversal task and the associations with trait-based AVAS factors receive broader empirical support.

Regardless, it would be of interest to examine the relative contributions of state-based cortical hyperexcitability in earlier and later areas of the visual cortex to different categories of hallucinations and distortions in line with the hodotopic framework (Ffytche, 2008; Silvertsein & Lai, 2021). The present methodology would be ideally suited for this purpose in being able to measure both hallucinations and distortions simultaneously and introduces a method to examine these as part of a perception-hallucination continuum, whereas photopic flicker studies focus solely on hallucinations (Billock & Tsou, 2007; 2012). Previous investigations have used highly focal forms of neuroimaging to parse out contributions of separate areas of the visual cortex, such as fMRI or MEG (Moradi et al., 2003; Sharon et al., 2007). Using these methodologies concurrently with the Pattern Glare reversal task would allow for observation of the activation of separate areas of the visual cortex during the occurrence of hallucinations and distortions of differing complexity. Alternatively, focal forms of brain stimulation such as multichannel transcranial direct current stimulation (MtDCS) or transcranial magnetic stimulation (TMS) could be used to directly manipulate the level of excitability within separate areas of the visual cortex (McKeefry et al., 2009; Ruffini et al., 2018; Salminen-Vaparanta et al., 2012). Observing the effects of this focal stimulation on the occurrence of hallucinations and distortions of differing complexity may equally reveal the contributions of separate areas of the visual cortex to aberrant visual experiences as posed in the hodotopic framework.

In addition, the use of neuroimaging may definitively demonstrate either cross-sensory entrainment or multi-timescale dynamics as underlying mechanisms for the cross-modal enhancement effect observed. Both have distinct signatures in EEG recordings, with entrainment activity phase-locked to an inducer stimulus (e.g. reversed gratings), and phase resetting / alignment showing perturbations of ongoing endogenous neural activity (for summary see Engel et al., 2013; Senkowski & Engel, 2024). This investigation may be informative on the neural mechanisms underlying cross-sensory enhancement in aberrant experiences, as well as cross-modal correspondences more broadly (Spence & Driver, 2004; Spence, 2011). Specifically, this may inform how multisensory processing networks coordinate and bind sensory signals during multisensory aberrant experiences, and exactly which patterns of aberration in neural activity underlie the observed cross-sensory enhancement effect.

Finally, although the present investigation demonstrates a cross-sensory enhancement effect, it does not necessarily distinguish between relevant neural processes occurring locally within auditory / visual cortices, or across a more distributed network of modality-specific and multisensory cortical areas. The association of multiple AVAS factors with cross-sensory enhancement may suggest involvement from broader multisensory cortical areas, particularly given the significant association with the Voice-hearing Experiences (VHE) factor. Experiences of voice-hearing are associated with a state-based rise in excitability in areas of the cortex associated with multisensory integration such as the TPJ (Jardri et al., 2013; Silbersweig et al., 1995), as well as altered functional and structural connectivity of the TPJ with sensory and frontal cortical regions (Alderson-Day, McCarthy-Jones & Fernyhough, 2015; McCarthy-Jones et al., 2015; Vercammen et al., 2010a; Vercammen et al., 2010b). This may suggest a common involvement of hodological and / or topological aberrations surrounding the TPJ in both voice-hearing and sensory cross-talk. Future studies may wish to measure (via neuroimaging) or manipulate (visa neurostimulation) neural activity at the TPJ during the present paradigm to examine the involvement of broader cortical regions beyond the visual and auditory cortex in the cross-sensory enhancement effect observed. Such an investigation may help to establish a neurobiological explanation for sensory cross-talk and cross-modal correspondences more broadly (Spence & Driver, 2004; Spence, 2011).

4.6 Conclusion

The present study examined the selective enhancement of hallucinations, distortions, and visual irritation with irritating spatial and temporal properties in a novel phase reversal Pattern Glare paradigm. Hallucinations and distortions were selectively enhanced by 10 and 15 Hz phase reversals applied to a medium-frequency Pattern Glare grating. In addition, these experiences were examined for their selective propensity for cross-sensory enhancement by pairing visual reversed Pattern Glare gratings with frequency modulated auditory tones. This revealed selective enhancement of hallucinations and irritation in audiovisual trials, which again was specific to 10 and 15 Hz phase reversals, and was heightened in individuals who showed elevated trait-based susceptibility to aberrant perceptual experiences.

It was hypothesised that this cross-sensory enhancement likely reflects a failure or misallocation of cross-modal gain, leading to cross-sensory facilitation of visual neural signals, because aberrant gain control processes fail to optimise the signal-to-noise ratio by appropriately attenuating neural responses to the auditory stimulus. When exploring associations with trait-based cortical hyperexcitability, cross-sensory enhancement showed significant correlations with all three factors of the trait-based AVAS measure whereas previous work with static stimuli (see Chapter 3) revealed a selective association with the MVAS factor only. This further supports that the relationship between state-based and trait-based factors of predisposition to aberrant perceptual experiences is complex and dynamic, extending prior findings from both the visual (Braithwaite et al., 2015; Fong et al., 2019; Fong et al., 2020) and auditory (Kühn & Gallinat, 2012; Mo et al., 2024; Zmigrod et al., 2016) domains into multisensory contexts.

Together these findings suggest cross-sensory enhancement of aberrant visual experiences may be somewhat fractionated across the perception-hallucination continuum. This supports the hodotopic framework's suggestion of subtle differences in mechanism underlying a continuum of complexity (Ffytche, 2008; Silverstein & Lai, 2021), while extending these concepts into multisensory domains. Findings are discussed in terms of the integration of cross-modal correspondence (Spence & Driver, 2004; Spence 2011), cortical gain control (Aston-Jones & Cohen, 2005; Ferguson & Cardin, 2020), and precision-weighted predictive coding (Kanai et al., 2015) as complementary explanatory frameworks for the observed cross-sensory enhancement effect.

Chapter 5

Theta Burst Stimulation of the Left Temporoparietal Junction Modulates Sensory Cross-talk in the Context of Aberrant Perceptual Experiences

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Abstract

The Temporoparietal Junction (TPJ) has been suggested as a crucial hub for cross-sensory integration processes underlying the occurrence of aberrant multisensory experiences. The present investigation aimed to examine this hypothesis using Theta Burst Stimulation (TBS), a subthreshold form of non-invasive brain stimulation. Participants completed the multisensory Pattern Glare test; a test of aberrant cross-modal integration whereby anomalous visual experiences elicited by irritating visual gratings (AVDs) are enhanced by concurrent presentation of an irritating auditory tone. This was completed both before and after stimulation on two occasions: once with excitatory intermittent TBS (iTBS), and once with inhibitory continuous TBS (cTBS). Participants also completed a trait-based measure of cortical hyperexcitability, the Audiovisual Aberration Scale (AVAS). Prior to stimulation, AVDs were enhanced by co-presentation of an irritating auditory stimulus, replicating the cross-sensory enhancement effect. After iTBS a decoupling effect was observed, whereby AVDs in the irritating cross-sensory condition were no longer significantly different from the visual-only (grating-only) condition. No significant effects of cTBS were observed. The magnitude of this decoupling effect with iTBS was found to vary in sympathy with both state-based and trait-based indications of cortical hyperexcitability. The observed relationship with cortical hyperexcitability supports a cortically mediated mechanism for both cross-sensory enhancement and the subsequent decoupling effect, with the TPJ as a key hub underlying aberrant integration processes. Findings are discussed in terms of a synthesis between cortical gain control mechanisms and the cross-modal correspondence framework for sensory cross-talk. A hodotopic account of the interplay between state-based and trait-based mechanisms is also considered.

Introduction

1.1 Cortical Hyperexcitability

The occurrence of anomalous perceptual experiences (*e.g.* hallucinations, distortions, sensory irritation) is frequently associated aberrant patterns of increased electrophysiological activity in the cerebral cortex, collectively termed cortical hyperexcitability (Braithwaite et al., 2013a; Braithwaite et al., 2013b; Braithwaite, Mevorach & Takahashi, 2015; Ffytche, 2008; Jardri et al., 2016; Kompus et al., 2013). Increasingly, cortical hyperexcitability is fractionated into: i) state-based hyperexcitability reflecting the current electrophysiological state of the cortex and ii) trait-based hyperexcitability reflecting a latent background predisposition to aberrant perceptual experiences over time (Braithwaite et al., 2015; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Joshi et al., 2024; see also Chapter 2, Chapter 3 & Chapter 4).

Investigations of associations between state-based and trait-based factors of predisposition to aberrant perceptual experiences paint a fractionated picture of these two components. In auditory and visual hallucination research, state-based factors typically reflect localised perturbations of neural activity in sensory cortical regions (Abraham & Duffy, 2001; Bressloff et al., 2002; Ffytche, 2008; Kühn & Gallinat, 2012; Mo et al., 2024; Zmigrod et al., 2016), whilst trait-based factors typically reflect broader perturbations in largely non-sensory cortical regions and aberrations in cortico-cortical and cortico-subcortical connectivity (Collerton, Dudley & Mosimann, 2011; Erskine et al., 2019; Ford et al., 2015; van Ommen et al., 2023). As such, examining both state and trait-based factors of predisposition to aberrant perceptual experiences in tandem, and their associations, is essential to comprehensively understanding the neurocognitive basis of aberrant perceptual experiences.

1.2 Cortical Gain and Precision-weighted Predictive Coding

One explanatory framework for the association between cortical hyperexcitability and aberrant perceptions is through cortical gain control, a neural gating process that modulates the amplitude of neural responses according to stimulus salience (Aston-Jones & Cohen, 2005; Carandini & Heeger, 2012; Cardin, Palmer & Contreras, 2008; Chance, Abbott & Reyes, 2002; Kremkow, Aertsen & Kumar, 2010). Conceptually, cortical gain states may be defined by the slope of a neuronal input-output function, typically modelled as a non-linear function such as a sigmoidal function. In high gain states this slope would be steep with rapid increases in neural firing rate with relatively little change in neuronal input, whilst in low gain states this slope would be shallow with relatively little change in neural firing rate for a given neuronal input (Carandini & Heeger, 2012; Ferguson & Cardin, 2020). Cortical gain control typically functions to optimise the signal-to-noise ratio of neuronal responses by suppressing irrelevant signals and facilitating salient / relevant signals (Carandini & Heeger, 1997; Carandini & Heeger, 2012; Ferguson & Cardin, 2020; Vogels & Abbott, 2009).

However, under conditions of aberrant neuronal activity (*e.g.* cortical hyperexcitability), cortical gain control processes may be compromised (McColl & Wilkinson, 2000; Porciatti et al., 2000; Tsai et al., 2011). Here gain control processes may fail to suppress irrelevant background signals or stabilise highly salient neuronal responses, creating conditions of ‘perceptual uncertainty’ – where neuronal representations of perceptual information become decoupled from sensory inputs and hence become highly unreliable (Hillyard, Vogel & Luck, 1998; Hénaff et al., 2020; Scolari & Serences, 2009; Woolley et al., 2005). As these neuronal signals do not faithfully represent veridical sensory information, the likelihood of distortions, misperceptions, and anomalous perceptual experiences increases.

Cortical gain has also been incorporated into the predictive coding framework, which seeks to explain anomalous perceptual experiences as emerging through aberrations in a Bayesian process of active inference for constructing perceptual representations (Corlett, Frith & Fletcher, 2009; Corlett et al., 2019; Friston, 2005; Powers, Kelley & Corlett, 2017; Powers, Mathys & Corlett, 2017; Rao & Ballard, 1999). Predictive coding would argue that perceptual representations are shaped by both incoming sensory information and prior expectations around external events (or '*priors*'), where a mismatch between sensory information and priors occurs this creates increased '*prediction error*' (Powers, Kelley & Corlett, 2016; Powers, Kelley & Corlett, 2017; Powers, Mathys & Corlett, 2017). The salience of a prediction error is weighted, via cortical gain control mechanisms, dependent on the relative precision associated with priors and sensory information (Barrett & Simmons, 2015; Bastos et al., 2012; Feldman & Friston, 2010; Kanai et al., 2015). When sensory signals are highly uncertain or excessively noisy (*i.e.* under conditions of cortical hyperexcitability) and prediction errors are weighted as highly salient, priors dominate incoming sensory information in shaping perceptual representations, creating greater predisposition to non-veridical (*i.e.* aberrant) sensory information (Kanai et al., 2015; Millidge, Seth & Buckley, 2021; Powers, Mathys & Corlett, 2017).

As such, precision-weighted predictive coding provides a neurocognitive explanatory framework for the occurrence of aberrant perceptual experiences. Under conditions of hyperexcitability cortical gain control processes are perturbed, resulting in noisy / lower precision sensory signals and hence an overweighting of prediction error. These overweighted prediction errors subsequently reflect a bias towards priors in constructing perceptual representations from limited noisy sensory signals. This combination of noisy sensory input and overly strong priors creates susceptibility to perceptual aberrations. Therefore, a state-dependent cortical instability may underlie this susceptibility to perceptual aberration in a given moment, whilst trait-based susceptibility to cortical hyperexcitability may reflect a susceptibility to perceptual aberration over time.

1.3 Multisensory Aberrant Experiences

Across various clinical and neurotypical populations, several studies have shown that most individuals who report the occurrence of aberrant perceptual experiences report these symptoms across multiple perceptual domains (Dudley et al., 2018; Dudley et al., 2023a; Dudley et al., 2023b; Li et al., 2024; Toh et al., 2020; Toh et al., 2024; Rogers et al., 2023). Such findings support the idea that cortical hyperexcitability, as a concept, may not be confined to a particular unitary sensory domain (e.g., just vision: Welch et al., 1990; Schoenen, 1996). From a precision-weighted predictive coding perspective, this may predict that a prediction error in one sensory domain could indeed have consequences for perceptual processing in another perceptual domain, resulting in a form of 'sensory cross-talk', or aberrant cross-modal correspondence (Parise & Spence, 2008; 2009; Spence & Driver, 2004; Spence, 2011; Walker, Walker & Francis, 2012; 2015; Walker et al., 2010; Walker, 2012; see Chapters 3 & 4).

Cross-modal correspondences refer to occurrences of sensory input in one modality which modulate perceptual processing in another, this is thought to occur through failures in resolving the 'binding problem' where neural processes determine which sensory signals should be integrated at a given moment (Spence & Driver, 2004; Spence, 2011). Consequently, aberrations in binding processes could be seen as a form of cross-sensory prediction error, where typically high-level statistical features of stimuli (e.g., temporal, spatial, phonetic, or semantic features) may guide the binding process at the neural level (Körding et al., 2007; Noppeney, 2021; Sato et al., 2007; Shams & Beierholm, 2010). These processes may be compromised in high-gain states, as the perceptual precision of these critical signals are compromised with insufficient gating of neural 'noise' (Balz et al., 2016; Hoshino, 2014; Ishiyama et al., 2016). Therefore, co-occurring sensory signals in different sensory domains may lead to an over binding of sensory information, and hence an aberrant form of elevated sensory cross-talk, in high-gain states (see cross-sensory enhancement effect in Chapters 3 & 4). This over-binding may lead to a weakening or interference between sources of sensory information (Spence, Pavani & Driver, 2004; Spence, Ranson & Driver, 2000), or equally a cross-sensory enhancement or boosting of sensory information (see Chapters 3 & 4), dependent on the context of cross-modal correspondence.

1.4 Examining Sensory Cross-talk

Behavioural Approaches

One behavioural example of a cross-sensory enhancement is the sound-induced flash illusion (SIFI), where the presentation of two brief auditory tones in quick succession paired with a single visual flash stimulus can lead to the illusory perception of a second visual flash (Shams, Kamitani & Shimojo, 2000; 2002). However, there are several limitations to the SIFI as a model for understanding aberrant multisensory experiences. First, SIFI restricts phenomenological aspects of aberrant multisensory experiences down to a highly simplistic visual flash; reports of aberrant multisensory experiences vary extensively (for overview see Dudley et al., 2023; Toh et al., 2020; Toh et al., 2024), and it is unclear how representative SIFI is of more phenomenologically rich aberrant experiences.

In addition, SIFI has been criticised for examining decision-making rather than perceptual processes, which has been demonstrated by priming participants to expect more or fewer flashes, or monetarily rewarding participants for correct responses, which can modulate the degree of illusion experienced (Rosenthal, Shimojo & Shams, 2009; Wang et al., 2019). These factors may explain why some individuals with heightened predisposition to aberrant multisensory experiences, such as in migraine-with-aura, do not show heightened susceptibility to SIFI (Brighina et al., 2014; Brighina et al., 2015; Maccora et al., 2019; Maccora et al., 2020), as the SIFI may reflect limited neurocognitive overlap with processes underlying aberrant multisensory experiences.

To address these methodological concerns, two novel paradigms for examining aberrant cross-sensory enhancement were devised in Chapters 3 and 4. Each extended the visual Pattern Glare (PG) task, which has been used extensively to demonstrate an association between the occurrence of aberrant visual experiences and both state-based and trait-based cortical hyperexcitability (Braithwaite, Mevorach & Takahashi, 2015; Braithwaite et al., 2015; Evans & Stevenson, 2008; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022; Haigh et al., 2012; Harle & Evans, 2004; Huang et al., 2003; O'Hare & Hibbard, 2011; Wilkins, 1995). PG tasks use static square-wave gratings of different spatial frequencies, some of which are known to be irritating and overwhelm visual neurons, resulting in elementary visual distortions, hallucinations, and increased visual sensitivity and irritation / visual discomfort, collectively termed Pattern Glare (Braithwaite et al., 2013a; Braithwaite et al., 2013b; Evans & Stevenson, 2008; Wilkins, 1995). These grating patterns consist of: i) a low frequency baseline grating at 0.5 cycles-per-degree (cpd) of visual angle, ii) the crucial highly irritating medium-frequency grating at 3 cpd, and iii) a high-frequency baseline grating at 14 cpd. For each grating the degree of Pattern Glare is measured by the Associated Visual Distortions (AVDs) questionnaire, where participants rate the intensity of predefined Pattern Glare experiences on a scale of 0 ('Not at all') to 6 ('Extremely intense') (for similar approach see Braithwaite et al., 2013a; Braithwaite et al., 2013b; Braithwaite, Mevorach & Takahashi, 2015; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022).

In Chapter 3 these gratings were presented in concert with irritating and non-irritating auditory pure tones, finding a selective and significant enhancement of AVDs where visual gratings were paired with irritating auditory pure tones. In Chapter 4 rhythmic phase reversals were added to the visual gratings (somewhat akin to photic flicker studies; see Billock & Tsou, 2007; 2012) at irritating and non-irritating temporal frequencies to induce additional visual hallucinations, and these reversed gratings were paired with frequency-modulated tones to create temporally matched audiovisual stimuli. Here a selective enhancement of AVDs at irritating reversal rates, and with irritating tones, was shown again demonstrating a cross-sensory enhancement effect. Crucially, across both methodologies the extent of sensory cross-talk varied in sympathy with signs of elevated state-based and / or trait-based cortical hyperexcitability.

Both these PG developments provide important new evidence for the occurrence of a cross-sensory enhancement effect underlying aberrant perceptual experiences associated with cortical hyperexcitability. In addition, the presence and role of cortical hyperexcitability suggests underlying cortical gain control mechanisms, commensurate with the precision-weighted predictive coding framework. Cortical gain control provides a tentative explanatory framework for why sensory cross-talk may be elevated in individuals with heightened predisposition to aberrant perceptual experiences. Therefore, taking these methodologies forward under the cortical gain control framework presents a logical direction for establishing a neurobiological framework for the occurrence of aberrant multisensory experiences.

Neural Approaches

A number of neuroimaging investigations have been conducted examining the neural underpinnings of multisensory hallucinations, and how these differ from unisensory hallucinations (for review see Fernyhough, 2019; Montagnese et al., 2021). Generally, findings suggest a network-level dysfunction between sensory cortices and intermediate multisensory regions (often referred to as ‘hubs’) may underpin multisensory hallucinations (Fernyhough, 2019; Montagnese et al., 2021).

A handful of functional magnetic resonance imaging (fMRI) investigations have compared neural activity between individuals experiencing unisensory and multisensory hallucinations both at resting-state (trait-based) and during hallucinations (state-based). Whilst the occurrence of both unisensory and multisensory hallucinations is associated with heightened activity in relevant sensory cortices, multisensory hallucinations are additionally associated with heightened activity at the temporoparietal junction (TPJ) and anterior insular cortex, both forming structures within the default mode network (DMN, see discussion below; Jardri et al., 2013; Silbersweig et al., 1995). However, resting-state imaging suggests that relative to unisensory hallucinators, multisensory hallucinators show aberrations in functional connectivity between the TPJ and other hubs of the DMN, as well as subcortical structures including the hippocampal complex and amygdala (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015). Collectively, these studies suggest that aberrant localised hyperexcitability at the TPJ may be associated with state-based predisposition to multisensory hallucinations, whilst aberrant functional connectivity within a network of cortical and subcortical areas, including the TPJ, may be associated with trait-based biases and predisposition to multisensory hallucinations.

Such findings could be seen as generally in line with the Dysconnection hypothesis, which states that aberrant interactions (and connectivity) between brain regions is an underlying pathophysiological factor predisposing individuals to aberrant experiences (Friston, 1998; Friston, 1999; Friston et al., 2016; Stephan, Baldeweg & Friston, 2006; Stephan, Friston & Frith, 2009). More specifically, the division between localised state-based processes and broader connective trait-based processes may support a multisensory extension of the hodotopic framework (Ffytche, 2008; Silverstein & Lai, 2021).

Broadly, the hodotopic framework states that in the visual domain, the hallucination state arises through *topological* (or localised ‘within-system’) abnormalities in neural activity, whilst the hallucination trait itself reflects *hodological* (connectivity ‘between-system’) abnormalities (Ffytche et al., 1998; Catani & Ffytche, 2005; Ffytche, 2008). In the multisensory context, state-based within-system aberrations may be reflected in a localised multisensory circuit comprising of the constituent sensory cortices and TPJ (Jardri et al., 2013; Silbersweig et al., 1995). However, trait-based between-system aberrations may manifest more broadly within the DMN and subcortical structures (Amad et al., 2014; Rolland et al., 2015), with the TPJ forming a crucial junction between state-based and trait-based systems.

In addition, both localised and network-level aberrations would be seen as consistent with cortical gain control as an explanatory framework, which emphasises gain as a non-unitary process, capable of being regulated at both local (circuit level) and global (neuromodulatory) scales (Aston-jones & Bloom, 1981; Ferguson & Cardin, 2020; Friston et al., 2012; Foote, Aston-jones & Bloom, 1980). Irregularities in localised cortical gain control within the TPJ likely reflect aberrations in excitatory-inhibitory interactions which typically act to normalise neuronal responsiveness (Ferguson & Cardin, 2020; Harris & Thiele, 2011; Li et al., 2020). However, aberrations at a more global level may be expressed through diffuse neuromodulatory pathways (noradrenergic / dopaminergic; Aston-jones & Bloom, 1981; Foote, Aston-jones & Bloom, 1980; Happel, 2016; Kroener et al., 2009; Sara, 2009) or multisensory corticothalamic pathways (Colonnese & Phillips, 2018; Hindriks & van Putten, 2013; Kostopoulos, 2001; Sherman, 2017).

1.5 The Temporoparietal Junction (TPJ) in Sensory Cross-talk

The TPJ forms part of the default mode network (DMN), a higher-order neurocognitive system associated with several complex processes which support conscious perceptual experience such as awareness, or the conscious processing of internal and external stimuli (Fernández-Espejo et al., 2012; Raichle, 2015). Within the DMN, the TPJ is implicated in '*functional integration*' - the process by which neural systems associated with both bottom-up sensory processing and top-down higher order processes, are co-ordinated (Hagmann et al., 2008; Raichle, 2015; van den Heuvel & Sporns, 2011). From a precision-weighted predictive coding perspective, this may suggest the TPJ has a crucial role in the precision-weighting process by integrating incoming multisensory information and priors so that the degree of cross-sensory prediction can be determined (Hoemann & Feldman-Barrett, 2019; Rockland & Graves, 2023; Seghier, 2013; 2022).

Exactly how cross-sensory prediction error is determined awaits clarification; however, one possibility is that precise information around the timing of sensory signals is coalesced across sensory modalities at the TPJ to determine cross-modal coherence of sensory information (Davis, Christe & Rorder, 2009; Spierer, Bernasconi & Grievel, 2009). In animal models, increases in cortical gain have been shown to vary in sympathy with the synchronicity of cross-sensory neuronal inputs; that is, the closer together two cross-sensory signals converge to a singular point of neuronal input, the greater the resulting increase in localised cortical gain (Meredith, Nemitz & Stein, 1987; Meredith & Stein, 1986; Wallace & Stevenson, 2014). In humans, fMRI investigations have demonstrated that in cross-sensory audiovisual tasks requiring highly precise temporal information (such as simultaneity judgements), an increased BOLD (blood-oxygen level dependent) response occurs at the TPJ (Binder, 2015; Love et al., 2018). This elevated BOLD response is thought to correspond to the formation of a bound audiovisual signal from two component unisensory signals (Binder, 2015). This may suggest that the TPJ serves the function of a neuronal temporal binding window, defining the period within which two sensory signals must co-occur (*i.e.* arrive at the TPJ) in order to be bound together (Powers, Hevey & Wallace, 2012; Zmigrod & Zmigrod, 2015). Where two signals are bound together, gain increases at the TPJ to increase the weighting, or perceptual precision, of the bound signal.

The TPJ may be uniquely suited for this precision-weighting process in cases of cross-sensory audiovisual signals given its extensive anatomical connections to both auditory (Cammoun et al., 2015; Petit et al., 2023; Wu et al., 2016; Yakar et al., 2023) and visual cortices (Niu & Palomero-Gallagher, 2023; Uddin et al., 2010; Wu et al., 2016). This would suggest that the TPJ receives both auditory and visual inputs, which must themselves be integrated via precision-weighting mechanisms for comparison against priors, and hence the gain state of the TPJ may partially determine the extent to which auditory and visual signals are bound together. Therefore, the neurophysiological properties of the TPJ make it a clear candidate for investigating how modulation of cortical gain processes may affect sensory cross-talk.

Previous investigations have sought to examine the role of the TPJ in sensory cross-talk using the SIFI, demonstrating that inhibitory repetitive transcranial magnetic stimulation (rTMS) applied to the right angular gyrus, has been shown to reduce susceptibility to the SIFI (Hamilton et al., 2013; Kamke et al., 2012). In targeting the right TPJ these findings may reflect a misallocation of early cross-modal attention processes rather than a disruption of the binding mechanism itself (Seghier et al., 2023). Rather targeting the left TPJ with its role as a binding hub in multisensory hallucinations (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015; Silbersweig et al., 1995) may provide insight on the neurocognitive factors underlying aberrant cross-sensory binding.

Overview of the Current Study

The present study examined the role of the left TPJ (a binding hub) in both state-based and trait-based predisposition to cross-sensory enhancement of aberrant perceptual experiences in a neurotypical sample. In Chapter 3 the multisensory Pattern Glare test was developed by pairing Pattern Glare gratings with irritating and non-irritating auditory tones. This revealed a new selective cross-sensory enhancement effect, where AVD ratings increased with the addition of irritating auditory tones. Crucially, the elevated cross-sensory enhancement showed a significant association with elevated signs of state-based and trait-based cortical hyperexcitability, mirroring previous findings demonstrating a positive association between predisposition to aberrant perceptual and both state-based and trait-based cortical hyperexcitability (*e.g.* Braithwaite, Mevorach & Takahashi, 2015; Fong, Braithwaite & Takahashi, 2019; Fong et al., 2020).

The present study extended the examination of the enhancement effect, and its underlying mechanisms by investigating how alterations of cortical hyperexcitability at the left TPJ may mediate sensory cross-talk. The rationale was that if this ‘coupling’ effect observed between auditory and visual sensory signals was mediated by cortical hyperexcitability / cortical gain processes, then exogenously altering cortical hyperexcitability should subsequently mediate the degree of coupling observed. Given the neuroimaging evidence for the role of the TPJ in both state-based and trait-based predisposition to aberrant multisensory experiences (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015; Silbersweig et al., 1995), it was predicted that this region would likely be implicated in the coupling of auditory and visual signals, and therefore altering excitability at the TPJ may mediate this coupling. More specifically, it was predicted that increasing excitability would increase the degree of cross-sensory enhancement, and conversely that decreasing excitability would decrease the degree of cross-sensory enhancement.

The potential role of the left TPJ was assessed by applying two forms of Theta Burst Stimulation (TBS: a high frequency form of repetitive TMS), to the left angular gyrus across two separate experimental sessions. The two selected forms of Theta Burst stimulation were as follows: i) intermittent theta burst stimulation (iTBS) which typically exerts excitatory effects on neuronal activity, and ii) continuous theta burst stimulation (cTBS) which typically exerts inhibitory effects on neuronal activity (Huang et al., 2005).

This matched design, directly comparing effects of excitatory and inhibitory stimulation against each other, was selected due to concerns over an appropriate sham condition for the present investigation. Typically, investigators may compare each individual protocol against task performance to a sham location, where TBS is applied to serve as a baseline for comparison due the sham location's functional irrelevance to the task or behaviour examined (Parkin, Ekhtiari & Walsh, 2015). Typically, this would be the vertex, however recent evidence suggests TBS applied to the vertex can induce behaviourally-relevant changes in electrophysiological activity, calling into question its suitability as a control site for TBS (Pizem et al., 2022). More specifically to the present investigation, TBS protocols applied to the vertex and TPJ have been shown to induce similar changes in functional connectivity (Machner et al., 2021). The vertex could not therefore be determined as an appropriate control site. Instead, by directly comparing between excitatory and inhibitory conditions, specificity of the direction of the effect (*i.e.* that cross-sensory enhancement is not enhanced or suppressed equally by both excitatory and inhibitory stimulation) could be determined, thus accounting for generalised experimental factors (*e.g.* changes in overall arousal, attentional distraction, or perceptual load) as explanations for any observed effect.

In altering the degree of neuronal excitability, these two TBS protocols may provide crucial insight into how cortical gain control processes at the TPJ modulate cross-sensory enhancement. Failures of selective gain allocation, leading to amplification (or up-weighting) of all sensory signals regardless of modality or salience, is a core signature of sensory systems operating in a high-gain state (Hillyard, Vogel & Luck, 1998; Le Masson et al., 2002; Scolari & Serences, 2009; Woolley et al., 2005). Therefore, when applied to multisensory Pattern Glare, heightening neuronal excitability at the left TPJ may exacerbate aberrant cortical gain processes which erroneously enhance irrelevant input from the auditory domain during integration with visual signals, leading to an additional increase in the cross-sensory enhancement effect.[19]

Conversely, suppressing neuronal excitability at the left TPJ with inhibitory cTBS may restrict these aberrant gain control processes, thus inhibiting / suppressing the erroneous enhancement of auditory signals and their over-binding into the visual domain and impairing the cross-sensory enhancement effect. This would support the notion that the state-based occurrence of aberrant multisensory experiences is associated with a heightened degree of neurophysiological activity at the TPJ (Jardri et al., 2013; Silbersweig et al., 1995).

To examine this, participants completed the multisensory Pattern Glare task (see Chapter 3) at ‘baseline’ (pre-stimulation) and after receiving TBS (post-stimulation) for each protocol, therefore completing both pre-stimulation and post-stimulation testing for iTBS and cTBS separately. The use of multisensory Pattern Glare provides a mixture of visual-only and cross-sensory enhanced (in multisensory trials; see Chapter 3) AVDs, therefore comparing

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[19] Although theoretically heightened cortical excitability could reflect a ‘ceiling effect’ where excitability cannot be increased further, this was mitigated in the present study with the use of neurotypical participants. Chapter 3 demonstrated an enhancement of AVDs via sensory cross-talk in Migraineurs, who typically display elevated cortical hyperexcitability relative to neurotypical individuals (Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Fong et al., 2022). Therefore, these participants should have ‘room’ to demonstrate increased responses.

pre-stimulation and post-stimulation AVDs can establish whether effects of TBS protocols are specific to multisensory trials, thus directly testing the role of the left TPJ in this cross-sensory binding mechanism. Where effects are specific to audiovisual trials, which have previously demonstrated a cross-sensory enhancement effect, this would strongly suggest the consequences of TBS protocols on AVDs are due to a disruption of an aberrant cross-sensory binding mechanism.

To further determine the specificity of the effects of TBS to this coupling / binding mechanism, the present study examined whether modulation via TBS was associated with trait-based and state-based cortical hyperexcitability. In visual-only Pattern Glare, Braithwaite, Mevorach and Takahashi (2015) demonstrated that an elevated trait-predisposition to aberrant perceptual experiences was significantly associated with an increase in intensity of AVDS after excitatory transcranial direct current stimulation (tDCS) over the visual cortex. Given both visual-only and multisensory Pattern Glare have been shown to relate to similar trait-based and state-based factors (Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; see Chapters 3 &4), it was predicted here that modulation of cross-sensory enhancement via TBS in the present investigation would be mediated by predisposition to aberrant perceptual experiences.

To examine trait-based cortical hyperexcitability participants completed the Audiovisual Aberration Scale (AVAS: see Chapter 2). The AVAS is a proxy measure of trait-based cortical hyperexcitability across auditory and visual domains, building on the visual-only equivalent, the Cortical Hyperexcitability Index II (CHi_II; Braithwaite et al., 2015; Fong et al., 2019: See Chapter 2). The AVAS can be devolved into distinct factors of aberrant experiences, namely: (i) Heightened Sensory Sensitivity and Discomfort (HSSD), (ii) Migrainesque Visual Aura Symptoms (MVAS), and (iii) Voice Hearing Experiences (VHE).

As the occurrence of multisensory hallucinations is associated with cortical hyperexcitability at the TPJ (Jardri et al., 2013; Silbersweig et al., 1995), it was predicted that excitatory iTBS would selectively enhance the intensity of AVDs for specific sensory cross-talk conditions (medium-frequency visual grating, 4 kHz auditory tone). Conversely, it was predicted that inhibitory cTBS would selectively attenuate the intensity of AVDs for these same stimuli associated with sensory cross-talk. In addition, it was also predicted that a significant relationship between ΔAVD score and changes in AVD score from pre-stimulation to post-stimulation trials would be observed. Finally, given previous associations between facilitation of AVDs via brain stimulation and predisposition to aberrant perceptual experiences (Braithwaite, Mevorach & Takahashi, 2015), it was predicted that selective factors of the AVAS measure would show correlations with changes in AVD score from pre-stimulation to post-stimulation trials.

Methods

2.1 Participants

Thirty-eight participants (52.63% Female, 47.37% Male) aged 18 - 38 (*M* = 21.89, *SD* = 4.30) were recruited via Lancaster University's SONA recruitment system. Participants were compensated with a £50 voucher. All participants had normal or corrected-to-normal visual acuity (minimum 20/25), and clinically normal hearing confirmed by a Pure Tone Hearing Threshold test following the procedure outlined by the British Society of Audiology (BSA, 2018). All participants provided informed consent prior to commencement of any data collection.

Participants completed a pre-screen form before each experimental session to confirm their eligibility in-line with ethical requirements for the Pattern Glare paradigm itself, and for general requirements of receiving TMS. Participants were deemed ineligible to receive TMS on account of: i) any history of psychological or neurological conditions, ii) pacemakers or any fitted / implanted metal or medical devices, iii) any personal or close family history of epilepsy or seizures of unknown origin, iv) individuals who are pregnant / unsure if they are pregnant, v) use of medication which alters seizure threshold. In addition, participants were required to refrain from consuming any alcohol, caffeine, undeclared medications, or recreational drugs up to 24 hours prior to stimulation, and were required to sleep within +/- 2 hours of their typical duration the night before an experimental session. Those who were not deemed eligible were excluded from the study prior to data collection. Participants were deemed ineligible on account of Pattern Glare with any neurological or psychological conditions which may affect perception and / or response tendencies in this study, including: vi) epilepsy or seizures, vii) tinnitus, hearing loss, sight loss, or optical conditions (astigmatism, colour blindness etc.), viii) neurological or psychological condition, ix) having previously undergone neurosurgery (including eye or ear surgery).

2.2 Theta-Burst Stimulation (TBS)

To create a mirrored design with both excitatory and inhibitory stimulation conditions, sub-threshold Theta Burst Stimulation (TBS) protocols were selected for the present study. TBS is a form of repetitive TMS which broadly consists of high-frequency (50 Hz) stimulation delivered in bursts of triplets (3 pulses) with an inter-burst interval at 5 Hz, with variations which have been shown to alter the direction of stimulation effects on neuronal excitation (Huang et al., 2005).

In addition, TBS protocols are typically applied at a scaled intensity relative to each participant's active or resting motor threshold. For the present study, TBS protocols were delivered at 70% of participants' individual RMTs which were acquired at the beginning of each experimental session (Chen et al., 1998). As such, sessions consisted of two phases of TMS stimulation: i) RMT acquisition, and ii) TBS protocol delivery.

2.2.1 Resting Motor Threshold Acquisition

RMTs were acquired using a BF70 figure-of-eight coil (diameter 70mm) connected to a monophasic DuoMAG single-pulse stimulator unit (Deymed Diagnostic, Czech Republic). The coil was oriented tangential to the skull at a 45° angle to achieve poster-anterior flow of the magnetic current, thus maximising the amplitude and input / output curve steepness for resulting motor-evoked potentials (Sommer et al., 2006; Sommer & Paulus, 2008). This posterior-anterior flow produces largest amplitude MEPs for monophasic stimulators (Brasil-Neto et al., 1992; Stephani, Paulus & Sommer, 2016) and is therefore the most conservative estimate of an individual's RMT. Participants wore sound-attenuating ear plugs during this procedure in adherence to guidelines surrounding hearing safety concerns during TMS exposure (Rossi et al., 2009; Tringali et al., 2012). Coordinates and coil locations and orientations were saved during sessions using Brainsight Neuronavigation software (Rogue Research Inc., Montreal, Canada). Pulses were delivered at a low intensity, initially 40% of maximum output, where an MEP could not be established at 40% this was increased stepwise in jumps of 2% up to a maximum of 50% of maximum output. Where an MEP could not be established at ≤ 50% of maximum output participants were excluded due to safety guidelines surrounding the risk of seizure in TMS (Rossi et al., 2009).

RMTs were acquired from the first dorsal interosseous muscle of the participant's right hand, thus TMS was targeted to the left primary motor area. Localisation for the right hand area was achieved using a variation of the hotspot method (Möttönen et al., 2014). Single pulses were delivered in incremental movements (approx. 5mm) from the vertex towards the left preauricular point, leaving gaps of 5-10 seconds between pulses to allow neuronal depolarisation to return to baseline. Pulses were delivered until a contraction of the first dorsal interosseus muscle (indicated by twitch of right index finger) coinciding with an MEP (from live electromyography, EMG) was observed. Location and orientation of coil were then recorded in Brainsight and used as a reference point from which to move the coil incrementally (approx. 5mm steps) around to examine whether a more optimal location can be achieved (indicated by larger MEP amplitude). If a more optimal location was achieved, location and orientation of coil were recorded in Brainsight as a reference point and location optimisation was repeated until the optimal location was determined. The location was recorded in experimental session one and used as a starting point from which location optimisation could be repeated in experimental session 2 rather than starting from the vertex.

Once the location was determined, the participant's RMT was determined by gradually altering the intensity of stimulation until the lowest possible intensity consistently evoking an MEP could be established (Möttönen et al., 2014). This was defined as the lowest intensity at which a detectable (by EMG) MEP was evoked on 5 out of 10 pulses. Initially intensity was reduced stepwise in 1% increments until an MEP was no longer detectable (two pulses per increment, 10 seconds between pulses). Intensity was then increased by an increment of 1%, and up to 10 pulses were delivered (10 seconds between pulses) to establish whether MEPs could be detected from 5 out of 10 pulses. If this was not achieved, the procedure was repeated with stepwise increases of 1% stimulation intensity until MEPs were detected from 5 out of 10 pulses.

2.2.2 Theta Burst Stimulation Protocol Delivery

TBS was delivered using the same BF70 figure-of-eight coil connected to a biphasic DuoMAG XT-100 repetitive stimulator unit (Deymed Diagnostic, Czech Republic). The centre of the coil was held tangentially to the skull at a 90° angle. Participants wore customised sound-attenuating ultra-shielded insert earphones (ER-2; Intelligent Hearing Systems, FL) in adherence to guidelines surrounding hearing safety concerns during TBS exposure (Rossi et al., 2009; Schraven et al., 2013). TBS was applied to the left angular gyrus (l-AG); this was defined by an MNI co-ordinate of [-44, -65, 36] based on an average co-ordinate from a recent review paper of TMS studies targeting the left angular gyrus (Wagner & Rusconi, 2023). Co-ordinates were stored in Brainsight Neuronavigation software (Rogue Research Inc., Montreal, Canada) and applied to the MNI152 average structural MRI template (Fonov et al., 2009; Fonov et al., 2011) for target localisation. The centre of the coil was held over this point as indicated by Brainsight Neuronavigation whilst the experimenter positioned the coil as described, and coil location and orientation were stored.

Participants received iTBS (excitatory stimulation) and cTBS (inhibitory stimulation) across separate sessions; a summary of the key differences between protocols selected for the present study is presented in Table 1. Both protocols consisted of 600 pulses of 50 Hz stimulation delivered in bursts of triplets with a 5 Hz inter-burst interval, delivered at 70% of the participant's RMT. For iTBS these were delivered in 2 second trains of triplets delivered every 10 seconds (8 second inter-train interval) for a duration of approximately 190 seconds. For cTBS these were delivered as one continuous train for a duration of approximately 40 seconds. A visual representation of the two pulse trains is presented in Figure 1. Peak modulatory effects for both of these protocols on neuronal excitability have been found between 5 – 30 minutes post stimulation (for review see Chung et al., 2016). Participants were randomly assigned to receive either cTBS or iTBS first prior to their first session, then received the alternate form of stimulation in their second session. Participants' second sessions took place between 7 and 14 days after their first session, providing a minimum wash out period of 7 days between the two protocols.

Table 1.

TBS Protocol Differences

TBS Type	Neuronal effects	Train duration (s)	Inter-train interval (s)	Total Duration (s)
iTBS	Excitatory	2	8	190
cTBS	Inhibitory	40	N/A	40

Neuronal effects reflect typical effects of these protocols on neuronal excitability (see Huang et al., 2005).

Figure 1.

Pulse Train Structures of iTBS and cTBS

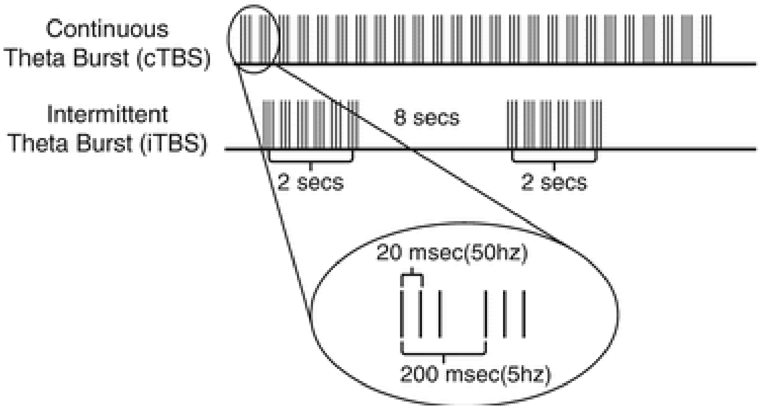

Figure adapted from the Florida TMS Clinic (2025)

2.3 Materials

2.3.1 Multisensory Pattern Glare

Participants were presented with square wave grating stimuli, some of which are visually irritating and hence capable of eliciting aberrant visual experiences (see Figure 2 for examples). There is a low-frequency baseline grating (0.5 cycles-per-degree: cpd), the crucial medium-frequency (3 cpd) grating, and a baseline high-frequency (14 cpd)[20] grating. In the current study, on the majority of trials the presentation of the gratings was combined with the presentation of auditory pure tones at a non-irritating (0.5 kHz) or irritating (4 kHz) auditory frequencies. The co-presentation of the medium-frequency grating with a high-frequency tone has previously demonstrated a cross-sensory enhancement effect on reported aberrant

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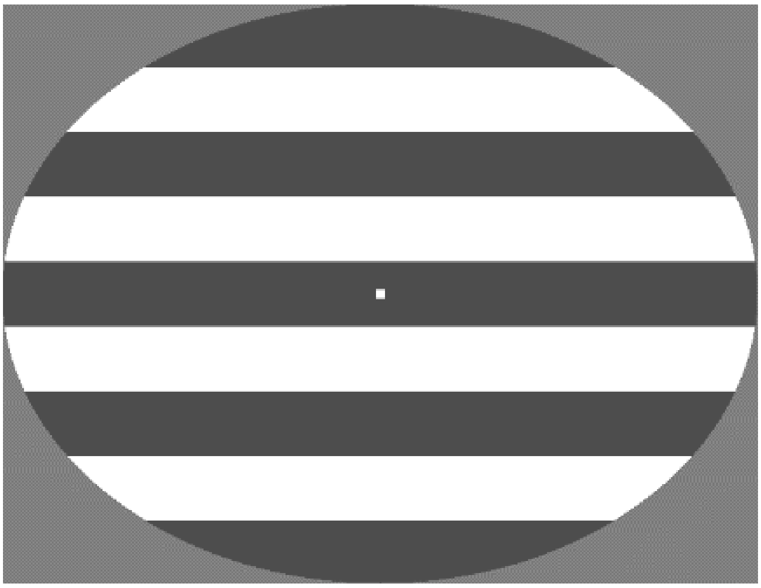
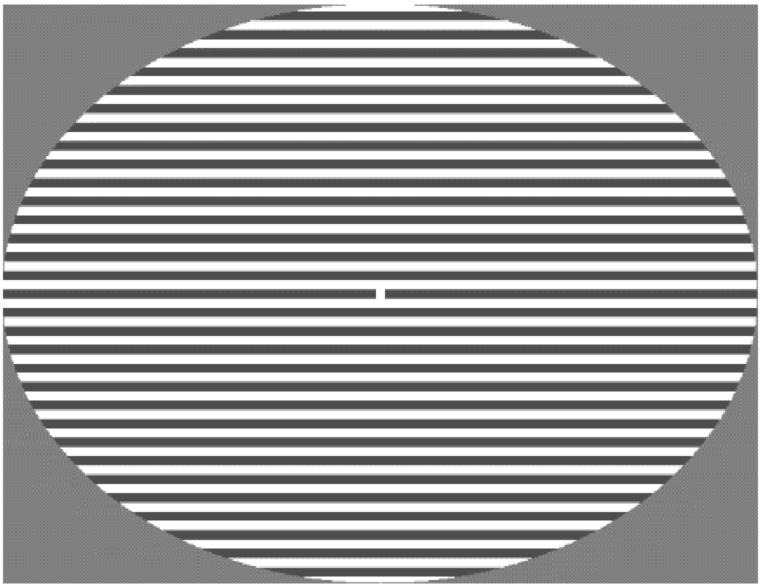
[20] Note, in pattern-glare tasks the baseline gratings should not be thought of as being devoid of potential visual effects, more so that the degree of effects experienced are far greater for the medium-frequency grating which likely reflect the involvement of more central cortical processes.

visual experiences (see Chapter 3). Collectively, this created a mixture of typical visual-only (baseline), and audiovisual trials.

Figure 2.

Examples of Low and Medium Frequency Visual Grating Stimuli.





Illustrations of the low-frequency (top) baseline grating and the crucial medium-frequency (bottom) irritative grating. The high-frequency grating is not shown here as it cannot be shown faithfully due to the high spatial frequency which suffers aliasing when rescaled, thus image is not demonstrative of experimental stimulus. Note: The exact cycles-per-degree may vary here due to the rescaling of image here.

The experiment was conducted in a dimly lit sound-attenuating booth. The task took approximately twenty-five minutes to complete. Visual and auditory stimuli were created with custom code in MATLAB and presented in Psychopy. All visual stimuli had Michelson contrast set to 0.75 cd/m^2 and mean luminance across the three stimuli was 40 cd/m^2. Grating patterns were presented as an ellipse (height × width = 154mm × 198mm) of black and white horizontal lines on a dark grey background (luminance 20 cd/m^2). Gratings were presented at eye-level on a 27” Iiyama G-MASTERGB2788HS-B1 monitor (1920 × 1080 resolution, max. 144 Hz refresh rate). Participants were fixed in place on an office chair at an 80cm viewing distance which was maintained with a chinrest so as not to obscure the exact cycles per degree of stimuli by changing the visual angle (11.0 × 14.1 degrees). Auditory stimuli were presented through Sennheiser HD650 impedance-matched cabled headphones. All tones were presented at a fixed volume of 60 dB SPL as verified with a Brüel & Kjær Type 4153 Artificial Ear.

The intensity of elicited aberrant experiences is measured through a series of Associated Visual Distortions (AVDs) Likert-scale responses (see Appendix C). Here, participants are presented with a list of 16 aberrant visual experiences typically associated with PG and asked to rate the intensity of each aberrant experience from 0 (‘Not at all’) - 6 (‘Extremely intense’), giving an AVD score out of 96 per trial. A mean overall AVD score is calculated across several stimulus presentations. Each trial began with a four second blank inter-stimulus interval, followed by a twelve second presentation of a given visual or audiovisual stimulus. After twelve seconds, participants responded to the AVD items.

Crucially, despite the inclusion of the auditory stimuli, the AVD scale asked participants to rate their visual experiences only. That is to say, all AVD questions were focused on the perceptual effects of the visual PG grating, and not the auditory tones. Participants were explicitly instructed that the auditory stimuli were incidental, and that they were not rating the tones, and to solely rate their experiences in relation to perceived effects from the presentation of the visual gratings.

Individuals who scored exceptionally highly in the Pattern Glare test (‘extreme responders’) were identified prior to analyses. In line with previous investigations of the Pattern Glare Test (e.g. Fong et al., 2019), the upper limit for ‘typical’ scoring on the low-frequency grating was defined by the 95th percentile, and participants scoring above this benchmark were excluded from all analyses as this is often taken to imply a potentially confounding response bias.

2.3.2 State-dependency Pre-task

State-based differences in the excitability of neuronal tissue at the time of stimulation are known to influence the efficacy of TMS (Silvanto et al., 2007; Silvanto & Pascual-Leone, 2008; Silvanto, Muggleton & Walsh, 2008). One way to combat this variation is to selectively increase the susceptibility of target brain regions to neural stimulation via adaptation or priming of the neurons to a particular state of neural excitation during stimulation (Silvanto & Cattaneo, 2014; Silvanto & Cattaneo, 2017; Hartwigsen & Silvanto, 2023). Evidence suggests that exciting neurons of the target brain region can optimise the uptake of stimulation in the desired target region (Karabanov et al., 2015; Bergmann et al., 2016; Bergmann, 2018; Bradley et al., 2022). For this purpose, an audiovisual pre-task which emulates the audiovisual conditions of multisensory PG was designed, intending to engage the left angular gyrus during the delivery of TBS protocols with slightly different stimuli than the main task to avoid habituation to the critical stimuli.

The visual stimulus was a non-irritating black and white checkerboard (0.5 cpd vertically and horizontally). Grating specifications and viewing conditions were matched to visual stimuli in the main PG task. Auditory stimuli were non-irritating pure tones at frequencies below tones used in the main PG task (250 Hz, 375 Hz). Both auditory and visual stimuli were created using custom code in MATLAB. Auditory presentation specifications were matched to the main PG task, and volume levels for pre-task tones were also verified with a Brüel & Kjær Type 4153 Artificial Ear. All trials were audiovisual, using the same checkerboard stimulus in combinations with either pre-task tone (250 Hz, 375 Hz). This created two stimulus combinations in the pre-task which were presented in a randomised order in Neurobehavioural Systems Presentation. The AVD scale was not presented during the pre-task to maximise time exposed to audiovisual stimulation and thus (potentially) maximise the uptake of stimulation in the left Angular Gyrus during stimulation. Pre-task duration was specific to the TBS session; 190 seconds for iTBS, and 40 seconds for cTBS.

2.3.3 Audiovisual Aberration Scale (AVAS)

The Audiovisual Aberration Scale (AVAS) is a recently devised 35-item proxy measure of trait-based cortical hyperexcitability in the auditory and visual domains (see Chapter 2), building on the foundations of the visual-only Cortical Hyperexcitability Index (CHi_II; Braithwaite et al., 2015; Fong et al., 2019). The AVAS examines the frequency and intensity of aberrant visual and auditory experiences, the occurrence of which is thought to reflect an elevated degree of background cortical excitability (i.e. trait hyperexcitability). An Exploratory Factor Analysis conducted with Parallel Analysis revealed an underlying three-factor structure, with each factor measuring a distinct category of perceptual experience and demonstrating excellent internal reliability, suggesting questions within each factor represent a unified facet of trait-based cortical hyperexcitability. These three factors are as follows; i) Heightened Sensory Sensitivity and Discomfort (HSSD), ii) Migrainesque Visual Aura

Symptoms (MVAS), and iii) Voice Hearing Experiences (VHE). The AVAS presents a series of brief statements referring to a relevant perceptual experience, and participants respond on two 0 – 6 Likert scales to indicate the relative frequency (0 = Not at all, 6 = All the time) and intensity (0 = Not at all, 6 = Extremely intense) of each experience, giving a total score /12 for each item and /420 for the overall measure. The factor structure of the AVAS means that it can be examined in terms of separate subcomponents which make up trait-based cortical hyperexcitability as an overall concept.

2.4 Procedure

Participants completed the AVAS questionnaire and TMS safety form online prior to the first testing session, then repeated the TMS safety form at the beginning of each session. First, participants received verbal instructions from the experimenter about the multisensory PG task. They were instructed to keep their chin on the chinrest and keep their eyes fixed on the screen throughout the experiment. They were then given time to familiarise themselves with the definitions of AVDs before completing four practise trials of multisensory PG. After successfully completing four practise trials, participants completed the full multisensory PG task prior to any stimulation (pre-stimulation). A ten-minute comfort break was then implemented before commencing with the TBS portion of the experiment.

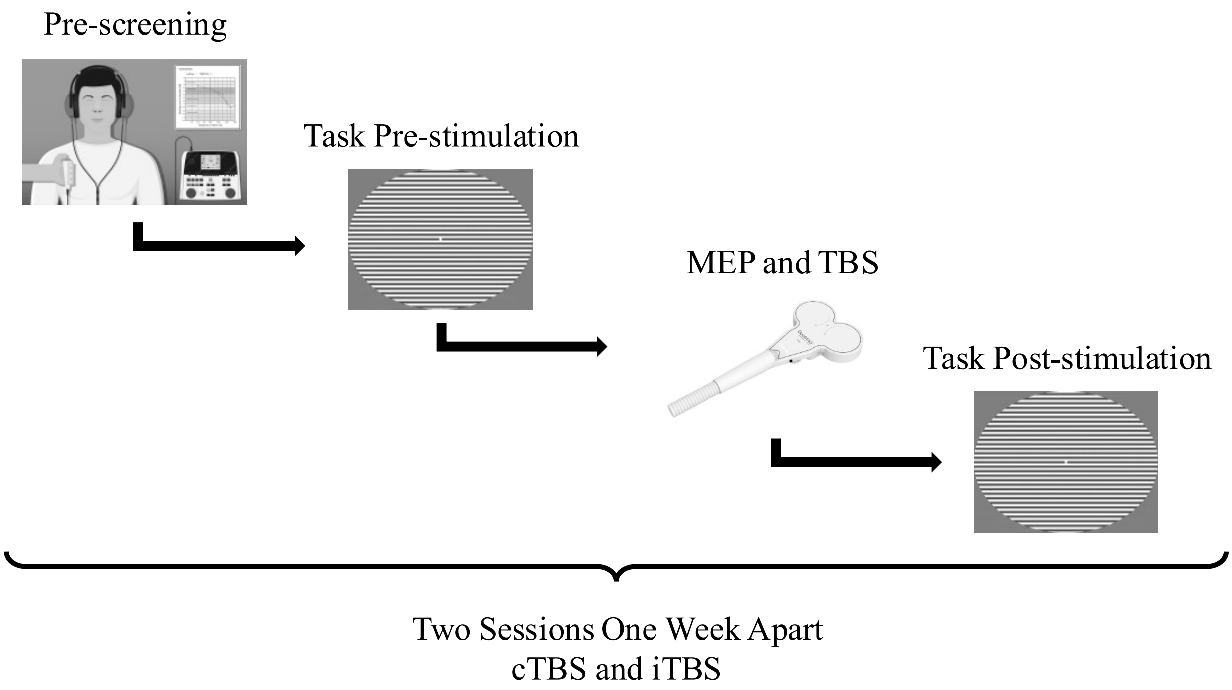
Following baseline testing, participants were familiarised with single-pulse TMS prior to collecting MEPs. This involved applying single pulses of TMS to the experimenter’s hand, the participant’s hand, and the participant’s head (at vertex). At each location pulses were applied at 30% and 50% of maximum output, and participants were given the opportunity to withdraw if they did not feel comfortable continuing after TMS familiarisation. Following this, participants were prepped for EMG by cleaning the skin with an alcohol wipe and applying adhesive electrodes to the participants right hand following manufacturer guidelines for acquiring MEPs from the first dorsal interosseus muscle. MEPs were then acquired following the adapted hotspot procedure outlined above. After acquisition of the MEP the EMG kit was removed, and participants took a short comfort break prior to receiving TBS.

Before commencing with TBS, participants went through a familiarisation procedure with a short train (1x 2 second train) of TBS. The train was applied to the experimenter's hand and the participant's hand at the intensity used for stimulation (70% of participant's RMT). Again, participants were given the opportunity to withdraw at this point if they did not feel comfortable continuing after TBS familiarisation. Participants were then seated 80cm from the screen, the coil was held over the left angular gyrus guided by Brainsight Neuronavigation and TBS was delivered for the appropriate duration dependent on TBS type whilst the participant passively engaged with the pre-task.

After TBS participants were instructed to wait five minutes before recommencing the multisensory PG task. Participants then completed the task again post-stimulation following the same procedure, and again the duration of the task was approximately 25 minutes. After completing the procedure in session two, participants were thoroughly debriefed. A visual summary of the experimental procedure is presented in Figure 3.

Figure 3.

Visual Summary of Experimental Procedure



Note –state-dependency pre-task occurred during delivery of the TBS protocol.

2.5 Analysis

Analysis consisted of analysis of variance (ANOVA) models, Pearson's r correlations, and linear regression models. ANOVAs were chosen to first assess the propensity of specific combinations of PG gratings and tones to elicit AVDs, thus examining whether the cross-sensory enhancement effect (Chapter 3) was replicated in pre-stimulation trials.

Following this, ANOVAs were selected to assess the effects of iTBS and cTBS on AVDs elicited by specific combinations of PG gratings and tones. For each condition (grating-tone combination), a stimulation difference score was created by subtracting pre-stimulation score from post-stimulation score ($\Delta TBS = AVD_{post\text{-}stimulation} - AVD_{pre\text{-}stimulation}$).

For each combination this was calculated for both iTBS and cTBS, allowing for comparison between the two types of stimulation. ANOVAs were then calculated for each grating separately, examining the effects of each TBS protocol on AVDs in each auditory condition (no tone, 0.5 kHz, 4 kHz).

Correlations were then selected to examine whether state-based cortical hyperexcitability could predict the effects of TBS protocols (ΔTBS score). Here ΔAVD score was calculated as a measure of state-based cortical hyperexcitability; AVD score in response to the high frequency grating was subtracted from AVD score in response to the medium frequency grating ($\Delta AVD = AVD_{\text{medium-frequency}} - AVD_{\text{high-frequency}}$) in the no tone condition. This creates a baseline-corrected delta score which is more conservative than analysing AVD scores in the medium frequency alone (Evans & Stevenson, 2008: see also Braithwaite et al., 2013 for a similar approach). ΔAVD score was therefore implemented as a (trait-based) predictor of ΔTBS score.

Finally, correlations were also selected to examine whether trait-based cortical hyperexcitability was associated with the extent of effects of TBS protocols (ΔTBS score). AVAS scores were broken down into the three factors of: i) Heightened Sensory Sensitivity and Discomfort (HSSD), ii) Migrainesque Visual Aura Symptoms (MVAS), iii) Voice Hearing Experiences (VHE). Each represents a distinct, but related facet of trait-based cortical hyperexcitability. AVAS factor scores were correlated with ΔTBS score to examine the relationship between the two.

Where multiple related comparisons were conducted, the False Discovery Rate (FDR; Benjamini & Hochberg, 1995) was applied. This was intended both to correct for inflated type I error rates and to assess the relative strength of the relationships between each AVAS factor and Pattern Glare. FDR assigns a new critical value (B&H) to each comparison by ranking each *p*-value in ascending order, then applying the equation B&H = (i/k) * Q, where i is the original rank, k is the number of comparisons, and Q is the relevant threshold of significance (here .05). The highest ranked significant *p* value where $p <$ B&H is deemed significant, along with all comparisons ranked below where $p <$ B&H. Where a comparison is deemed statistically significant but $p >$ B&H, that comparison and all subsequent comparisons would be deemed not statistically significant upon adjustment.

Bayesian analyses estimate a Bayes Factor (BF_{10}) value which makes a comparison of whether the data are more in favour of the null or alternative hypothesis. Bayes factors were interpreted in line with Jeffreys' theory of probability (Jeffreys, 1998; see also, Lee & Wagenmakers, 2014). As such, $BF_{10} < 1.0$ would be taken as indicating the probability of the data being in favour of the null hypothesis, and $BF_{10} > 1.0$ taken as indicating the probability of the data being in favour of the alternative hypothesis. Values closer to zero are deemed stronger evidence for the null hypothesis (e.g., 0.01 – 0.10 considered very strong, 0.10 – 0.33 considered substantial) and larger values above 3 are deemed stronger evidence for the alternative hypothesis (3 – 10 considered substantial, 10 – 100 considered strong / very strong, and > 100 considered decisive). Values between 0.33 – 3 are considered insensitive or anecdotal evidence for either hypothesis. These values can additionally be interpreted in terms of a numerical likelihood; for example, a BF_{10} of 10 suggests the data fit 10 times better with the alternative hypothesis than the null hypothesis. Equally, a BF_{10} of 0.1 suggests the data fit 10 times better with the null hypothesis than the alternative hypothesis. For all Bayesian analyses, the Cauchy prior value was set to the default conservative value of 0.707 (Wagenmakers et al., 2018).

Results

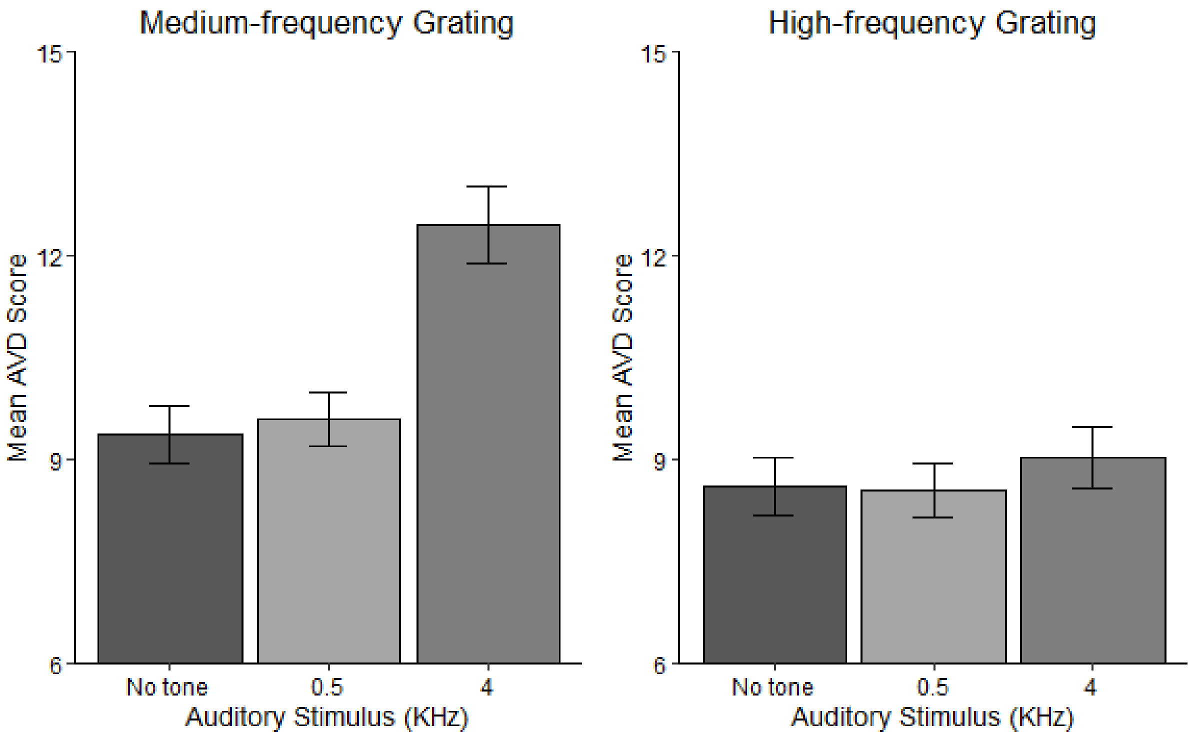
Initial outlier identification was conducted by determining the 95th percentile value for mean AVD score in the low frequency (0.5 cycles-per-degree) condition within the static Pattern Glare gratings pre-stimulation, which was determined as 4.54. Two participants' mean scores in the control condition exceeded this value, and hence their responses were omitted from all analyses. This left a final sample of 36 participants (52.78% Female, 47.22% Male) aged 18 – 38 (*M* = 22.00, *SD* = 4.38).

3.1 Pre-stimulation Multisensory Pattern Glare

Responses from pre-stimulation experimental blocks across the two sessions were pooled, and mean AVD scores for each visual-only and audiovisual stimulus combination were calculated. Descriptive statistics are presented in Figure 4.

Figure 4.

Descriptive Statistics for AVDs in Pre-stimulation Trials



To examine the presence of cross-sensory enhancement in pre-stimulation trials, a 3 (Auditory Stimulus (kHz), within-participants; no tone, 0.5, 4) × 2 (Visual Frequency, within-participants; medium, high) ANOVA with interaction term was calculated with AVD Score as the outcome variable. The model revealed significant main effects of Auditory Stimulus ($F(2, 1722) = 9.51$, $\eta_p^2 = 0.011$, $p < .001$, $BF_{10} = 63.02$) and Visual Stimulus ($F(1, 1722) = 22.37$, $\eta_p^2 = 0.013$, $p < .001$, $BF_{10} > 1000$), as well as a significant interaction between Auditory Stimulus and Visual Stimulus ($F(2, 1722) = 5.29$, $\eta_p^2 = 0.006$, $p = .005$, $BF_{10} > 1000$).

This interaction was explored further with Tukey's HSD, used to examine for which combinations of visual gratings and auditory tones participants reported the most intense AVDs. A summary of these results is presented in Table 2. For the medium-frequency grating, significantly more intense AVDs were reported when paired with the 4 kHz tone in comparison to both the 0.5 kHz tone and the no tone condition. There was however no significant difference between the 0.5 kHz tone and no tone condition for the medium-frequency grating. For the high-frequency grating, there was no difference between the 4 kHz, 0.5 kHz, or no tone conditions.

Table 2.

Tukey's HSD for Interaction of Auditory and Visual Stimulus on AVDs, Pre-stimulation

Grating Type	Auditory Tones	Difference	- 95 CI	+ 95 CI	*p*
Medium-frequency	4 kHz – No tone	3.09	1.26	4.91	< .001***
	4 kHz – 0.5 kHz	2.86	1.03	4.68	< .001***
	0.5 kHz – No tone	0.23	- 1.60	2.05	.999
High-frequency	4 kHz – 0.5 kHz	0.47	- 1.35	2.29	.978
	4 kHz – No tone	0.41	- 1.41	2.23	.988
	No tone – 0.5 kHz	0.06	- 1.76	1.88	.999

* Denotes significance - *** = $p < .001$.

These results demonstrate a selective effect of an irritating auditory tone (4 kHz) enhancing AVDs in combination with an irritating medium-frequency visual grating only. This replicates the cross-sensory enhancement effect (see Chapter 3 & 4) and supports the assumption that the current sample did indeed show reliable biases on these measures.

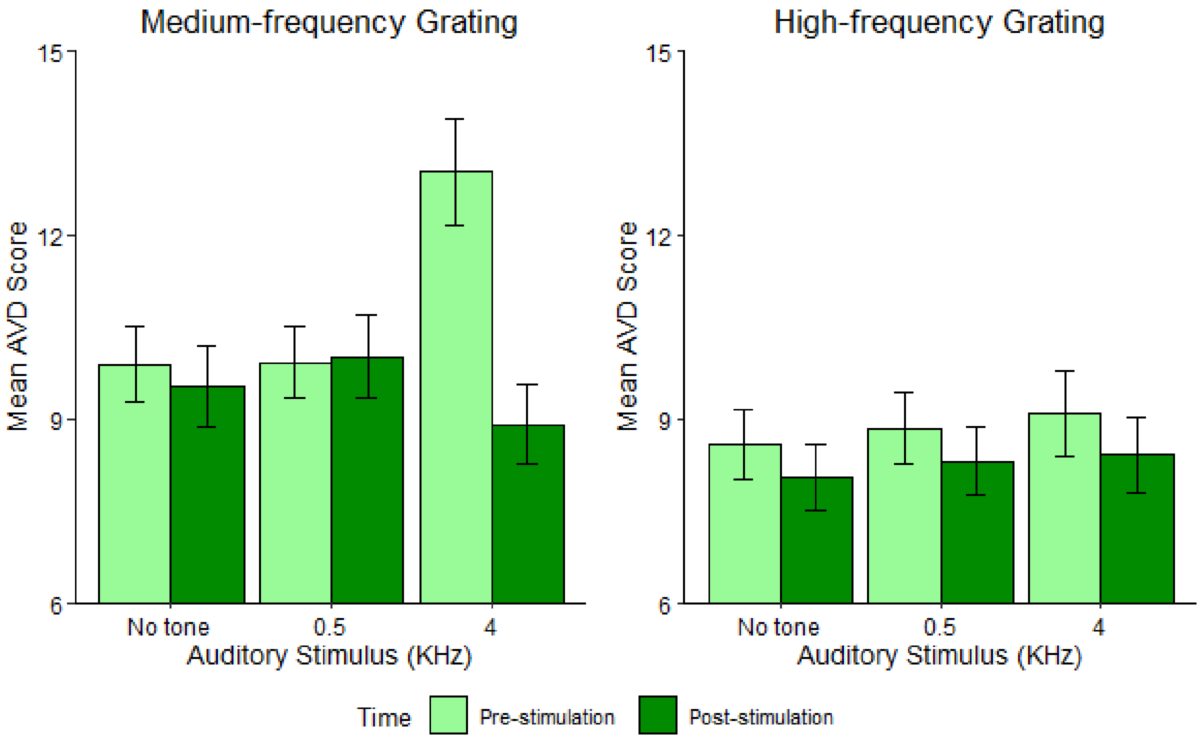
3.2 Theta Burst Stimulation (TBS) Effects

Intermittent Theta Burst Stimulation (iTBS)

Descriptive statistics for pre-stimulation and post-stimulation AVD scores in iTBS sessions are presented in Figure 5.

Figure 5.

Descriptive Statistics for AVDs Pre-stimulation and Post-stimulation, iTBS



Medium-frequency Grating. To examine the effects of iTBS on AVDs for the medium-frequency grating, a 3 (Auditory Stimulus (kHz), within-participants; no tone, 0.5, 4) × 2 (Time, within-participants; pre-stimulation, post-stimulation) ANOVA with interaction term was calculated with AVD score as the outcome variable. This revealed a significant main effect of Time ($F(1, 858) = 6.84$, $\eta_p^2 = 0.008$, $p = .009$, $BF_{10} = 2.08$), as well as a significant interaction between Time and Auditory Stimulus ($F(2, 858) = 5.66$, $\eta_p^2 = 0.013$, $p = .004$, $BF_{10} = 0.83$). There was no significant main effect of Auditory Stimulus ($F(2, 858) = 1.90$, $\eta_p^2 = 0.004$, $p = .151$, $BF_{10} = 0.08$).

This interaction was explored further with Tukey's HSD to examine for which co-presented auditory stimuli AVD scores differed between pre-stimulation and post-stimulation trials. A summary of these results is presented in Table 3. When the medium-frequency grating was paired with a 4 kHz tone, participants reported significantly less intense AVDs post-stimulation compared to pre-stimulation. When the medium-frequency grating was presented alone in no tone trials or paired with a 0.5 kHz tone, there was no significant difference in the intensity of AVDs between pre-stimulation and post-stimulation trials.

Table 3.

Tukey's HSD for AVD Score Pre-stimulation and Post-stimulation, Medium-frequency

Auditory Tone	Time (-stimulation)	Difference	- 95 CI	+ 95 CI	*p*
4 kHz	Post > Pre	4.12	1.35	6.89	< .001***
No tone	Post > Pre	0.37	- 2.40	3.14	.999
0.5 kHz	Post > Pre	0.09	- 2.68	2.86	.999

* Denotes significance - *** = $p < .001$.

These findings demonstrate that participants reported a significant reduction in the intensity of AVDs after iTBS in audiovisual trials when the irritating medium-frequency grating was paired with an irritating 4 kHz tone (a reduction in the cross-sensory enhancement effect). This effect was specific to the irritating audiovisual trials and did not occur in visual-only trials, nor when the irritating medium-frequency grating was paired with a non-irritating 0.5 kHz tone.

High-frequency Grating. To examine the effects of iTBS on AVDs for the high-frequency grating, a 3 (Auditory Stimulus (kHz), within-participants; no tone, 0.5, 4) × 2 (Time, within-participants; pre-stimulation, post-stimulation) ANOVA with interaction term was calculated with AVD score as the outcome variable. This failed to reveal significant main effects of Auditory Stimulus ($F(2, 858) = 0.28$, $\eta_p^2 < 0.001$, $p = .759$, $BF_{10} = 0.02$) or Time ($F(1, 858) = 1.44$, $\eta_p^2 = 0.002$, $p = .231$, $BF_{10} = 0.15$), and failed to reveal a significant interaction between Time and Auditory Stimulus ($F(2, 858) = 0.01$, $\eta_p^2 < 0.001$, $p = .990$, $BF_{10} < .01$).

These findings demonstrate that participants' AVD scores did not differ significantly between pre-stimulation and post-stimulation trials for the high-frequency grating. This was true for visual only trials, and for trials paired with 0.5 kHz and 4 kHz tones.

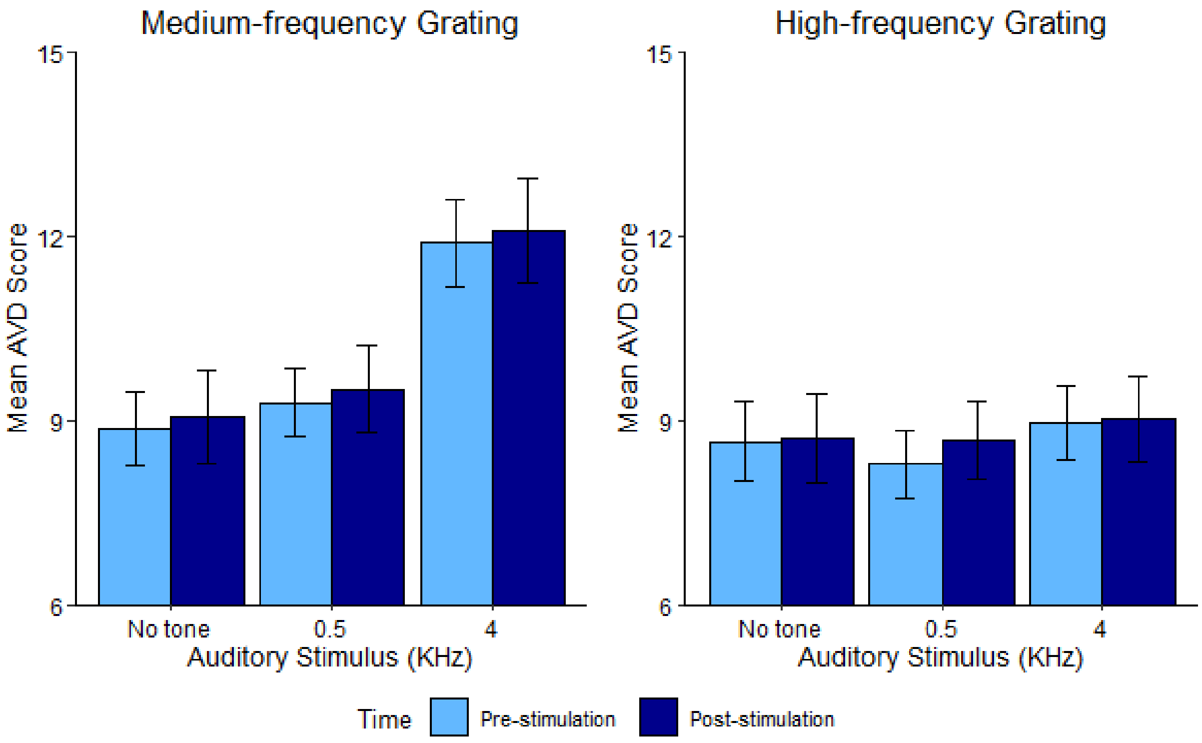
Together these results demonstrate a highly selective effect of the iTBS protocol on the intensity of AVDs reported. A significant difference between pre-stimulation and post-stimulation trials was observed only in audiovisual trials where the aversive medium-frequency grating was paired with an irritating 4 kHz tone. The direction of this effect suggested that participants reported significantly weaker AVDs post-stimulation in comparison to pre-stimulation in these trials (with the effect ostensibly abolished).

Continuous Theta Burst Stimulation (cTBS)

Descriptive statistics for pre-stimulation and post-stimulation AVD scores in cTBS sessions are presented in Figure 6.

Figure 6.

Descriptive Statistics for AVDs Pre-stimulation and Post-stimulation, cTBS



Medium-frequency Grating. To examine the effects of cTBS on AVDs for the medium-frequency grating, a 3 (Auditory Stimulus (kHz), within-participants; no tone, 0.5, 4) × 2 (Time, within-participants; pre-stimulation, post-stimulation) ANOVA with interaction term was calculated with AVD score as the outcome variable. This revealed a significant main effect of Auditory Stimulus ($F(2, 858) = 10.74$, $\eta_p^2 = 0.024$, $p < .001$, $BF_{10} = 397.02$). The model failed to reveal a significant main effect of Time ($F(1, 858) = 0.13$, $\eta_p^2 < 0.001$, $p = .719$, $BF_{10} = 0.08$), or significant interaction between Auditory Stimulus and Time ($F(2, 858) = 0.01$, $\eta_p^2 < 0.001$, $p = .999$, $BF_{10} = 0.80$).

Tukey's HSD was used to explore the main effect of Auditory Stimulus. Where the medium-frequency grating was paired with a 4 kHz tone, participants reported significantly more intense AVDs than in visual only (no tone) trials (Diff = 3.04, $p < .001$) and in trials where the grating was paired with a 0.5 kHz tone (Diff = 2.60, $p < .001$). There was no significant difference between trials where the grating was paired with a 0.5 kHz tone and no tone trials (Diff = 0.44, $p = .805$).

These findings show that the intensity of AVDs in cTBS trials did not differ from pre-stimulation to post-stimulation for the medium-frequency grating. This was true across visual-only and audiovisual trials. The cross-sensory enhancement effect, whereby the intensity of AVDs increases when paired with a 4 kHz tone, persisted in post-stimulation trials.

High-frequency Grating. To examine the effects of cTBS on AVDs for the high-frequency grating, a 3 (Auditory Stimulus (kHz), within-participants; no tone, 0.5, 4) × 2 (Time, within-participants; pre-stimulation, post-stimulation) ANOVA with interaction term was calculated with AVD score as the outcome variable. The model failed to reveal a significant main effect of Auditory Stimulus ($F(2, 858) = 0.32$, $\eta_p^2 < 0.002$, $p = .727$, $BF_{10} = 0.02$) or Time ($F(1, 858) = 0.10$, $\eta_p^2 < 0.001$, $p = .952$, $BF_{10} = 0.08$), and failed to reveal a significant interaction between Auditory Stimulus and Time ($F(2, 858) = 0.05$, $\eta_p^2 < 0.001$, $p = .952$, $BF_{10} < 0.01$).

These findings show that the intensity of AVDs in cTBS trials did not differ as a consequence of TBS brain stimulation for the high-frequency grating. This was the case across visual-only and audiovisual trials.

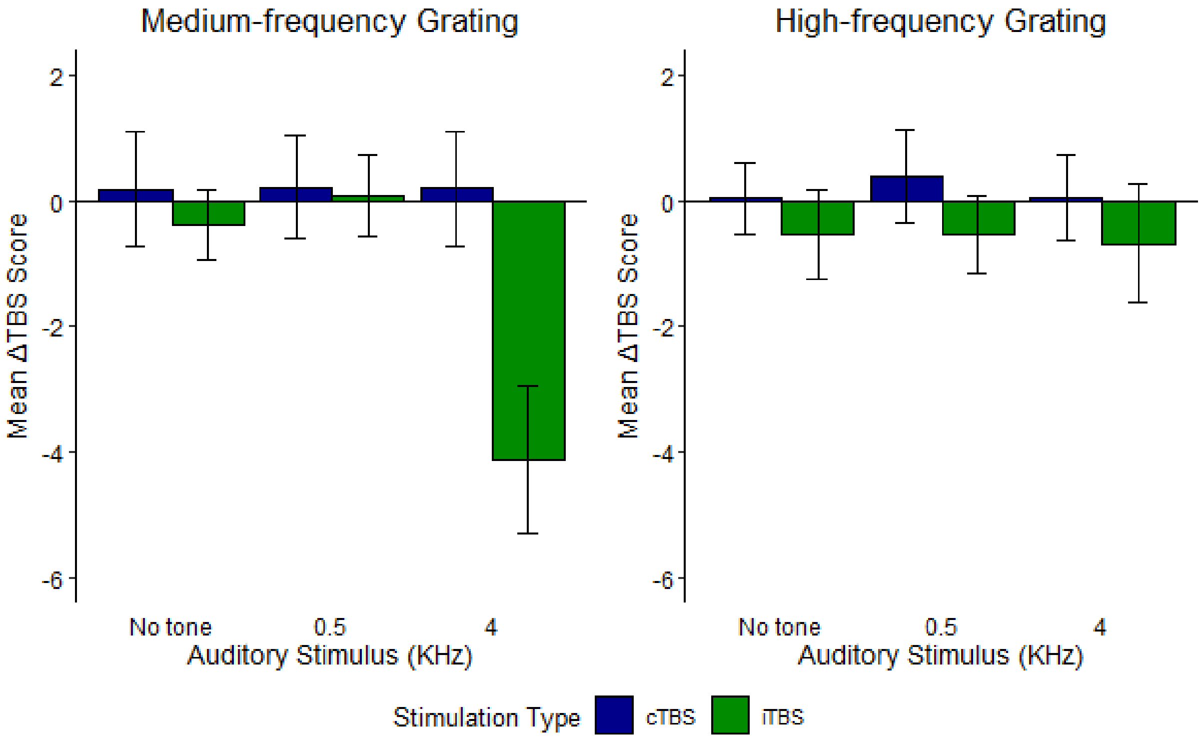
Together these findings demonstrate that AVDs did not differ from pre-stimulation trials to post-stimulation trials for the cTBS protocol. This was true across both grating types, across both visual-only and audiovisual trials. For the medium-frequency grating, the cross-sensory enhancement effect observed with a concurrent 4 kHz tone persisted in post-stimulation trials with cTBS (i.e., it was not perturbed by brain stimulation).

3.3 Baseline-corrected TBS Effects (ΔTBS Score)

To directly compare the effects of the two TBS protocols on AVDs, the ΔTBS score was calculated by subtracting each participant's pre-stimulation mean AVD score from their post-stimulation mean AVD score ($\Delta TBS = AVD_{post\text{-}stimulation} - AVD_{pre\text{-}stimulation}$). This was calculated for both iTBS and cTBS for each combination of visual stimulus and auditory stimulus. Descriptive statistics for ΔTBS scores for both iTBS and cTBS are presented in Figure 7.

Figure 7.

Descriptive Statistics for ΔTBS Scores



Note - a more negative ΔTBS score indicates a smaller AVD score in post-stimulation trials than pre-stimulation trials.

Medium-frequency Grating

An ANOVA was calculated to examine the effects of TBS on AVDs for the medium-frequency grating. This consisted of a 3 (Auditory Stimulus (kHz), within-participants; no tone, 0.5, 4) × 2 (TBS Protocol, within-participants; iTBS, cTBS) ANOVA with interaction term, with ΔTBS score as the outcome variable. The model revealed significant main effects of Auditory Stimulus ($F(2, 210) = 3.64$, $\eta_p^2 = 0.034$, $p = .028$, $BF_{10} = 1.03$) and TBS Protocol ($F(1, 210) = 5.73$, $\eta_p^2 = 0.027$, $p = .018$, $BF_{10} = 1.90$), as well as a significant interaction between Auditory Stimulus and TBS Protocol ($F(2, 210) = 3.63$, $\eta_p^2 = 0.033$, $p = .028$, $BF_{10} = 3.56$).

This interaction was explored further with Tukey's HSD, used to examine for which auditory tones the ΔTBS differed between the two TBS protocols. A summary of these results is presented in Table 4. In trials where the medium-frequency grating was paired with a 4 kHz tone, ΔTBS Score differed significantly between iTBS and cTBS. Here ΔTBS score was significantly lower for iTBS than for cTBS. For both the 0.5 kHz and No tone trials, there was no significant difference in ΔTBS scores between iTBS and cTBS.

Table 4.

Tukey's HSD for ΔTBS Score*, Medium-frequency*

Auditory Tone	TBS Protocols	Difference	- 95 CI	+ 95 CI	*p*
4 kHz	cTBS > iTBS	4.33	0.84	7.81	.006**
No tone	cTBS > iTBS	0.56	- 2.92	4.04	.999
0.5 kHz	cTBS > iTBS	0.13	- 3.35	3.61	.999

* Denotes significance - ** = $p < .01$.

These results demonstrate that ΔTBS scores for the medium-frequency grating only differed between iTBS and cTBS where the grating was paired with a 4 kHz tone. This again demonstrates the highly selective effect of iTBS in attenuating the intensity of AVDs in post-stimulation trials where the irritating medium-frequency grating but only when it is paired with the irritating 4 kHz tone.

High-frequency Grating

An ANOVA was calculated to examine the effects of TBS on AVDs for the high-frequency grating. This consisted of a 3 (Auditory Stimulus (kHz), within-participants; no tone, 0.5, 4) × 2 (TBS Protocol, within-participants; iTBS, cTBS) ANOVA with interaction term, with ΔTBS score as the outcome variable. The model failed to reveal a significant main effect of Auditory Stimulus ($F(2, 210) = 0.06$, $\eta_p^2 < 0.001$, $p = .941$, $BF_{10} = 0.05$) or TBS Protocol ($F(1, 210) = 1.62$, $\eta_p^2 = 0.008$, $p = .204$, $BF_{10} = 0.32$), or a significant interaction between Auditory Stimulus and TBS Protocol ($F(2, 210) = 0.03$, $\eta_p^2 < 0.001$, $p = .969$, $BF_{10} < 0.01$).

These results demonstrate that ΔTBS scores for the high-frequency grating did not differ significantly between iTBS and cTBS across both visual-only and audiovisual trials.

Together these results demonstrate a highly selective effect of TBS protocols on AVD scores after baseline-correction for pre-stimulation AVD scores (i.e. ΔTBS). A significant difference between the two TBS protocols was only observed for trials where the irritating medium-frequency grating was paired with an irritating 4 kHz tone. All other comparisons between the two stimulation protocols were not significant, suggesting no significant difference in the effects of cTBS and iTBS on AVDs in post-stimulation trials for these stimulus combinations. For the medium-frequency grating and 4 kHz tone pairing, ΔTBS scores were significantly more negative for iTBS than cTBS, suggesting that participants reported significantly less intense AVDs in post-stimulation trials after iTBS.

3.4 State-based Cortical Hyperexcitability (ΔAVD) and ΔTBS Score

To examine the relationship between state-based cortical hyperexcitability and participants' ΔTBS scores, a baseline-corrected measure of cortical hyperexcitability (ΔAVD; for similar approach see Braithwaite et al., 2013a; Braithwaite et al., 2013b; Fong et al., 2019) was calculated. Participants' mean AVD scores in response to the high-frequency grating (no tone) were subtracted from their mean AVD scores in response to the medium-frequency grating (no tone), giving a ΔAVD score for each participant ($\Delta AVD = AVD_{medium\text{-}frequency} - AVD_{high\text{-}frequency}$). The ΔAVD score was calculated in pre-stimulation trials from each participant's iTBS session, giving a baseline measure of state-based cortical hyperexcitability against which the baseline-corrected effect of TBS (ΔTBS) could be examined.

Although both variables here are similar in that they include some form of subtraction for baseline correction, there is a clear separation between the two. ΔAVD score is calculated only in pre-stimulation trials, and is an established measure of intrinsic state-based cortical hyperexcitability used in the standard visual-only Pattern Glare test (Braithwaite et al., 2013a; Braithwaite et al., 2013b; Evans & Stevenson, 2008; Fong et al., 2019). However, the ΔTBS score indexes the induced effects of TBS in this investigation by comparing scores within a single stimulus pairing in pre-stimulation and post-stimulation trials. As such, any relationship observed between the two variables does not constitute a circular relationship.

As significant effects of the TBS protocols were limited to the medium-frequency grating, only ΔTBS scores for the medium-frequency grating were taken forward for these analyses. This created six Pearson's r correlations between ΔTBS score (medium-frequency grating, iTBS and cTBS) and pre-stimulation ΔAVD score, which were controlled with Benjamini-Hochberg adjustments and supplemented with Bayes factors. A summary of these analyses is presented in Table 5.

Table 5.

Correlations Between ΔTBS Scores (Medium-frequency) and ΔAVD Scores

		Frequentist				Bayesian		
TBS	Auditory Tone	*r*	*p*	B&H	Sig?	BF_{10}	Hypothesis	Support
iTBS	4 kHz	- .56	< .001	.0083	Yes	86.34	Alternative	Very Strong
cTBS	4 kHz	.26	.121	.0167	No	1.05	Null	Anecdotal
iTBS	0.5 kHz	.25	.139	.0250	No	0.96	Null	Anecdotal
cTBS	No tone	.24	.156	.0333	No	0.87	Null	Anecdotal
cTBS	0.5 kHz	.24	.160	.0417	No	0.89	Null	Anecdotal
iTBS	No tone	.00	.998	.0500	No	0.37	Null	Anecdotal

Results revealed a significant relationship between ΔTBS score in the 4 kHz condition and pre-stimulation ΔAVD score. No significant correlation was observed between ΔAVD and ΔTBS score for either the 0.5 kHz or no tone condition. No significant correlations were observed for any auditory stimulus between ΔAVD and ΔTBS score. These results demonstrate that the consequential effects of iTBS on AVDs under multisensory (4 kHz) conditions was related to the magnitude of participants' state-based cortical hyperexcitability (ΔAVD). Here a negative relationship was observed, suggesting that greater state-based cortical hyperexcitability prior to stimulation, the greater reduction in intensity of AVDs under multisensory conditions after iTBS (*i.e.* ΔTBS score).

3.5 Trait-based Cortical Hyperexcitability (AVAS) and ΔTBS Score

To examine whether trait-based cortical hyperexcitability was an underlying factor in the effects of TBS in the present investigation, correlations were calculated between ΔTBS score and the separate factors of the MVAS questionnaire. This allowed for examination of whether the observed attenuation of AVDs in post-stimulation trials (*i.e.* ΔTBS) was associated with trait-based factors of cortical hyperexcitability. This may help to suggest whether the initial occurrence of sensory cross-talk, and the subsequent attenuation via iTBS, may be mediated by an underlying mechanism of trait-based cortical hyperexcitability.

When initially examining the effects of the two TBS protocols (see Section 3.2 *Theta Burst Stimulation (TBS) Effects)* a significant attenuation of AVDs in post-stimulation trials was only observed for the medium-frequency grating and 4 kHz tone combination after iTBS. In addition, when ΔTBS scores were calculated ($\Delta\text{TBS} = \text{AVD}_{\textit{post-stimulation}} - \text{AVD}_{\textit{pre-stimulation}}$), only the ΔTBS score for the medium-frequency grating and 4 kHz tone combination demonstrated a significant correlation with the baseline index of cortical hyperexcitability (ΔAVD). Therefore, only this critical ΔTBS score was taken forward for correlation with AVAS factors to limit the number of comparisons and control (as far as possible) the inflation of alpha rate through multiple comparisons.

Three Pearson’s r correlations were conducted between ΔTBS score (medium-frequency grating, 4 kHz, iTBS) and participants’ scores on each of the AVAS factors. These correlations were controlled with Benjamini-Hochberg adjustments and supplemented with Bayes factor analysis. A summary of these analyses is presented in Table 6.

Table 6.

Correlations Between ΔTBS Scores (Medium-frequency, 4 kHz, iTBS) and AVAS Factors

	Frequentist				Bayesian		
AVAS Factor	*r*	*p*	B&H	Sig?	BF_{10}	Hypothesis	Support
VHE	- .72	< .001	.0167	Yes	> 1000	Alternative	Decisive
MVAS	- .70	< .001	.0333	Yes	> 1000	Alternative	Decisive
HSSD	- .25	.156	.0500	No	0.90	Null	Anecdotal

VHE – Voice Hearing Experiences; MVAS – Migrainesque Visual Aura Symptoms; HSSD – Heightened Sensory Sensitivity and Discomfort.

Results revealed significant correlations between this critical ΔTBS score and both the Voice-hearing Experiences (VHE) and Migrainesque Visual Aura Symptoms (MVAS) factors of the AVAS. However, no significant relationship was observed between this critical ΔTBS score and the Heightened Sensory Sensitivity and Discomfort (HSSD) factor of the MVAS. This suggests that the attenuation of sensory cross-talk observed after iTBS is dependent on trait-based cortical hyperexcitability. The direction of the observed effect was negative, suggesting attenuation of AVDs after iTBS (*i.e.* more negative ΔTBS) is associated with elevated trait-based cortical hyperexcitability as measured by selective factors of the AVAS. This suggests that the attenuation effect observed after iTBS may be more prominent in individuals with a trait predisposition to aura-like hallucinations (MVAS) and voice-hearing experiences (VHE).

Discussion

The present study examined the role of the left TPJ in mediating predisposition to cross-sensory enhancement of aberrant perceptual experiences. Participants completed the multisensory Pattern Glare test, a behavioural measure of susceptibility to cross-sensory enhancement of aberrant perceptual experiences, before and after receiving both excitatory and inhibitory TBS. The study provided both a trait-based and a state-based measure of cortical hyperexcitability which were used to examine the effects of brain stimulation on the cross-sensory enhancement effect.

In pre-stimulation trials the typical cross-sensory enhancement effect was observed. Pairing a 4 kHz auditory tone with the concurrent presentation of a medium-frequency visual grating significantly enhanced the intensity of AVDs relative to baseline combinations of stimuli.

When examining the effects of iTBS, a selective decrease in the intensity of AVDs was observed. Here, for stimuli which demonstrated a cross-sensory enhancement effect (medium-frequency visual grating, 4 kHz auditory tone), the intensity of AVDs decreased significantly in post-stimulation trials relative to pre-stimulation trials. For all other stimulus combinations there was no significant difference between pre-stimulation and post-stimulation trials (*i.e.*, brain stimulation had no reliable effect). However, when examining cTBS trials there were no significant differences between pre-stimulation and post-stimulation trials for any of the stimulus combinations. For cTBS the cross-sensory enhancement effect observed at baseline was also observed in post-stimulation trials and remained specific to the medium-frequency visual grating in combination with the 4 kHz auditory tone.

To examine state-based and trait-based cortical hyperexcitability in relation to the observed effects of TBS on cross-sensory enhancement, a ΔTBS score ($\Delta TBS = \Delta AVD_{post\text{-}stimulation} - \Delta AVD_{pre\text{-}stimulation}$) was calculated. State-based cortical hyperexcitability revealed a significant negative relationship between ΔAVD score and the ΔTBS score, suggesting elevated state-based cortical hyperexcitability at baseline was associated with a greater attenuation of cross-sensory enhancement after iTBS. Trait-based cortical hyperexcitability with AVAS factors additionally revealed significant negative relationships between ΔTBS score and; (i) predisposition to aura-like visual hallucinations and distortions (MVAS), and (ii) auditory-verbal hallucinations (VHE). Together these findings support the idea that aberrant neural processes at the TPJ may mediate both state-based and trait-based predisposition to aberrant multisensory experiences (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015; Silbersweig et al., 1995).

4.1 Intermittent Theta Burst Stimulation (iTBS) Effects

iTBS demonstrated a highly selective '*decoupling*' effect; in trials which demonstrated cross-sensory enhancement pre-stimulation (medium-frequency grating, 4 kHz auditory tone), the intensity of AVDs decreased significantly in post-stimulation trials. This does support the notion that aberrations in neural activity at the TPJ may mediate the state-based occurrence of aberrant multisensory experiences (Jardri et al., 1995; Silbersweig et al., 1995).

This effect is best conceptualised as a decoupling rather than a suppression as AVDs did not fall significantly below visual-only scores, rather the post iTBS scores reflect a return to this visual-only baseline score. AVDs were reported at similar intensity level to visual-only trials. Here, decoupling refers to the selective disruption of cross-modal modulation of AVDs by auditory stimuli, without recourse to a general suppression of aberrant visual signals.

Consequently, there was a reduction in the ‘over-binding’ that underlies the cross-sensory enhancement effect. This is an important point in supporting the role of the TPJ in cross-sensory functional integration (Hagmann et al., 2008; Raichle, 2015; van den Heuvel & Sporns, 2011), as it suggests the disruption caused by iTBS has attenuated the degree of cross-sensory prediction error between visual and auditory information.

As iTBS typically exerts excitatory effects on neuronal activity (Huang et al., 2005) the attenuation of aberrant cross-sensory facilitation after iTBS would appear to contrast with neuroimaging investigations of multisensory experiences. These demonstrate a heightened degree of neuronal activity (increased BOLD, blood-oxygen level dependent, response) at the TPJ in individuals experiencing multisensory hallucinations relative to unisensory hallucinations (Jardri et al., 2013; Silbersweig et al., 1995) and may therefore predict greater binding (*i.e.* an enhancement of aberrant cross-sensory processes) after excitatory iTBS.

However, this interpretation likely oversimplifies the underlying neural dynamics. The increased BOLD response at the TPJ may not necessarily reflect an elevation in the number of generated action potentials, or an increase in baseline membrane potentials. Instead, converging evidence suggests that BOLD amplitude more closely tracks synchronisation and coordination of neuronal activity within the TPJ and its connected networks (Heeger & Ress, 2002; Scheeringa & Fries, 2009; Scheeringa et al., 2011). High-resolution intracranial electrophysiological recordings combined with fMRI have demonstrated that a localised increase in BOLD activity is closely correlated with an increase in synchronisation and synaptic coupling of adjacent neuronal populations (Hermes, Winawer & Nguyen, 2017; Nir et al., 2007; Ojemann, Ramsey & Ojemann, 2013). Therefore, although the BOLD response at the TPJ can be elevated during multisensory hallucinations (Jardri et al., 2013; Silbersweig et al., 1995), this may reflect an increase in synchronisation of neuronal populations at the TPJ rather than a baseline increase in neuronal activity. This would suggest that synchronisation, not just summation, of neuronal activity is crucial to the cross-sensory binding process.

One possibility is that iTBS may have altered the latency of neuronal signalling within the audiovisual neuronal circuitry centred around the TPJ to create this decoupling effect in individuals with a heightened predisposition to sensory cross-talk. iTBS is known to enhance long-term potentiation (LTP)-like plasticity processes, meaning the ability for neurons to activity-dependently modify synaptic strength is enhanced (Aceves-Serrano, Neva & Doudet, 2022; Diao et al., 2022; Müller-Dahlhaus, Ziemann & Classen, 2010; Todd, Flavel & Ridding, 2009). LTP-like processes may additionally have been enhanced in the present investigation with the use of the state-dependency pre-task. This pre-task was designed to place the relevant audiovisual network into a state of neuronal excitation at the time of stimulation to maximise the functional engagement of iTBS outcomes within this network (Silvanto & Cattaneo, 2014; Silvanto & Cattaneo, 2017; Hartwigsen & Silvanto, 2023). As synaptic strengthening is activity-dependent, the pre-task could theoretically drive LTP-like effects within the audiovisual network surrounding the TPJ. This increased LTP can alter various aspects of synaptic processes, including the efficacy and latency (i.e., timing) of synaptic transmission (Bennett, 2000; Boudkkazi et al., 2010). Therefore, iTBS boosts LTP in high-gain networks causing timing and latency distortions in neuronal signalling which interfere with cross-modal synchrony, ultimately leading to a perceptual decoupling.

An additional consideration in cross-sensory processing is the differences in intrinsic latency within the auditory and visual systems, with auditory processing showing shorter latency than visual processing (Maunsell & Gibson, 1992; Recanzone, Guard & Phan, 2000; Reccanzone, 2009). This is exacerbated under bimodal stimulation with visual areas showing longer response latencies than auditory areas (Galindo-Leon et al., 2019). Alterations of neuronal function within the audiovisual network enacted by LTP-like aftereffects of iTBS may exacerbate these latency differences further, creating an aberrant audiovisual convergence latency. This may be particularly true with an exaggerated degree of non-linearity within the audiovisual system under conditions of high cortical gain, as changes in neuronal output may rise (or saturate) for a given change in neuronal input more readily than in a low-gain state (Carandini & Heeger, 2012; Ferguson & Cardin, 2020; see upcoming theoretical discussion on cortical gain).

To summarise, the observed decoupling after iTBS is a novel effect and may represent shifts in localised temporal processes at the TPJ. The integration of audiovisual signals is thought to be dependent on precise summation of temporal information at TPJ; iTBS may exacerbate the intrinsic latency differences in auditory and visual system and therefore disrupt the typical coalescence of auditory and visual signals at the TPJ (Barraclough et al., 2005; Cohen & Andersen, 2002; Linden, Grunewald & Andersen, 1999; Mazzoni et al., 1996). From a precision-weighted predictive coding perspective this may be explained through the combination of highly non-linear dynamics in high gain states and induced LTP-like aftereffects, leading to desynchronisation of audiovisual integration and hence a down-weighting of the perceptual precision of the ‘bound’ audiovisual signal (see theoretical implications).

Relationship with State-based Cortical Hyperexcitability

This timing-based account of the decoupling effect is strengthened by the relationship between state-based cortical hyperexcitability, as measured by ΔAVD score, and the magnitude of the decoupling effects of iTBS. The positive association between state-based cortical hyperexcitability and cross-sensory enhancement (see Chapter 3) suggests that anomalous multisensory experiences may be mediated by aberrant cross-modal gain allocation. A characteristic feature of sensory systems operating in high gain states is a failure to optimise signal-to-noise ratios within neural signals by inappropriately enhancing all signals, regardless of salience or sensory modality (Hillyard, Vogel & Luck, 1998; Le Masson et al., 2002; Scolari & Serences, 2009; Woolley et al., 2005). Therefore, the aberrant binding process likely represents a failure of cortical gain-based filtering mechanisms to dampen irrelevant auditory signals, leading to an upweighting of the bound audiovisual signal.

This failure of gain-based filtering mechanisms is characterised by a shorter latency and greater amplitude of neuronal responses to highly salient stimuli due to insufficient neuronal gating (*i.e.* steep input-output slope; McColl & Wilkinson, 2000; Schwartz & Simoncelli, 2001). This relationship has been demonstrated in visual-only Pattern Glare with functional near infra-red spectroscopy (fNIRS) imaging of neural responses in individuals with elevated cortical hyperexcitability (Coutts et al., 2012; Haigh, Cooper & Wilkins, 2015). This may explain why aftereffects of iTBS are more prevalent in hyperexcitable individuals when considering LTP is an activity-dependent process. The insufficiently filtered neuronal responses to the functional steering pre-task under conditions of cortical hyperexcitability within the relevant audiovisual network would subsequently drive stronger LTP-like aftereffects (Diao et al., 2022). This supports the notion that the decoupling effect observed after iTBS would occur via an interaction with mechanisms underlying state-based cortical hyperexcitability and would likely be heightened in individuals whose sensory systems are operating in a high-gain state (*i.e.* elevated state-based cortical hyperexcitability).

4.2 Continuous Theta Burst Stimulation (cTBS) Effects

Interestingly, cTBS demonstrated no significant effects on AVDs across all stimulus combinations; the cross-sensory enhancement effect (see Chapters 3 & 4) persisted in both pre-stimulation and post-stimulation trials and remained unaffected. Although interpreting null effects should be approached with caution, the analysis of the Bayes Factors (as well as the balanced design with iTBS) supported the null hypothesis in relation to cTBS effects ($BF_{10} = 0.08$). Therefore, some tentative suggestions can be explored.

Differences in efficacy between cTBS and iTBS could be explained, in part, in terms of differences in their rhythmic structure. Both protocols feature complex rhythms of nested theta-gamma frequencies which mimics a common pattern of hippocampal pyramidal neuronal discharge known to trigger synaptic modifications (Larson & Lynch, 1986; Larson & Lynch, 1989; Larson & Muncaksy, 2015). These structured bursts are known to exert network-level effects by altering functional connectivity between brain regions which are intrinsically functionally connected through ongoing neural oscillations in the theta (4 – 8 Hz) frequency range (Iwabuchi et al., 2015; Li et al., 2019; Vidal-Pineiro et al., 2015). These changes in functional connectivity are mediated by neuronal aftereffects which mimic long-term potentiation (LTP; strengthened synaptic coupling) and long-term depression (LTD; weakened synaptic coupling) within glutamatergic (typically excitatory) and GABA-ergic (typically inhibitory) neuronal networks (Li et al., 2019; Vidal-Pineiro et al., 2015). Therefore, evidence for differences in the efficacy of LTP and LTD should be considered.

One additional explanation is that the intensity of stimulation used was insufficient to induce LTD-like effects at the TPJ. A recent review comparing effects of iTBS and cTBS in the parietal cortex found that, generally, effects of cTBS were less observable than with iTBS (Kirkovski et al., 2023). There are some suggestions that cTBS may require a higher intensity of stimulation to produce LTD-like aftereffects than is needed for iTBS to produce LTP-like aftereffects. Some investigations have found maximal induction of LTD-like aftereffects in the motor cortex with cTBS protocols delivered between 120 – 150% of RMT (Hordacre et al., 2017; Vallence et al., 2015), where the present study used 70%[21].

Additionally, the angular gyrus itself is heterogenous in its distribution of neurotransmitter receptors, with a higher concentration of GABA-ergic receptors ($GABA_A$ / $GABA_B$) than glutamatergic (NMDA / AMPA) receptors (Caspers et al., 2012; Niu & Pallamero-Gallagher, 2023; Zilles & Palamero-Gallagher, 2001). This may suggest that differences in GABA-ergic mechanisms of iTBS and cTBS could make the angular gyrus more conducive to LTP-like aftereffects than LTD-like aftereffects. Some inconsistency has been observed in the efficacy of GABA-ergic mechanisms for inducing LTD-like aftereffects in cTBS (Labedi et al., 2014; Mix, Benali & Funke, 2014; Trippe et al., 2009), which would indicate that LTP-like aftereffects occur more readily than LTD-like aftereffects in GABA-ergic neurons. Therefore, neurophysiological architecture may mean that angular gyrus was more susceptible to iTBS than cTBS in the present study.

Ultimately, the present investigation cannot provide a definitive explanation for the failure of cTBS to show any reliable effects on the cross-sensory enhancement effect. However, these tentative suggestions may partially explain why iTBS, and not cTBS, reliably exerted effects given the targeted stimulation site.

4.3 Effects of Trait-based Cortical Hyperexcitability

The relationship between iTBS effects (ΔTBS) and trait-based cortical hyperexcitability, as measured by factors of the AVAS questionnaire, support a fractionated view of cortical

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[21] This intensity was selected in line with typical recommendations for TBS protocols to counteract concerns around safety of high-frequency TMS, which note that an increased stimulation intensity may carry an increased risk of adverse events such as seizure (Huang et al., 2005). Stimulation intensities between 120 – 150% are highly non-standard, and do not have consensus safety and efficacy guidelines.

hyperexcitability (see Chapters 3 & 4, also Braithwaite et al., 2015; Fong, Takahashi & Braithwaite, 2019; Joshi et al., 2024 for similar findings). Significant relationships with ΔTBS score were observed for the Migrainesque Visual Aura Symptoms (MVAS) and Voice-hearing Experiences (VHE) factors only. Both indicated significant negative relationships, suggesting individuals with an elevated trait predisposition to visual hallucinations and distortions (MVAS) and auditory hallucinations (VHE) displayed a greater decoupling effect after iTBS. There were no significant effects for the factor of Heightened Sensory Sensitivity and Discomfort (HSSD).

Previous investigations have noted an association with heightened trait-based predisposition to aura-like hallucinations and the state-based occurrence of Pattern Glare experiences, as well as their cross-sensory enhancement (Fong et al., 2019; Fong et al., 2020; see also Chapters 3 & 4). In addition, Joshi et al. (2024) noted an association between heightened susceptibility to aura-like hallucinations (measured by the CHi_II) and the efficacy of brain stimulation in attenuating autonomic responses to emotionally salient stimuli. The present findings mesh with these previous observations, suggesting an association between trait predisposition to aura-like hallucinations and attenuation of the cross-sensory enhancement effect via brain stimulation.

The significant association between the decoupling effect and the VHE factor is somewhat surprising, as no association was observed with cross-sensory enhancement of static Pattern Glare gratings such as those used here (see Chapter 3). This would suggest that, although processes associated with trait predisposition to voice-hearing experiences are not necessarily associated with the occurrence of cross-sensory enhancement, they may mediate the efficacy of brain stimulation in attenuating cross-sensory enhancement (see theoretical implications).

No such significant association was observed with the Heightened Sensory Sensitivity and Discomfort (HSSD) factor. This is consistent with the initial null relationship between HSSD and the cross-sensory enhancement of Pattern Glare with static gratings (see Chapter 3). This highlights the fractionated view of trait-based cortical hyperexcitability suggesting that, although related, the underlying concepts measured by each factor of the AVAS have a degree of unique variance and likely reflect diverse underlying mechanisms (see Chapters 2, 3 & 4, also Braithwaite et al., 2015; Fong, Takahashi & Braithwaite, 2019; Joshi et al., 2024).

In summary, the findings in relation to trait-based cortical hyperexcitability support the notion that investigating both state-based and trait-based factors of predisposition to aberrant perceptual experiences is a more comprehensive approach for understanding the neurocognitive mechanisms underlying such aberrant experiences. Crucially the present study supports the notion that trait-based and state-based factors of predisposition to aberrant perceptual experiences do not form a one-to-one relationship (Abraham & Duffy, 2001; Bressloff et al., 2002; Collerton, Dudley & Mosimann, 2011; Erskine et al., 2019; Ffytche, 2008; Ford et al., 2015; Kühn & Gallinat, 2012; Mo et al., 2024; van Ommen et al., 2023; Zmigrod et al., 2016), as only selective trait-based factors demonstrated a significant association with the observed decoupling effect. As such, the relationship between state-based and trait-based factors remains an important direction for future research into aberrant perceptual experiences, bolstered somewhat by the present findings.

4.4 Theoretical Implications

Collectively, the present findings support the notion that aberrations in neuronal processes at the TPJ contribute to aberrant multisensory experiences (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015; Silbersweig et al., 1995). Importantly, the attenuation of these aberrant multisensory experiences demonstrated significant associations with both state-based and trait-based measures of cortical hyperexcitability. These findings therefore support the notion that the TPJ forms a crucial junction between localised state-based (Jardri et al., 2013; Silbersweig et al., 1995) and diffuse trait-based (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015) mechanisms associated with aberrant multisensory experiences in line with neuroimaging evidence. Additionally, this may suggest that similar state-based and trait-based mechanisms mediated the efficacy of iTBS in altering neuronal activity at the TPJ (and within relevant connected neuronal networks) in the present investigation.

This complex interplay of more connective trait-based and more localised state-based factors could be taken to support a Hodotopic interpretation of the present findings (Ffytche, 2008; Silverstein & Lai, 2021). Within the visual domain, factors mediating the occurrence of aberrant visual experiences are dissociated into localised (within-system, or '*topological*') fluctuations in state-based cortical excitability, and trait-based susceptibility to these fluctuations associated with aberrations in connective (between-system, or '*hodological*') processes. This mirrors neuroimaging evidence of factors underlying the occurrence of multisensory hallucinations, which may be split into localised aberrations in activity at the TPJ underlying the hallucination state (Jardri et al., 2013; Silbersweig et al., 1995), and connective aberrations in the TPJ and associated neuronal networks underlying the hallucination trait (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015). A crucial observation from these imaging studies is that the TPJ forms a junction between these proposed localised (state-based) and distributed (trait-based) mechanisms, which may explain why both state-based and trait-based cortical hyperexcitability demonstrated significant associations with the decoupling effect observed in the present investigation.

Notably, the observed decoupling effect was specific to the medium-frequency Pattern Glare grating paired with the irritating 4 kHz auditory tone. Medium-frequency gratings have long been established as the most potent Pattern Glare gratings and are reliably associated with elevated reporting of AVDs in association with both state-based and trait-based cortical hyperexcitability (Braithwaite, Mevorach & Takahashi, 2015; Braithwaite et al., 2015; Evans & Stevenson, 2008; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022; Haigh et al., 2012; Harle & Evans, 2004; Huang et al., 2003; Wilkins, 1995). In addition, both a heightened sensitivity to irritating auditory tones (Haigh et al., 2023), and a cross-sensory enhancement of Pattern Glare with irritating auditory tones (Chapter 3), have been demonstrated to vary in sympathy with state-based and trait-based cortical hyperexcitability. By contrast no significant effects were observed for the high-frequency grating (AVDs thought to be more optically mediated; Conlon et al., 2001), or for the non-irritating (0.5 kHz) auditory tone which has not previously shown a cross-sensory enhancement effect (Chapter 3). These points suggest the observed decoupling effect is cortically mediated and jointly influenced by both state-based (ΔAVD) and trait-based (AVAS) factors.

Given this decoupling was specifically observed for the irritating (medium-frequency) grating and irritating (4 kHz) tone, the decoupling could be seen as a removal of an aberrant cross-modal correspondence (Driver & Spence, 1998; Spence & Driver, 2004; Spence, 2011). The cross-modal correspondence framework suggests that occurrences of sensory input in one modality can modulate perceptual processing in another where continuity across sensory domains is perceived (Spence, 2011). The decoupling effect could be seen as a breaking up of this perceived perceptual continuity between sensory signals pertaining to the visual grating and auditory tone.

Cross-modal correspondences are thought to occur through failures in resolving the ‘binding problem’ where neural processes determine which sensory signals should be integrated at a given moment (Spence, 2011). In the present investigation, two forms of cross-sensory correspondence may be crucial. First the synchronous onset of the two stimuli may create a temporal congruence, whereby alignment or synchrony of streams may promote perceptual binding (see Chapter 4). Second, the irritating spatial frequency of the grating and irritating frequency of the auditory tone may indicate a form of affective or synaesthetic congruence (see Chapters 3 & 4). Therefore, the decoupling effect exhibited by iTBS may reflect a disruption of neurobiological processes underpinning these correspondences.

Present and previous findings (see Chapters 3 & 4) suggest that aberrant cross-modal correspondences may arise under conditions of elevated cortical hyperexcitability. As such, aberrations in cortical gain control may well be implicated. Typically, this gain control mechanism should enact gain-based filtering to regulate cross-modal representations of sensory information, but under conditions of neural instability such as cortical hyperexcitability, this filtering mechanism may become compromised (McColl & Wilkinson, 2000)

Crucial to the present investigation, cortical gain control mechanisms may be expressed at multiple localised (circuit level) and globalised (neuromodulatory) scales (Aston-jones & Bloom, 1981; Ferguson & Cardin, 2020; Friston et al., 2012; Foote, Aston-jones & Bloom, 1980). The occurrence of a decoupling may reflect a localised perturbation of gain control at the TPJ initiated by iTBS which alters localised excitatory-inhibitory interactions (Ferguson & Cardin, 2020; Harris & Thiele, 2011; Li et al., 2020). However, more diffuse, trait-based mechanisms expressed through neuromodulatory or corticothalamic systems may form a latent modulatory mechanism which additionally governs neuronal susceptibility to this localised perturbation (Aston-jones & Bloom, 1981; Foote, Aston-jones & Bloom, 1980; Happel, 2016; Kroener et al., 2009; Sara, 2009). The significant associations of both state-based and trait-based measures of cortical hyperexcitability with the observed decoupling may point to these separate mechanisms which interact to regulate the unitary concept of cortical gain control.

Localised Gain State and Neuronal Latency

The present findings implicate cortical gain control mechanisms in the aberrant cross-modal enhancement of aberrant perceptual experiences. Cortical gain can be defined as the tangential slope of a neuron or neuronal population's input-output function; gain control mechanisms may steepen (*i.e.* increase output to a given input) or flatten (*i.e.* decrease output to a given input) this slope to optimise signal-to-noise ratio in sensory signals and calibrate their precision-weighting (Aston-Jones & Cohen, 2005; Carandini & Heeger, 2012; Kanai et al., 2015; Schwartz & Simoncelli, 2001). Under typical conditions gain control would steepen the slope for salient signals whilst suppressing irrelevant or excessively noisy fluctuations. However, under conditions of compromised gain control this balance collapses leading to indiscriminate amplification or suppression of both signal and noise (McColl & Wilkinson, 2000). In high-gain states this may manifest as amplification, leading to an enhancement of all sensory signals regardless of modality or salience (Adams, Popovich & Staines, 2017; Aurora & Wilkinson, 2007; Hugdahl, 2009; Tass, 1995; Welch et al., 1990), and hence an aberrant binding across sensory domains (see Chapters 3 & 4).

Previously both Pattern Glare experiences and their cross-sensory enhancement have been demonstrated to occur more readily under conditions of elevated state-based cortical hyperexcitability (Braithwaite, Mevorach & Takahashi, 2015; Braithwaite et al., 2015; Evans & Stevenson, 2008; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022; Haigh et al., 2012; Harle & Evans, 2004; Huang et al., 2003; Wilkins, 1995; see also Chapter 3), suggesting a similar underlying mechanism of localised aberrant gain control may underlie the aberrant cross-sensory enhancement state. Both neuroimaging evidence of multisensory hallucinations (Jardri et al., 2013; Silbersweig et al., 1995) and the present findings would implicate localised gain control mechanisms at the TPJ in these aberrant cross-sensory experiences.

Under concurrent conditions of localised excitability in auditory and visual domains, neuronal signals associated with the auditory tone and visual grating would be highly unstable and low in perceptual precision, providing highly unreliable representations of sensory information (Hillyard, Vogel & Luck, 1998; Hénaff et al., 2020; Scolari & Serences, 2009; Woolley et al., 2005). Under the cross-modal correspondence framework this would be interpreted as providing limited sensory evidence to resolve the binding problem (Spence, 2011). To combat this lack of sensory evidence, gain control processes are enacted to enhance salient underlying sensory representations thus enhancing their precision weighting relative to background noise signals (Kanai et al., 2015). However, as the TPJ is in a hyperexcitable and hence high-gain state (Jardri et al., 2013; Silbersweig et al., 1995), enhancement is applied indiscriminately to both salient visual signals and irrelevant auditory noise, further limiting sensory evidence to resolve the binding problem.

With this limited sensory evidence, only relatively crude sensory information around the tone and grating (affective properties, matched temporal onset) can be drawn upon to resolve the binding problem. The present results would suggest iTBS disrupted one or both of these factors. The proposed mechanism by which iTBS exerts these changes is through LTP-like aftereffects, whereby the synaptic strength of neuronal connections in enhanced where neurons are co-activated (Aceves-Serrano, Neva & Doudet, 2022; Diao et al., 2022; Müller-Dahlhaus, Ziemann & Classen, 2010; Todd, Flavel & Ridding, 2009). These LTP-like aftereffects can alter both the efficacy and latency of synaptic communication (Bennett, 2000; Boudkkazi et al., 2010), and as such may alter affective and temporal congruence as communicated via neuronal signalling.

Haemodynamic responses to highly negative affective sensory stimuli are characterised by shorter latency, higher amplitude responses, this is particularly true under conditions of cortical hyperexcitability, in line with cortical gain accounts (Coutts et al., 2012; Haigh, Cooper & Wilkins, 2015). Therefore, in altering the intrinsic association between the two stimuli, LTP-like aftereffects would seemingly decrease the latency or amplitude of underlying neuronal responses. Whilst LTP is not typically associated with a decrease in neuronal response amplitude, LTP can cause a decrease in the latency of synaptic communication (Shors & Matzel, 1990; Krug, Bergado & Rutherich, 1990; Voronin et al., 1996). This decreased latency is thought to occur as a consequence of activating so-called 'silent synapses' – structurally normal synapses which do not typically participate in synaptic transmission, but can transmit signals during activity-dependent processes such as LTP (Arendt, Sarti & Chen, 2013; Kerchner & Nicoll, 2008; Kullman, 2003; Malenca & Nicoll, 1997; Montgomery, Pavlidis & Madison, 2001).

This change in latency may have consequences for the synchronised convergence of auditory and visual signals at the TPJ. As discussed, auditory and visual systems have different intrinsic latencies from sensory organ (eye, ear) to sensory cortex (visual cortex, auditory cortex; Galindo-Leon et al., 2019; Maunsell & Gibson, 1992; Recanzone, Guard & Phan, 2000; Reccanzone, 2009). However, if LTP-like aftereffects alter the latency of synaptic transmission between the TPJ and sensory cortices, this convergence would be further offset. This would then lead to a desynchronisation of neuronal activation which, from a precision-weighting predictive coding perspective, would amount to a decrease in the perceptual precision of the bound audiovisual signal (Kanai et al., 2015).

Decoupling and the Temporal Binding Window

In addition to shifting neuronal latency, it is possible that localised shifts in gain state at the TPJ altered the efficacy of the neuronal mechanism for deciding whether signals should be treated as '*bound together*' – the Temporal Binding Window (TBW: Cecere, Rees & Romei, 2015; Davis, Christe & Rorder, 2009; Powers, Hevey & Wallace, 2012; Schoffelen, Pesci & Noppeney, 2024; Spierer, Bernasconi & Grievel, 2009; Venskus & Hughes, 2021; Zmigrod & Zmigrod, 2015). Given the pivotal role of temporal precision in determining cross-sensory prediction errors, perturbations of intrinsic neuronal activity at the TPJ may subsequently offset the function of the TBW, resulting in changes in the cross-sensory binding processes (for review see Mierau, Klimesch & Lefebvre, 2017). TBW's are strongly associated with neural oscillatory activity in parietal regions such as the TPJ within the alpha frequency range (8 – 13 Hz; Chancel, Iriye & Ehrsson, 2022; D'Angelo et al., 2025; Graziano, Cooke & Taylor, 2005; Grivaz, Blanke & Serino, 2017; Limanowski & Blankenburg, 2016). Here each phase (*i.e.* one complete oscillatory cycle) of the alpha wave is thought to represent a window in time within which two stimuli must co-occur to be bound (Cecere, Rees & Romei, 2015; Schoffelen, Pesci & Noppeney, 2024; Venskus & Hughes, 2021). This account has been extended to include alpha's interaction with gamma oscillations (30 – 200 Hz), with gamma oscillations forming a feedforward mechanism carrying sensory information to higher regions of the sensory processing pathway where the TBW may bind or segment two perceptual streams (Galindo-Leon et al., 2019; Keil & Senkowski, 2018; Osipova, Hermes & Jensen, 2008; Roux et al., 2013).

This may suggest iTBS mediates decoupling through altering ongoing neural oscillations in the alpha and gamma frequency bands. In the motor cortex, the application of iTBS has been demonstrated to increase phase-synchrony of gamma oscillations across functionally connected regions, and to increase power of localised alpha oscillations

(Pellegrino et al., 2024). When extrapolating to the discussed roles of alpha and gamma in cross-sensory perception at the TPJ, the increased phase-synchrony of gamma oscillations may represent the increase in LTP within audiovisual networks which, as discussed, may have the trade-off of slower latency and desynchronised transmission of component signals to the TPJ (Shors & Matzel, 1990; Krug, Bergado & Rutherich, 1990; Voronin et al., 1996). This would result in signals which are relatively high in perceptual precision but desynchronised in reaching the TPJ, increasing cross-sensory prediction error and enacting localised gain control mechanisms to inhibit the 'bound' audiovisual signal. With a localised increase of alpha power, these gating mechanisms have greater power both to suppress the bound audiovisual signal and to enhance the unisensory visual signal (van Diepen, Foxe & Mazaheri, 2019). As such, the perceptual precision of the visual-only signal is greater than the bound audiovisual signal, leading to decoupling from the auditory signal and predominance of the visual-only signal in sensory representation. As the present investigation did not make electroencephalographic recordings this account remains somewhat speculative at this stage, however this provides a neurobiologically plausible account for how known effects of iTBS on neuronal activity may underlie the observed cross-sensory decoupling.

Trait Mechanisms and Cross-sensory Prediction Error

In the initial investigation (see Chapter 3), moderation analysis suggested the association between the cross-sensory enhancement effect and the MVAS (Migrainesque Visual Aura Symptoms) factor was not present in the neurotypical sample. In addition, no significant association between cross-sensory enhancement and the VHE (Voice-hearing Experiences) factor was observed. This may suggest the observed decoupling effect is additionally mediated by mechanisms associated with trait-based predisposition to visual and auditory hallucinations, and not only state-based interactions between the TPJ and sensory cortices. This would also support the notion that trait predisposition to aberrant multisensory experiences is associated with broader cortico-cortical and cortico-subcortical networks centred around the TPJ, particularly within the default mode network (DMN; Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015).

Predisposition to both aura-like visual hallucinations (Faragó et al., 2017; Hu et al., 2023; Tessitore et al., 2015; Veréb et al., 2020) and voice-hearing experiences (Alonso-Solís et al., 2020; Diederen et al., 2013; Vercammen et al., 2010a; Vercammen et al., 2010b) are associated with decreased functional connectivity between inferior parietal regions such as the TPJ and the DMN at resting state. Although the exact role of the DMN remains debated, one theory in relation to precision-weighted predictive coding is that its co-activation with sensory and multisensory brain regions reflects unresolved prediction error (Berkes et al., 2010; Carhart-Harris & Friston, 2010; Carhart-Harris et al., 2013). Therefore, the decreased functional connectivity may represent a failure of sensory systems to communicate the occurrence of low-precision sensory signals to the DMN, resulting in ‘short-cuts’ from the DMN in overweighting priors relative to sensory evidence in perceptual representations. This could explain the association between the observed decoupling effects, and MVAS and VHE factors, a trait predisposition to overweighting of priors under conditions of low perceptual precision is interrupted by iTBS.

The discussed alterations in neuronal activity at the TPJ may do so directly, as neuronal coding of prediction error signals has been observed in parietal regions (Duhamel, Colby & Goldberg, 1992; Umeno & Goldberg, 1997; Walker, Fitzgibbon & Goldberg, 1995). This may allow parietal prediction error mechanisms to bypass the DMN and directly resolve cross-sensory prediction errors. Alternatively, iTBS may alter functional connectivity between the TPJ and other areas of the DMN. Other forms of TMS, such as rTMS, when applied to the left TPJ have been found to increase functional connectivity with the right anterior insula of the DMN corresponding with a decrease in intensity of hallucinations (Vercammen et al., 2010b). Although these effects have not been replicated in non-clinical hallucinators, the same functional disconnection between left TPJ and the DMN has been observed in non-clinical hallucinators (Vercammen et al., 2010a). In line with the discussed theory of DMN co-activation representing unresolved prediction error (Carhart-Harris & Friston, 2010; Carhart-Harris et al., 2013), this may represent increased communication of sensory signals to the DMN for prediction error resolution. Although the present investigation cannot distinguish between these two mechanisms, these present neurobiologically plausible explanations for the association between trait-based cortical hyperexcitability (MVAS, VHE) and the observed decoupling effect after iTBS.

4.5 Limitations and Future Research

Whilst the present investigation did not directly measure or manipulate synchrony of auditory and visual signals, the present findings mesh well with findings in relation to neuronal latencies in high-gain states (Coutts et al., 2012; Haigh, Cooper & Wilkins, 2015), and the crucial aspect of temporal cohesion in cross-modal integration (Cecere, Rees & Romei, 2015; Schoffelen, Pesci & Noppeney, 2024; Venskus & Hughes, 2021). In addition, the specificity of cross-modal enhancement, and subsequent decoupling, to the medium-frequency grating and 4 kHz tone support an underlying cortically-mediated mechanism which is sensitive to aberrations in cortical gain control (Braithwaite, Mevorach & Takahashi, 2015; Fong et al., 2020; Fong et al., 2022; Joshi et al., 2024; Jurkovičová et al., 2024). As such, alterations in timing of neuronal circuits receives broader empirical support as an explanation for the present findings.

However, it would be of interest to examine how perceptual synchrony affects the cross-sensory enhancement mechanism, and the subsequent decoupling via iTBS. One method for this would be with stimulus onset asynchrony (SOA's) – staggering the onset of the visual and auditory stimuli at different short time intervals (Bushara, Grafman & Hallet, 2001; Samaha & Postle, 2015). By gradually altering the SOA between the visual grating and auditory tone, this may weaken the temporal congruence between the two streams and determine a critical point of onset asynchrony at which the two streams are no longer bound together – a behavioural equivalent of the decoupling effect observed after iTBS. This may additionally be informative on the role of TBW width in aberrant multisensory experiences by examining how far apart the two stimuli may be staggered and still bound together. In aberrant multisensory experiences of body ownership, both state-based and trait-based predisposition to aberrant multisensory integration is associated with a wider TBW (slower alpha oscillations, closer to 13 Hz) at resting state (trait-based) and in task-related measures (state-based; D'Angelo et al., 2025), as well as indications of cortical hyperexcitability (Braithwaite et al., 2013a; 2013b). This may suggest that aberrant cross-sensory binding mechanisms such as in the cross-sensory enhancement effect may be mediated by a wider TBW.

Perceptual synchrony at the neural level may be measured with haemodynamic responses. As discussed, slight differences in latency of auditory and visual signals can be observed at the neural level (Galindo-Leon et al., 2019). The present discussion makes the case that exacerbations of these latency differences via iTBS-induced LTP-like aftereffects could drive the decoupling observed. This could be tested directly by measuring the latency of cross-sensory responses before and after the iTBS protocol with functional near infrared spectroscopy (fNIRS), which has previously been used to demonstrate latency differences between hyperexcitable and non-hyperexcitable neuronal responses in Pattern Glare (Coutts et al., 2012; Haigh, Cooper & Wilkins, 2015). Alterations in neuronal latency under LTP-like aftereffects could be demonstrated by creating a difference score between auditory and visual neuronal response latencies and examining the relationship between neuronal latency and the magnitude of the decoupling effect after iTBS. A significant negative relationship between the two would clearly demonstrate that an altered latency of neuronal responses is related to an attenuation of the cross-sensory enhancement effect.

Finally, although the present investigation examines neurocognitive factors underlying aberrant multisensory experiences in neurotypical populations, many previous examinations focus largely on clinical populations such as in schizophrenia or psychosis (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015; Silbersweig et al., 1995). This may largely be due to the difficulty in measuring factors associated with aberrant cross-sensory experiences, particularly with state-based factors where observation is limited to the spontaneous occurrence of such experiences during neuroimaging (Jardri et al., 2013; Silbersweig et al., 1995). As such, it is somewhat unclear whether the same state and trait factors underlying aberrant perceptual experiences in clinical populations are continuous across non-clinical populations, although there is clear rationale to suspect this may be the case as presented above.

Regardless, examination of the continuity of these mechanisms across clinical and non-clinical populations marks a vital extension of the present work, with clear applications to continuum models of aberrant conscious experiences (Johns & van Os, 2001; van Os et al., 2008; Verdoux & van Os, 2002). This continuity of mechanism could be examined with an extension of the present work, identifying whether the same cross-sensory enhancement effect and subsequent decoupling via iTBS could be observed in relevant clinical populations, such as individuals with schizophrenia. Alternatively, using neuroimaging methods such as fMRI at resting-state could determine whether similar trait-based markers of aberrant perceptual experiences observed in clinical populations, such as functional disconnection of the DMN (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015) also underlie the cross-sensory enhancement effect in neurotypical populations.

4.6 Conclusion

The present investigation examined the role of cortical gain states at the TPJ in both state-based and trait-based predisposition to cross-sensory enhancement of aberrant perceptual experiences. Prior to stimulation, aberrant visual experiences elicited by irritative visual gratings (producing pattern-glare experiences, AVDs) were enhanced by the co-presentation of irritative auditory stimuli, supporting the notion of a cross-modal facilitatory effect which is mediated by elevated cortical hyperexcitability. After (excitatory) iTBS a decoupling effect was observed, whereby AVD scores in the irritating cross-sensory condition were no longer significantly different from the visual-only (grating-only) condition. No significant effects of (inhibitory) cTBS were observed. The magnitude of this decoupling effect demonstrated a significant relationship with both state-based and trait-based indications of cortical hyperexcitability, clearly supporting a cortically mediated mechanism for both the initial cross-sensory enhancement and its subsequent decoupling via iTBS. Collectively, these findings are commensurate with a cross-modal correspondence (Driver & Spence, 2004; Spence, 2011) framework of aberrant cross-sensory experiences, and extend theories of cortical hyperexcitability and cortical gain control mechanisms underlying aberrant perceptual experiences (Braithwaite et al., 2015; Braithwaite, Mevorach & Takahashi, 2015; Fong et al., 2019; Fong et al., 2020; Fong et al., 2022) into multisensory domains. The complex interplay between state-based and trait-based factors may be accounted for by a Hodotopic explanation of interacting localised and distributed mechanisms (Ffytche, 2008;

Silverstein & Lai, 2021). Future investigations may wish to explore the continuity of these localised and distributed processes across clinical and neurotypical populations with heightened predisposition to aberrant multisensory experiences.

Chapter 6

General Discussion

The present thesis examined neurocognitive factors underlying predisposition to aberrant multisensory experiences. To accomplish this, several novel methodologies were developed for examining individual predisposition to aberrant perceptual experiences across visual and auditory domains, and the potential for a sensory ‘cross-talk’ enhancement between vision and audition.

Several novel methodological developments and resultant insights are presented across these chapters. Both the multisensory Pattern Glare and phase-reversal Pattern Glare paradigms provide behavioural methods for examining the contribution of cross-sensory processes to phenomenologically rich aberrant perceptual experiences. In addition, the Audiovisual Aberration Scale (AVAS) allows for the quantification of multiple distinct factors underlying contributions from cortical hyperexcitability across multiple sensory domains. The AVAS builds on foundations from previous work in the visual domain with the cortical hyperexcitability index (CHi_II; Braithwaite et al., 2015; Fong, Takahashi & Braithwaite, 2019).

In addition, the use of subthreshold theta burst stimulation (TBS) protocols highlighted several crucial methodological considerations for neurostimulation. Here the direction of effects opposed studies using the so-called ‘lesion method’ of inhibiting the TPJ with high-intensity, suprathreshold inhibitory rTMS (Hamilton et al., 2013; Kamke et al., 2012). More subtle, subthreshold methods such as TBS may provide insights on neurodynamic functions associated with aberrant multisensory experiences rather than simply inferring a non-specific role of a target region. Furthermore, the association between trait-based measures and TBS effects highlights the modulatory role of baseline brain-states in shaping stimulation outcomes and their implications for experimental examinations and therapeutic interventions.

Theoretical contributions are discussed following a summary of the key findings across the experimental chapters.

Key Findings

i. The newly devised multisensory AVAS revealed three distinct, but related factors associated with cortical hyperexcitability. These were Factor 1 (HSSD; Heightened Sensory Sensitivity and Discomfort), Factor 2 (MVAS; Migrainesque Visual Aura Symptoms) and Factor 3 (VHE; Voice Hearing Experiences). This supports and extends previous vision-only trait-based measures.

ii. Pattern Glare elicited by irritating medium-frequency gratings demonstrated a cross-sensory enhancement effect. The intensity of visual Pattern Glare experiences increased with the simultaneous co-presentation of an irritating auditory tone. This cross-sensory enhancement effect was specific to the pairing of perceptually irritating stimuli (known to reflect increases in underlying cortical hyperexcitability).

iii. The cross-sensory enhancement effect was increased in individual displaying signs of elevated trait-based cortical hyperexcitability. This was specific to Factor 2 – Migrainesque Visual Aura Symptoms (MVAS).

iv. Phase-reversals of Pattern Glare gratings were found to induce a wide range of new aberrant visual experiences across the perception-hallucination continuum, namely: hallucinations, distortions, and visual irritation. Interestingly, when paired with frequency-modulated tones both hallucinations and irritations demonstrated a cross-sensory enhancement effect, whereas visual distortions did not.

v. A significant correlation was observed between the cross-sensory enhancement effect in phase-reversal Pattern Glare and all three factors of the trait-based AVAS measure of cortical hyperexcitability, likely reflecting the potency of the phase-reverse manipulation.

vi. Excitatory iTBS, but not inhibitory cTBS, applied to the left TPJ induced a decoupling of the multisensory enhancement effect. After iTBS the co-presentation of an irritating auditory stimulus no longer enhanced the intensity of visual Pattern Glare experiences (relative to visual Pattern Glare gratings presented alone).

vii. A significant correlation was observed between the magnitude of this decoupling effect and indications of elevated state-based cortical hyperexcitability. In addition, a significant correlation was observed between the magnitude of this decoupling effect and selective factors of the AVAS.

The Audiovisual Aberration Scale

The creation of the Audiovisual Aberration Scale (AVAS) presents a new tool for quantifying trait-based predisposition to aberrant perceptual experiences associated with cortical hyperexcitability across multisensory domains. The AVAS builds on and extends the contributions from the CHi_II measure (Braithwaite et al., 2015; Fong et al., 2019) but now extending it into the multisensory domain. The use of Exploratory Factor Analysis (EFA) statistically examines the extent to which these experiences cluster together to form latent factors which underlie the concept of cortical hyperexcitability (Bryant & Yarnold, 1995; Hayton, Allen & Scarpello, 2004; Horn, 1965; Schreiber, 2021; Williams, Onsman & Brown, 2010). In addition, the supplementation of EFA with Parallel Analysis provides an objective estimation of the number of factors over typical visual inspection of the scree plot, which can be somewhat subjective (Costello & Osborne, 2005; Osborne, 2015). Both the AVAS and the CHi_II therefore allow for complexities at both the phenomenological level, and at the level of underlying mechanisms, when considering cortical hyperexcitability as an overarching concept (Braithwaite et al., 2015; Fong et al., 2019).

Cortical Hyperexcitability and Aberrant Cross-modal Correspondence

Broadly speaking, the cross-modal correspondence framework proposes that sensory signals in one perceptual domain can have consequences on perceptual manifestations in another sensory domain (Driver & Spence, 1998; Spence & Driver, 2004; Spence, 2011). This interaction can take several forms such as cross-modal interference where one perceptual domain interferes with and detracts from the sensory qualities in another (Maravita et al., 2002; Spence, Kennett, & Driver, 2002; Spence, Ranson & Driver, 2000), or cross-modal enhancement where one perceptual domain enhances and boosts the sensory qualities in another (Spence & Driver, 1994; 1996; 1997; see also Chapters 3, 4, and 5).

Correspondences may be drawn through temporal characteristics such as matched onset and offset of perceptual inputs, or so-called ‘*synaesthetic*’ correspondences whereby non-redundant perceptual features across sensory domains (*e.g.* auditory pitch, visual lightness / brightness) convey continuity (Gallace & Spence, 2006; Parise & Spence, 2008; Parise & Spence, 2009; Spence, 2011). These correspondences are thought to occur through failures to resolve the ‘binding problem’, the degree to which two perceptually co-occurring stimuli should be treated as occurring from a single source and hence perceptually bound (Spence, 2011).

Whilst informative in delineating why specific stimuli may elicit cross-modal correspondences, the cross-modal correspondence framework lacks precision / specificity at the neural level and does not account for the factors underlying individual predisposition to aberrant cross-modal correspondence. The present findings point toward a theoretical convergence between the cross-modal correspondence framework and theories of cortical hyperexcitability, wherein heightened cortical responsivity may reflect or distort aberrant neural gain mechanisms that ordinarily constrain multisensory binding. This integration could provide a more mechanistic basis for understanding why some individuals are predisposed to aberrant or enhanced multisensory experiences (Braithwaite et al., 2013a; Braithwaite et al., 2013b; Braithwaite et al., 2015; Braithwaite, Mevorach & Takahashi, 2015; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Fong et al., 2022).

The enhancement of AVDs could be seen as an aberrant form of cross-modal enhancement, occurring due to the neural consequences of presenting an irritating medium-frequency visual grating (Braithwaite, Mevorach & Takahashi, 2015; Evans & Stevenson, 2008; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Wilkins et al., 1984; Wilkins, 1995) and an irritating auditory tone (Ashkenazi et al., 2009; Ashkenazi et al., 2010; Woodhouse & Drummond, 1993). Crucially, the degree of irritation experienced in response to both stimuli has been found to be elevated in individuals displaying indications of elevated cortical hyperexcitability (Ashkenazi et al., 2009; Ashkenazi et al., 2010; Braithwaite, Mevorach & Takahashi, 2015; Evans & Stevenson, 2008; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Haigh et al., 2023; Wilkins et al., 1984; Wilkins, 1995). This suggests that cortical hyperexcitability is not necessarily confined to a single cortical area or sensory domain, and may extend concurrently into multiple sensory domains and across multiple cortical regions (domain general: Aurora & Wilkinson, 2007; Coppola et al., 2007; Petrusic et al., 2018; Schoenen, 1996; Silvestro et al., 2022; Welch et al., 1990).

Cortical Gain Control and Sensory Cross-talk

The emergence of a domain-general, more cortically global aspect of cortical hyperexcitability supports cortical gain control as a plausible explanatory framework for the observed cross-sensory enhancement effect. Computationally cortical gain refers to the slope of the neuronal input-output function, which determines the amplitude or intensity of neuronal response relative to a given input (Aston-Jones & Cohen, 2005; Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001). In sensory perception, cortical gain control mechanisms regulate neuronal responsiveness according to the salience and reliability of incoming sensory evidence, simultaneously attenuating irrelevant noise while enhancing salient inputs, thus acting as a dynamic filter for signal-to-noise ratio optimisation (Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001). Under typical circumstances, this process enhances the stability of perceptual representations. However, in neural systems characterised by instability or excessive excitability, gain control mechanisms may become compromised leading to the dysregulated aberrant amplification of sensory noise and the destabilisation of perceptual representations (McColl & Wilkinson, 2000). This compromised state may be referred to as a ‘high-gain state’, characterised by misallocation of gain control mechanisms and hence aberrant enhancement of both salient sensory signals and irrelevant background noise (Aston-Jones & Cohen, 2005; Carandini & Heeger, 2012; Carandini & Heeger, 2012; Ferguson & Cardin, 2020; Schwartz & Simoncelli, 2001).

This aberrant amplification of both signal and noise may create conditions of low perceptual precision, often described as low ‘confidence’. Under such conditions, perceptual representations become increasingly biased by prior expectations about sensory events (or priors) rather than by incoming sensory evidence (Friston, 2005; Powers, Kelley & Corlett, 2017; Powers, Mathys & Corlett, 2017). Within such predictive-coding frameworks, priors and sensory evidence are aggregated through a Bayesian process of active inference. When the reliability of sensory evidence is low, mismatches between priors and sensory evidence (input) are more likely, producing larger ‘prediction errors’ that must be resolved to restore stability in perceptual representations (Bastos et al., 2012; Corlett, Frith & Fletcher, 2009; Corlett et al., 2019; Friston, 2005; Powers, Kelley & Corlett, 2017; Powers, Mathys & Corlett, 2017; Rao & Ballard, 1999; Sterzer et al., 2018).

Crucially, not all prediction errors are treated equally. Their weighting at the neuronal level is thought to be proportional to their salience (*i.e.* degree of divergence between priors and sensory signals), with this weighting process implemented by cortical gain control mechanisms (Kanai et al., 2015). As such, cortical gain control and precision-weighted predictive coding mechanisms can be viewed as complimentary explanatory frameworks for the observed cross-sensory enhancement effect: cortical gain mechanisms provide specificity regarding the underlying neural mechanisms or precision weighting, whereas predictive coding delineates the higher-level computational principles governing perceptual inference.

The cross sensory enhancement effect observed across Chapters 3 to 5 was specific to stimuli which are known to be highly irritating both at the perceptual and cortical level. In multisensory Pattern Glare this was observed with the cross-sensory enhancement of AVDs associated with highly irritating medium-frequency gratings and high-frequency pure tones (Ashkenazi et al., 2009; Ashkenazi et al., 2010; Braithwaite, Mevorach & Takahashi, 2015; Evans & Stevenson, 2008; Fong, Takahashi & Braithwaite, 2019; Fong et al., 2020; Wilkins et al., 1984; Wilkins, 1995).

With phase-reversal Pattern Glare this was observed with the specificity of a cross-sensory enhancement to critical temporal frequencies associated with the occurrence of hallucinations in photic flicker paradigms (Billock & Tsou, 2007; 2012). Aberrant perceptual experiences associated with both medium-frequency gratings (Braithwaite, Mevorach & Takahashi, 2015; Coutts et al., 2012; Fong et al., 2020; Fong et al., 2022; Haigh, Cooper & Wilkins, 2015; Huang et al., 2003; Huang et al., 2011) and photic flicker (Amaya et al., 2023; Amaya & Schmidt et al., 2023; Amaya & Behrens et al., 2023; Bartossek, Kemmerer & Schmidt, 2021; Ffytche, 2008) have been demonstrated in association with conditions of hyperexcitability at the cortical level. This would suggest that the cross-sensory enhancement of these experiences could be accounted for by a concurrent over-excitation of both visual and auditory systems, leading to a perceptual 'spill-over' of auditory information into the visual domain.

In cortical gain terms, the visual signal relating to the grating would form the predominant salient signal, whilst the concurrent auditory signal represents a source of noise irrelevant to the representation of the visual grating. As such, cortical gain control processes should dampen neuronal firing to suppress signals in the auditory domain and enhance visual signals to form a high-precision visual representation of the grating. However, systems operating in high-gain states are susceptible to misallocation of gain control processes, aberrantly enhancing all perceptual inputs regardless of salience or modality (Hillyard, Vogel & Luck, 1998; Le Masson et al., 2002; Scolari & Serences, 2009; Woolley et al., 2005). Therefore, in the present paradigm the co-presentation of both an irritating visual grating and irritating auditory tone may have the consequence of a perceptual 'spill-over' of auditory noise into visual signals, decreasing the stability (or precision) of visual signals relative to the presentation of a grating alone.

Under conditions of low perceptual stability, the available sensory evidence to resolve the binding problem would be extremely limited (Driver & Spence, 1998; Spence & Driver, 2004; Spence, 2011). This would mean auditory and visual signals cannot be simply coalesced or parsed out at the cortical level via high-level statistical properties typically associated with resolution of the binding problem (Körding et al., 2007; Noppeney, 2021; Sato et al., 2007; Shams & Beierholm, 2010).

However, lower-level statistical properties such as matched temporal onset (*i.e.* temporal congruence; Di Stefano & Spence, 2025; Shore, Barnes & Spence, 2006; Spence, 2007) or the simultaneous affective irritation experiences across sensory domains (*i.e.* synaesthetic congruence; Gallace & Spence, 2006; Parise & Spence, 2008; Parise & Spence, 2009) would suggest that the auditory and visual signals should be bound to a unitary percept based on prior experience of multisensory perception, creating a cross-sensory prediction error (Ferrari & Noppeney, 2021; Noppeney & Lee, 2018; Noppeney, 2021). With this limited sensory evidence, and the influence of priors suggesting signals should be bound based on this low-level correspondence across sensory domains, the bound sensory signal is weighted more heavily than unisensory signals. This creates a highly salient bound audiovisual signal, which is highly unstable and hence susceptible to aberrations in perceptual representation.

This high-gain interaction is depicted in Figure 1 within the conceptual framework of the sigmoid transfer functions representing $f(I)$ slopes[22] as outlined in the General Introduction. Visual (blue) and auditory (red) inputs each operate along their own sigmoidal $f(I)$ functions. At the point of multisensory integration, these inputs are weighted, via cortical gain mechanisms, which determine the extent to which auditory activity influences the visual representation. In a high gain state where precision is low and perceptual representations are unstable; the incoming auditory and visual information cannot be reliably segregated. There

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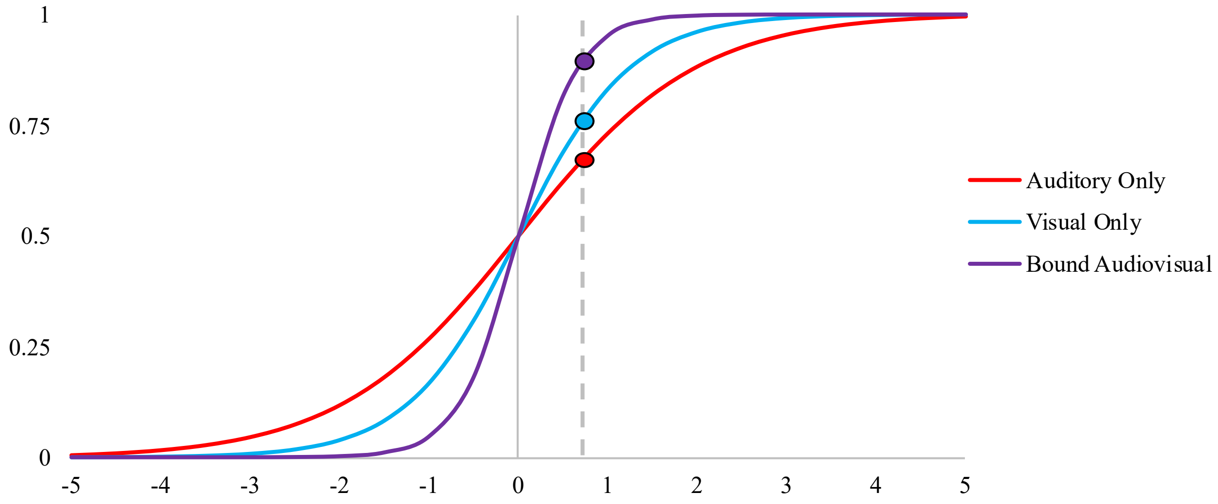
[22] $f(I)$ indicates a quantified relationship between neuronal input (I) and resultant firing rate, or neuronal output (f). Note, the use of the sigmoid here is not as an explicit mathematical structure, more a conceptual transfer function to help illustrate and visualise the concepts of hyperexcitability, cortical gain, and responsivity.

is a lack of perceptual resources for resolving the binding problem. Therefore, the visual and auditory inputs are weighted together, expressed conceptually as a cross-sensory prediction error resolved through limited low-precision sensory evidence (matched temporal onset, concomitant irritation effects) which suggests signals should be bound. The outcome is a bound cross-sensory sigmoid (purple), reflecting a weighted contribution of visual and auditory inputs.

Figure 1.

Cross-sensory Enhancement Expressed as a Conceptual Sigmoid Transfer Function



Here the bound audiovisual function represents a weighted amplification of the visual signal. For a given neuronal input, the output of the bound audiovisual curve is greater / steeper than the visual-only curve. The vertical difference between the visual-only and bound audiovisual signal represents the cross-sensory enhancement effect. Crucially, the magnitude of this enhancement is dependent on the level of underlying cortical hyperexcitability, greater excitability is associated with greater cross-sensory enhancement (see Chapters 3, 4 & 5). Example operating points (OPs) are included depicting relative neuronal output for each slope at the same input level.

Cortical Gain and the Hodotopic Framework

Crucially, cortical gain control is not a unitary process. Rather, it can be expressed at both localised (circuit-level) and more global (neuromodulatory) scales (Aston-jones & Bloom, 1981; Ferguson & Cardin, 2020; Friston et al., 2012; Foote, Aston-jones & Bloom, 1980). It is the combination of these factors which defines how the auditory and visual systems interact, whether they exhibit sensory cross-talk, or maintain the segregation of cross-sensory signals.

This separation of more localised process and more diffuse mechanisms which together form a unitary concept of cortical gain control could be seen as analogous to state-based and trait-based processes discussed in the present investigation, which together underpin the notion of cortical hyperexcitability (Braithwaite et al., 2015; Fong et al., 2019). Indeed, the notion that localised processes mediate state-based hyperexcitability, whilst more diffuse processes mediate trait-based hyperexcitability, would support a Hodotopic interpretation of the present findings (Ffytche et al., 1998; Ffytche, 2008).

Hodotopic Gain: Localised Gain Processes

The hodotopic framework differentiates between topological (localised) changes in neural activity and hodological (connectivity-based; diffuse) aberrations as mechanisms underlying abnormal perceptual experiences (Ffytche, 2008; Silverstein & Lai, 2021). This framework proposes that localised perturbations within the visual cortex reflect state-based topological aberrations, whilst corticothalamic dysconnectivity and altered neuromodulatory influences across higher-order forebrain networks represent trait-based hodological mechanisms (Ffytche, 2008; Silverstein & Lai, 2021). In addition, an extension of the perception-hallucination continuum (Fischer, 1969; Fischer, 1970; Fischer, 1971) was proposed, whereby different forms of aberrant perceptual experience, ranging from distortions to hallucinations, may reflect subtle variations in underlying neural (gain) mechanisms.

Findings reported in Chapter 4 support an extension of the hodotopic framework into the multisensory domain with the significant selective cross-sensory enhancement of hallucinations, but not distortions. This may suggest that, in addition to subtle differences in the state-based mechanisms underlying the occurrence of visual experiences themselves, there are also state-dependent differences governing their cross-sensory enhancement. Notably the cross-sensory enhancement of hallucinations was specific to the two critical reversal frequencies of 10 and 15 Hz, which in photic flicker studies are associated with aberrant cortical excitability in intermediate visual areas (V2 – V5; Ffytche, 2008; Billock & Tsou, 2012; Bartossek, Kemmerer, & Schmidt, 2021).

This may underlie the distinction between localised systems associated with hallucinations as well as distortions, as many distortions are thought to be mediated more so by localised changes in neural activity in early visual cortex (V1; Silverstein & Lai, 2021), which do not show the same perturbations in neural activity in the hallucination state (Ffytche, 2008). Therefore, it is likely that the topological (*i.e.* localised) systems for cross-sensory enhancement of hallucinations and distortions are somewhat distinct, and that the system implicated in hallucinations was predominantly perturbed by sensory cross-talk in this investigation.

This distinction between early and intermediate visual cortex is well established in their respective roles with regards visual processing, with early visual areas typically associated with lower-level analyses such as contour and edge detection (Lee et al., 1998; Lee et al., 2000), and intermediate visual areas implicated in the processing of more complex features such as colour and motion (Beckers & Zeki, 1995; Lee et al., 2000). Consequently, if sensory cross-talk targets distinct components of the visual cortex, cross-sensory enhancement would be expected to manifest differently at the perceptual level for hallucinations and distortions.

In both cases, the co-occurrence of auditory and visual input may exacerbate the misallocation of cortical gain, leading to failures to suppress irrelevant auditory signals on visual processing and thereby reducing the perceptual precision of the visual signal (Kanai et al., 2015; see Chapters 3, 4 & 5). Where such dysregulation occurs within early visual cortex, diminished precision in low-level visual features may produce certain forms of distortions. Conversely, when activity is exaggerated within intermediate visual cortex, reduced precision in higher level visual features such as colour and motion may give rise to hallucinatory percepts. In predictive-coding terms, these outcomes reflect prediction errors arising at different hierarchical levels of the visual system, each governed by distinct priors, which consequently produce qualitatively different perceptual aberrations.

Although electroencephalographic recordings were not obtained in Chapter 4 (phase reversal task), it is nevertheless important to consider how cortical gain processes may have interacted with neural oscillations in the alpha-frequency band (8 – 13 Hz) given the well-established association between high-amplitude alpha oscillations and photic flicker-induced hallucinations (e.g. Amaya, Nierhaus & Schmidt, 2025; Amaya & Schmidt et al., 2023; Amaya & Behrens et al., 2023; Bartossek, Kemmerer & Schmidt, 2021; Billock & Tsou, 2012; Ffytche, 2008). In the visual cortex, alpha oscillations are thought to reflect cyclical fluctuations in excitatory-inhibitory balance, providing a mechanism of for gain control that gates sensory processing by modulating cortical excitability (Jensen & Mazaheri, 2010; van Diepen, Foxe & Mazaheri, 2019). In this context, greater alpha power, reflecting increased synchronisation among alpha-generating neuronal populations, indicates more homogeneous inhibitory modulation over sensory representations (van Diepen, Foxe & Mazaheri, 2019).

Therefore, the localised dysregulation of gain control across intermediate visual cortex during cross-sensory enhancement may manifest as a focal increase localised increase in alpha power, consistent with heightened inhibitory synchrony and altered excitability within this region.

Under conditions of misallocated gain such as cortical hyperexcitability (McColl & Wilkinson, 2000) irrelevant sensory noise may be erroneously amplified, producing signals that are highly salient but intrinsically low in precision (Carandini & Heeger, 2012; Schwartz & Simoncelli, 2001). Within these low-precision states, the sensory evidence available to resolve the binding problem is limited. Normally, multisensory correspondence would be inferred from high; high-level statistical features, such as spatial and temporal cues, which support causal inference across sensory domains (Driver & Spence, 1998; Spence & Driver, 2004; Spence, 2011; Körding et al., 2007; Noppeney, 2021; Sato et al., 2007; Shams & Beierholm, 2010).

However, some residual correspondence may still be conveyed through the temporal coherence of neuronal activity, particularly via phase resetting and phase coherence of alpha oscillations across visual and auditory cortices (Kayser, Petkov & Logothetis, 2008; Mercier et al., 2013; Mercier et al., 2015; Senkowski & Engel, 2024; Senkowski et al., 2005; Thorne et al., 2011). Here the matched onset of the auditory and visual stimuli may align high-amplitude alpha oscillations in auditory and visual cortices, shifting oscillations together into excitatory phases of their cycle, and simultaneously driving highly salient signals from both auditory and visual cortices (Busch, Dubois & van Rullen, 2009; Fiebelkorn et al., 2013; Mathewson et al., 2009). These regularly co-occurring, highly salient signals arising under localised high-gain states may promote an erroneous perceptual correspondence between visual and auditory cortices, suggesting that temporal co-activation of neuronal signals can drive sensory ‘crosstalk’ and contribute to aberrant multisensory binding (Murray et al., 2016; Rohe & Noppeney, 2015; 2016; Welch & Warren, 1980).

Hodotopic Gain: Diffuse Gain Processes

In addition to localised gain processes, the significant correlation of AVAS factors with the cross-sensory enhancement effect indicates a contribution from more diffuse, trait-based mechanisms (Ffytche, 2008; Silverstein & Lai, 2021). Significant associations were observed across all three AVAS factors, suggesting that multiple, distinct trait-based dispositions may influence the propensity for sensory cross-talk. Notably, two AVAS factors not associated with the occurrence of hallucinations under visual conditions (Heightened Sensory Sensitivity and Discomfort, HSSD; Voice-hearing Experiences, VHE) were significantly related to the cross-sensory enhancement effect.

This pattern suggests that, in some cases, cross-sensory enhancement may be mediated by additional trait-based factors beyond those implicated in the initial unisensory experience. In this case, the occurrence of visual aberrations in visual-only trials was associated only with the Migrainesque Visual Aura Symptoms (MVAS) Factor. However, the cross-sensory enhancement of these visual aberrations did not vary in sympathy with the MVAS Factor alone, as both HSSD and VHE factors also showed significant associations with perceptual aberrations elicited in multisensory trials. This suggests that cross-sensory enhancement does not simply arise through an exacerbation of trait-based aberrations underlying the initial unisensory experience. Rather, when multisensory domains are implicated in the occurrence of a perceptual aberration, multiple trait-based factors may converge to modulate cortical gain control mechanisms. This supports the notion that cortical gain control is not a unitary mechanism and rather is implemented via multiple concurrent processes (Aston-jones & Bloom, 1981; Ferguson & Cardin, 2020; Friston et al., 2012; Foote, Aston-jones & Bloom, 1980).

The Left Temporoparietal Junction in Sensory Cross-talk

Although the exact nature of localised and diffuse systems implicated in cross-sensory enhancement await further clarification, previous studies have implicated the left Temporoparietal Junction (TPJ) in both localised and diffuse mechanisms underlying multisensory aberrant experiences (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015; Silbersweig et al., 1995). The state-based occurrence of multisensory hallucinations has been associated with a localised increase in electrophysiological activity at the TPJ and sensory cortices, suggesting these structures work in concert to form a topological multisensory system (Jardri et al., 2013; Silbersweig et al., 1995).

However, some research suggests that trait-based susceptibility to multisensory hallucinations appears to be more associated with aberrations in functional connectivity between the TPJ and other hubs of the default mode network (DMN), as well as between the DMN and subcortical structures such as the hippocampus and amygdala (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015).

Findings reported in Chapter 5 support the role for the TPJ in cross-sensory enhancement, given the observed decoupling effect following iTBS. After stimulation, the reported intensity of AVDs elicited by the medium-frequency visual grating in combination with the 4 kHz auditory tone no longer demonstrated the cross-sensory enhancement effect that had been present prior to iTBS. Essentially, these observations indicate a decoupling effect, whereby the auditory input no longer perturbs the perceptual precision of the visual input (decoupling their binding) thereby preventing cross-sensory processes from amplifying visual distortions. Therefore, although cortical gain processes may still be misallocated and fail to suppress overly salient signals in each component modality, the auditory and visual signals were no longer bound together, and so the auditory noise cannot 'spill-over' and modulate the precision of the visual signal.

The effects of iTBS are consistent with a decoupling, of the multisensory binding process, rather than an active suppression of the individual visual / auditory signals per se. Following iTBS the grand mean intensity of Pattern Glare experiences elicited by the critical stimuli (medium-frequency visual grating, 4 kHz auditory tone) decreased to a level comparable with that evoked by the visual-only medium frequency grating, but not significantly below it. This indicates that iTBS did not suppress the visual / auditory components themselves, but specifically disrupted the binding of auditory and visual inputs. This interpretation is in line with neuroimaging evidence implicating the TPJ in state-dependent multisensory integration, whereby the TPJ is co-activated with sensory specific cortices and functions as an intermediate hub linking these modalities (Jardri et al., 2013; Silbersweig et al., 1995).

The magnitude of this decoupling effect (ΔTBS, or $\text{AVD}_{\textit{post-stimulation}} - \text{AVD}_{\textit{pre-stimulation}}$) demonstrated significant associations with both state-based and trait-based measures of cortical hyperexcitability. This supports a gain-based interpretation of the decoupling effect, as it shows that more unstable (*i.e.* hyperexcitable; McColl & Wilkinson, 2000) systems which are more susceptible to cross-sensory enhancement (see Chapters 3 and 4) are also more susceptible to the disruption of sensory cross-talk. This also highlights why the observed effect is best characterised as a decoupling effect, and not an active suppression. For those individuals relatively lower in cortical hyperexcitability, who experience little sensory cross-talk, the intensity of Pattern Glare experiences were altered to a lesser extent after iTBS.

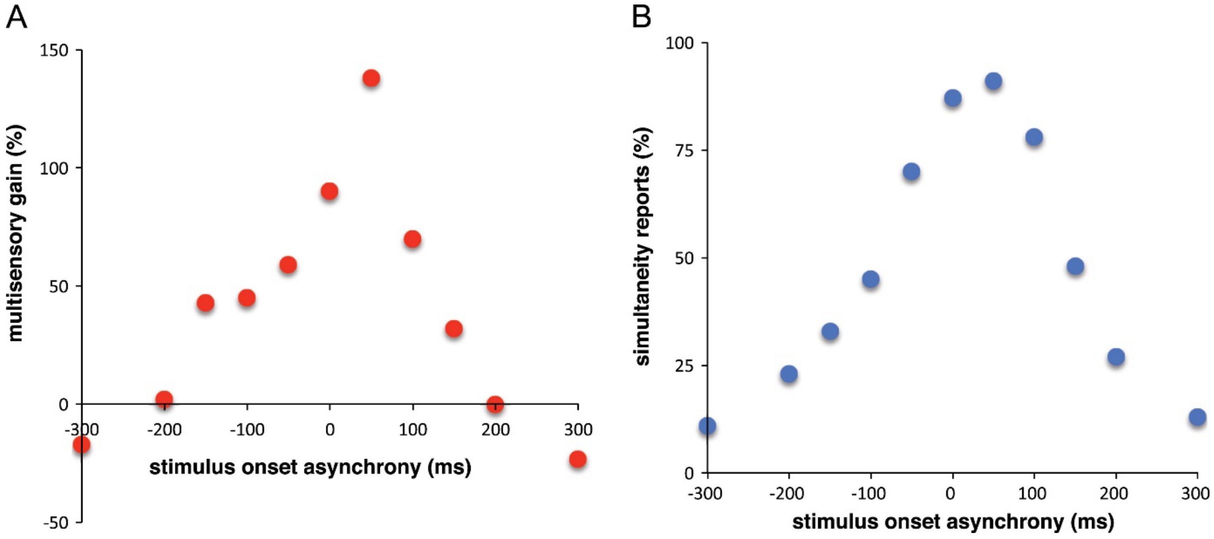
Broader Concepts: TPJ, Cross-sensory Filtering Mechanisms & Temporal-Binding Windows

The increased BOLD activity observed in fMRI investigations of the TPJ during multisensory hallucinations (Jardri et al, 2013; Silbersweig et al., 1995) may indicate an increase in neuronal synchronisation as the component auditory and visual signals are integrated (Hermes, Winawer & Nguyen, 2017; Nir et al., 2007; Ojemann, Ramsey & Ojemann, 2013). This interpretation aligns with the notion that the TPJ integrates precise temporal information across sensory modalities to establish coherence between perceptual streams (Davis, Christe & Rorder, 2009; Spierer, Bernasconi & Grievel, 2009). This could be seen as a neural analogue to temporal congruence under the cross-modal correspondence framework (Spence, 2011), whereby matched temporal aspects in auditory and visual streams increase the likelihood of the component unisensory signals being bound together.

In cortical gain terms, one would expect to see an increase in cortical gain where sensory signals are determined to be temporally congruent (Kanai et al., 2015). This has been demonstrated in animal models of cortical gain processes, which suggest that the closer together two cross-sensory signals converge at a singular point of neuronal input, the greater the resultant increase in localised cortical gain (see Figure 2; Meredith, Nemitz & Stein, 1987; Meredith & Stein, 1986; Wallace & Stevenson, 2014). An increase in cortical gain would increase the weighting of the bound signal (or decrease the degree of cross-sensory prediction error) and so increase the likelihood that signals are bound together in sensory representation. In humans, fMRI evidence suggests accurate performance on cross-sensory tasks requiring highly precise audiovisual information is associated with increased BOLD activity at the TPJ, thought to indicate the upweighting of the ‘bound’ audiovisual signal (Binder, 2015; Love et al., 2018). This effect has been suggested to indicate a neuronal temporal binding window (TBW) - the period within which two sensory signals must co-occur to be bound together (Powers, Hevey & Wallace, 2012; Zmigrod & Zmigrod, 2015). This would suggest the neural TBW is associated with precise temporal processes at the TPJ, and so the application of iTBS to the TPJ may have interfered with these processes by altering the timing of neuronal signals within the cross-sensory audiovisual system.

Figure 2.

Gain State Tracks the Temporal Binding Window



A) Temporal tuning function for a neuron in the cat superior colliculus under audiovisual stimulation. This plot indicates the gain in neuronal response as a function of the simultaneity of convergence of auditory and visual signals. Note gain state is maximal where visual signals are presented marginally before auditory signals (stimulus onset asynchrony marginally > 0), adjusting for the longer intrinsic latency of the visual system relative to the auditory system. B) Representative human responses on a simultaneity judgement task, where participants must judge whether audiovisual stimuli occurred at the same time or were offset. Note human behavioural data closely follows neural data from the animal model. Adapted from Wallace and Stevenson (2014).

iTBS may alter latency within this localised audiovisual binding system as it is known to enhance long term potentiation-like neuroplastic processes (LTP) – the ability for neurons to modify synaptic strength under activity-dependent conditions (Aceves-Serrano, Neva & Doudet, 2022; Diao et al., 2022; Müller-Dahlhaus, Ziemann & Classen, 2010; Todd, Flavel & Ridding, 2009). Although LTP can increase overall synaptic efficacy it can also increase synaptic latency as silent synapses which do not typically participate in synaptic transmissions, but can be triggered by activity-dependent processes, become activated (Shors & Matzel, 1990; Krug, Bergado & Rutherich, 1990; Voronin et al., 1996). This increase in latency arises as longer-latency polysynaptic potentials are generated and mask early monosynaptic potentials due to their greater potency (for overview see Romero-Barragán, Gruart & Delgado-Garcia, 2022). Such effects may be particularly prominent in the audiovisual network in Chapter 5 with the use of the state-dependency pre-task, which is designed to place the relevant audiovisual system into a place of excitation and hence may facilitate these activity-dependent changes under iTBS (Silvanto & Cattaneo, 2014; Silvanto & Cattaneo, 2017; Hartwigsen & Silvanto, 2023).

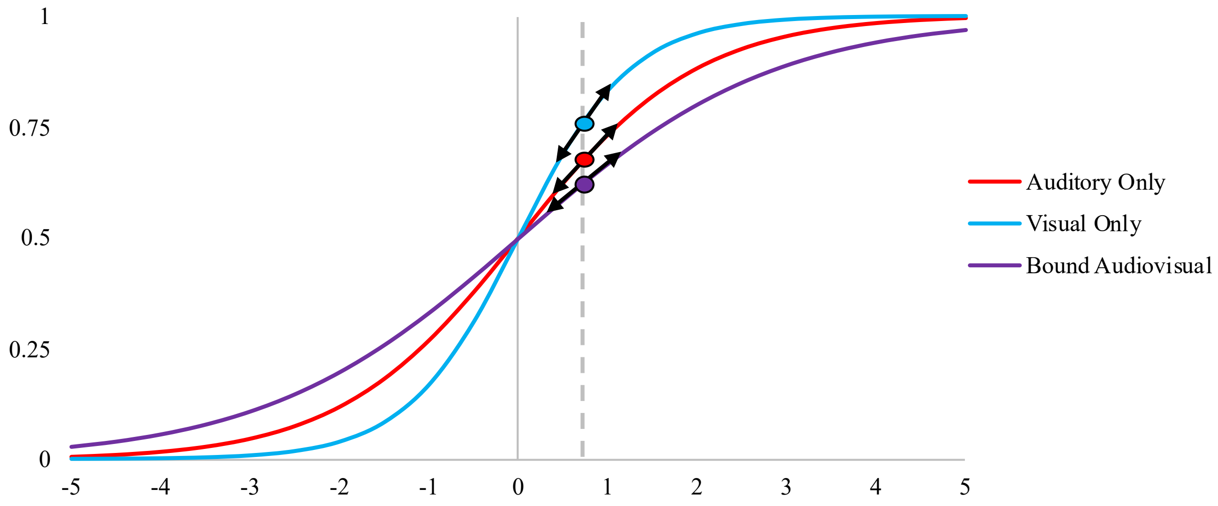
This alteration in latency may have consequences for the convergence of auditory and visual signals at the TPJ by exacerbating intrinsic latency differences between the auditory and visual pathways, where visual pathways typically demonstrate longer latency under multisensory input (Galindo-Leon et al., 2019). Crucially, as LTP is activity dependent, the extent of this exacerbation may well be greater where there is a high-gain state at baseline, such as in cortical hyperexcitability (McColl & Wilkinson, 2000). As a high-gain state is characterised by a steeper input-output slope, the state-dependency pre-task would produce faster, higher-amplitude neuronal responses under conditions of cortical hyperexcitability (Carandini & Heeger, 2012; McColl & Wilkinson, 2000; Schwartz & Simoncelli, 2001). This larger neuronal response would therefore drive greater activity-dependent LTP, manifesting as more extensive synaptic modification within the audiovisual system, and hence the extent of audiovisual latency modifications would be greater in cases of elevated state-based cortical hyperexcitability. This relationship was observed in Chapter 5, with the significant negative relationship between ΔTBS (magnitude of decoupling effect) and ΔAVD (state-based cortical hyperexcitability), suggesting a higher gain state prior to stimulation is associated with a greater magnitude of decoupling.

A temporal offset within the audiovisual system would decrease the likelihood that auditory and visual signals fall within a single temporal binding window and hence increase the likelihood they are 'decoupled' at the neural level (Meredith, Nemitz & Stein, 1987; Meredith & Stein, 1986; Wallace & Stevenson, 2014). However, it is unclear whether this decoupling occurs through more efficient filtering with greater ability for the system to resolve the binding problem, or an attenuation of the binding problem altogether, rendering the filtering process redundant.

One possibility is that the offsetting of auditory and visual signals may give the system greater perceptual resources to resolve the 'binding problem' in the temporal domain. At slight temporal offsets, although there may still be some increase in gain state where auditory and visual signals converge, this increase is comparatively weaker than when neuronal inputs are precisely temporally aligned (Meredith, Nemitz & Stein, 1987; Meredith & Stein, 1986; Wallace & Stevenson, 2014). A relative decrease in gain state may flatten the neuronal input-output curve (see Figure 3), as the converging cross-sensory inputs produce a relatively modest perturbation in neuronal output (Carandini & Heeger, 2012; Ferguson & Cardin, 2020; Schwartz & Simoncelli, 2001). As such, the weighting of the bound audiovisual input is decreased relative to its weighting prior to iTBS, and so the precision of the bound signal is weaker. In addition, the weighting of the bound signal is decreased relative to the weighting of the component visual only signal, which is unaffected by iTBS.

Figure 3.

Decoupling as a Flattening of the Audiovisual f(I) Curve

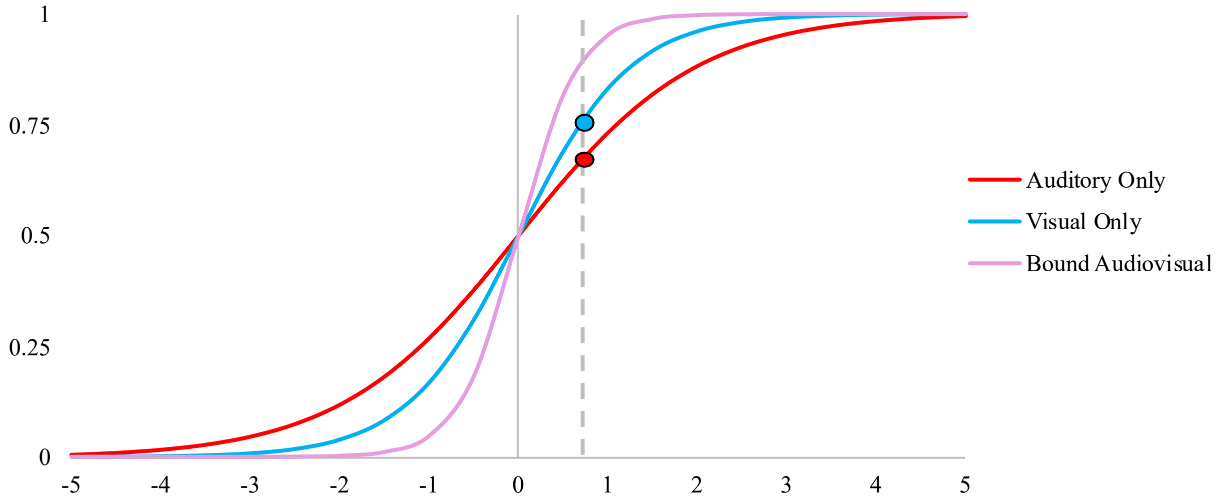


Here the tangential *f(I)* slope (black arrows) has flattened for the audiovisual curve (purple). This demonstrates a decrease in the gain state of the audiovisual system. With this decreased gain state, the weighting of the audiovisual signal is decreased. This explains how the visual only signal is weighted higher than the bound audiovisual signal, leading to better filtering of the visual signal from the irrelevant noise of the auditory signal, and hence the visual only signal dominates in perceptual representation.

Alternatively, the offset of auditory and visual signals may abolish the need to resolve the binding problem altogether. At greater levels of asynchrony, the effective gain within the multisensory neurons may be closer to zero, indicating that the component unisensory signals are significantly misaligned that their convergence does not create a ‘bound’ audiovisual signal (Meredith, Nemitz & Stein, 1987; Meredith & Stein, 1986; Wallace & Stevenson, 2014). As such, although auditory and visual streams continue to operate independently, the binding mechanism is not expressed – representing a dissolution of the input-output slope (see Figure 4).

Figure 4.

Decoupling as an Attenuation of the Audiovisual f(I) Curve



Significant misalignment of audiovisual signals abolishes activity of the binding mechanism – indicated by the opaque *f(I)* curve. The binding system is not activated by the auditory and visual signals, so there is no operating point or *f(I)* curve for a bound audiovisual signal as it is not producing a bound audiovisual signal. Rather than a reduction of cross-sensory prediction error, this represents a complete absence of cross-sensory prediction error.

The relationship between TBW and cortical gain states therefore emerges as a crucial direction for future research examining the neurocognitive mechanisms underlying aberrant multisensory experiences. Here two tentative explanations for the binding mechanism, and its subsequent decoupling, are explored. Although the present findings cannot necessarily distinguish between these two explanations, future adaptations of multisensory Pattern Glare may directly examine each account (see future research discussion).

TPJ and Diffuse Gain Processes

In addition to state-based cortical hyperexcitability associated with localised gain processes, a significant association was observed between the decoupling effect and MVAS and VHE factors of the trait-based AVAS measure. This would suggest contributions from more diffuse gain processes to the decoupling of the cross-sensory enhancement effect under the hodotopic framework (Ffytche, 2008; Silverstein & Lai, 2021). This supports the notion that trait predisposition to aberrant multisensory experiences is associated with broader cortico-cortical and cortico-subcortical networks centred around the TPJ (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015). Of particular interest is the TPJ's function as a node of the default mode network (DMN), a distributed neural network associated with several complex processes which support conscious perceptual experience such as awareness, or the conscious processing of internal and external stimuli (Fernández-Espejo et al., 2012; Raichle, 2015).

As discussed, predisposition to multisensory hallucinations is associated with broad aberrations in functional connectivity between the TPJ and other nodes of the DMN at resting state, thus indicating a trait systems-level aberration in neuronal function (Amad et al., 2014; Jardri et al., 2013; Rolland et al., 2015). Similarly, decreased resting-state functional connectivity between the TPJ and the DMN is observed in individuals experiencing migraine aura symptoms (Faragó et al., 2017; Hu et al., 2023; Tessitore et al., 2015; Veréb et al., 2020) and voice hearing experiences (Alonso-Solís et al., 2020; Diederen et al., 2013; Vercammen et al., 2010a; Vercammen et al., 2010b), the two factors of aberrant perceptual experience measured by MVAS and VHE factors. This highlights the DMN as a crucial network associated with trait-level predisposition to aberrant perceptual experiences more broadly. This may explain why the TPJ is associated with this trait predisposition to aberrant cross-sensory enhancement; it forms a junction between the audiovisual system associated with the state-based functions for sensory cross-talk, and the diffuse DMN which is associated with a more generalised trait-level predisposition to aberrant perceptual experiences. Such an account also aligns with the TPJ's role within the DMN in functional integration - the process by which neural systems associated with both bottom-up sensory processing and top-down higher order cognitive processes, are co-ordinated (Hagmann et al., 2008; Raichle, 2015; van den Heuvel & Sporns, 2011).

From a precision-weighting predictive coding perspective, the DMN may be crucial to the resolution of prediction error. Although its exact role remains debated, one account suggests the co-activation of DMN with sensory and multisensory brain regions reflects unresolved sensory prediction error (Berkes et al., 2010; Carhart-Harris & Friston, 2010; Carhart-Harris et al., 2013). A trait predisposition to aberrant multisensory experiences could therefore be seen as a failure of the TPJ to communicate the occurrence of low-precision cross-sensory signals due to the functional disconnection between the TPJ and higher-level nodes of the DMN (Amad et al., 2014; Jardri et al., 2013; Rolland et al., 2015). This would predict the DMN would overweight priors in the absence of reliable sensory evidence, and the dominance of these priors in perceptual representation may create heightened susceptibility to anomalous perceptual experiences (Kanai et al., 2015). This could explain the association between the observed decoupling effects and MVAS and VHE factors, as a trait predisposition to overweighting of priors under conditions of low perceptual precision is interrupted by iTBS.

Changes to this trait overweighting of priors could occur as a direct result of alterations in neuronal activity at the TPJ, allowing prediction error mechanisms associated with parietal regions to bypass the DMN and more directly resolve prediction errors (Duhamel, Colby & Goldberg, 1992; Umeno & Goldberg, 1997; Walker, Fitzgibbon & Goldberg, 1995). Alternatively, the application of iTBS to the TPJ may alter functional connectivity between the TPJ and other nodes of the DMN. An increase in functional connectivity between the right anterior insula and left TPJ has been observed with the application of rTMS, another form of excitatory repetitive TMS, to the left TPJ in individuals experiencing voice hearing (Vercammen et al., 2010b). Crucially, this increase in functional connectivity was associated with a significant decrease in the intensity of voice hearing experiences (Vercammen et al., 2010b). In line with the discussed theory of DMN co-activation representing unresolved prediction error (Carhart-Harris & Friston, 2010; Carhart-Harris et al., 2013), the reduction of voice-hearing experiences may represent increased communication of sensory signals to the DMN for prediction error resolution, and a reduced weighting of priors in perceptual representation. Although the present investigation cannot distinguish between these two mechanisms, these present neurobiologically plausible explanations for the association between trait-based cortical hyperexcitability (MVAS, VHE) and the observed decoupling effect after iTBS which await further investigation.

Future Research

The hodotopic framework has been examined across clinical and neurotypical populations in the visual domain, finding a continuity of mechanism across all populations (see Ffytche, 2008; Silverstein & Lai, 2021). Investigating this continuity of mechanism for multisensory domains represents an important next step to gaining a comprehensive understanding of neurocognitive mechanisms underlying aberrant multisensory experiences. This could take the form of extending the work in Chapters 3 to 5 with relevant clinical populations who demonstrate a heightened susceptibility to aberrant multisensory experiences, such as psychosis or schizophrenia populations (Dudley et al., 2018; Dudley et al., 2023a; Dudley et al., 2023b; Rogers et al., 2023), or continuing the exploratory work with migraineurs set out in Chapter 3. Examining predisposition to sensory cross-talk in these clinical populations, as well as its association with state-based and trait-based measures of cortical hyperexcitability, may be informative on whether these mechanisms are continuous across populations.

Alternatively, the discussed neuroimaging work on state and trait-based factors associated with predisposition to aberrant multisensory experiences could be extended into neurotypical populations. Previous investigations have been limited to clinical populations with resting-state neuroimaging of individuals experiencing aberrant multisensory experiences (Amad et al., 2014; Ford et al., 2015; Jardri et al., 2013; Rolland et al., 2015), or opportunist state-based imaging with spontaneously occurring aberrant multisensory experiences (Jardri et al., 2013; Silbersweig et al., 1995). The presented methodologies allow for state-based imaging of aberrant multisensory experiences occurring under conditions of sensory cross-talk, as well as resting-state imaging to establish trait-based aberrations associated with heightened sensory cross-talk. This makes neuroimaging of aberrant multisensory experiences more practical in non-clinical populations.

Although a clear rationale is presented for the critical role of temporal synchrony in neural signals and the TBW underlying sensory cross-talk, this could be investigated directly in the future with stimulus onset asynchronies (SOA's). Here one could stagger the onset of the auditory stimulus and visual stimulus at various short time intervals (Bushara, Grafman & Hallet, 2001; Samaha & Postle, 2015). By gradually altering the SOA between the visual grating and auditory tone, this may weaken the temporal congruence between the two streams and determine a critical point of onset asynchrony at which the two streams are no longer bound together – a behavioural equivalent of the decoupling effect observed after iTBS. This may additionally be informative on the role of TBW width in aberrant multisensory experiences by examining how far apart the two stimuli may be staggered and still bound together. In aberrant multisensory experiences of body ownership, both state-based and trait-based predisposition to aberrant multisensory integration is associated with a wider TBW (slower alpha oscillations, closer to 13 Hz) at resting state (trait-based) and in task-related measures (state-based; D'Angelo et al., 2025), as well as indications of cortical hyperexcitability (Braithwaite et al., 2013a; 2013b). This may suggest that aberrant cross-sensory binding mechanisms such as in the cross-sensory enhancement effect may be mediated by a wider TBW.

Alternatively, temporal synchrony at the neural level may be measured with haemodynamic responses. As discussed, slight differences in latency of auditory and visual signals can be observed at the neural level (Galindo-Leon et al., 2019). The present discussion makes the case that exacerbations of these latency differences via iTBS-induced LTP-like aftereffects could drive the decoupling observed. This could be tested directly by measuring the latency of cross-sensory responses before and after the iTBS protocol with functional near infrared spectroscopy (fNIRS), which has previously been used to demonstrate latency differences between hyperexcitable and non-hyperexcitable neuronal responses in Pattern Glare (Coutts et al., 2012; Haigh, Cooper & Wilkins, 2015). Alterations in neuronal latency under LTP-like aftereffects could be demonstrated by creating a difference score between auditory and visual neuronal response latencies and examining the relationship between neuronal latency and the magnitude of the decoupling effect after iTBS. A significant negative relationship between the two would clearly demonstrate that an altered latency of neuronal responses is related to an attenuation of the cross-sensory enhancement effect.

Conclusion

Despite the prevalence of aberrant multisensory experiences across clinical and neurotypical populations, few previous investigations had sought to investigate neurocognitive factors underlying their occurrence. This thesis examined whether cortical hyperexcitability may occur as a domain-general process, extending beyond a unitary sense, and increasing susceptibility to occurrences of aberrant experiences across sensory domains. The underlying motivation was that high gain states associated with cortical hyperexcitability may lead to a misattribution of neuronal filtering, creating susceptibility to perceptual ‘spill-over’ from one sensory domain into another. In Chapter 2 a novel tool was developed for examining trait-based predisposition to aberrant multisensory experiences associated with cortical hyperexcitability. Investigations across Chapters 3 to 5 presented evidence for a novel aberrant cross-sensory enhancement, where the occurrence of anomalous visual experiences was enhanced by concurrent stimulation in the auditory domain. This cross-sensory enhancement was found to vary in sympathy with signs of elevated state-based and trait-based cortical hyperexcitability. Finally, a ‘decoupling’ of this sensory cross-sensory enhancement was demonstrated with disruption of neural activity at the left Temporoparietal Junction (TPJ) via non-invasive Theta Burst Stimulation. This decoupling was also found to vary in sympathy with signs of elevated state-based and trait-based cortical hyperexcitability. A hodotopic interpretation of these results was presented, suggesting that localised cortical gain processes may mediate state-based cortical hyperexcitability, and diffuse cortical gain processes may mediate trait-based cortical hyperexcitability. Crucially, the TPJ may form a junction between these localised state-based and diffuse trait-based mechanisms. Investigations of the continuity of these mechanisms across clinical and neurotypical populations may seek to further validate this interpretation.

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Appendix A

Migraine Pre-screen Questionnaire

You responded '*Yes*' to having a history of migraine (with or without aura/hallucinations). Please read the following questions surrounding your experiences with migraine, and answer as accurately as you can.

Which of the following best describes your condition?

Migraine without aura   Migraine with aura

How long does your migraine typically last? (If Aura without Migraine, select 'Under 1 Hour')

Under 1 Hour   1-2 Hours   2-4 Hours   4-6 Hours   6-12 Hours   12-24 Hours   1 Day +

How long does your aura typically last?

<10 seconds   <1 minute   1-5 Minutes   5-10 Minutes   10-30 Minutes   30-60 Minutes   >1 Hour

My migraine is accompanied by aura (If Aura without Migraine, select '100%'):

Never   Always
0%   10%   20%   30%   40%   50%   60%   70%   80%   90%   100%

Do you become increasingly sensitive to light or certain visual patterns leading up to, or during, your migraine / aura?

Definitely not   Definitely yes
0   10   20   30   40   50   60   70   80   90   100

Do you experience visual discomfort during your migraine / aura?

Definitely not   Definitely yes
0   10   20   30   40   50   60   70   80   90   100

Do you experience auditory discomfort during your migraine / aura?

Definitely not   Definitely yes
0   10   20   30   40   50   60   70   80   90   100

Do you experience vertigo or nausea during your migraine / aura?

Definitely not   Definitely yes
0   10   20   30   40   50   60   70   80   90   100

Appendix B

Methods

Twenty participants aged 18 – 26 (*M* = 20.22, *SD* = 3.15) were invited back to the laboratory to complete the auditory tone rating procedure seven days after completing the multisensory Pattern Glare task.

Participants were presented with pure tones at 0.5 kHz, 4 kHz, and 8 kHz – the same three frequencies which were presented in concert with Pattern Glare gratings in the present chapter. Each auditory stimulus was presented four times, each for a duration of twelve seconds, for a total of twelve trials. Whilst listening to tones, participants were instructed to focus on a fixation point (black '+' symbol) presented in the centre of the computer screen on a dark grey background (luminance 20 cd/m^2). Stimuli were presented in a pseudorandomised order so that the same stimulus was never presented on consecutive trials. For each tone, participants were asked '*To what extent did you find the tone to be irritating?*', analogous to the visual irritation scale which can be used to assess Pattern Glare (see Braithwaite et al., 2013). Responses were given on an eleven-point bipolar scale ranging from -5 ('*Extremely Non-irritating*') to +5 ('*Extremely Irritating*') (for similar approach in visual Pattern Glare see Braithwaite et al., 2013).

Auditory stimuli were presented through Sennheiser HD650 impedance-matched cabled headphones at a fixed volume of 60 dB SPL and were calibrated externally using a Brüel & Kjær Type 4153 Artificial Ear. Fixation points were presented at eye-level on a 27" Iiyama G-MASTERGB2788HS-B1 Red Eagle monitor (1920 × 1080 resolution, 144 Hz refresh rate). Participants were fixed in place on an office chair at an 80cm viewing distance. The experiment was conducted in a dimly lit laboratory. Participation took approximately fifteen minutes.

Results

A one-way ANOVA was conducted to determine the effects of Tone Frequency (within-participants; 0.5 kHz, 4 kHz, 8 kHz) on Irritation Score. This revealed a significant main effect of Tone Frequency $F(1, 237) = 21.85$, $p < .001$, $\eta^2\rho = 0.156$, $BF_{10} > 1000$.

Tukey's HSD was used to determine at which auditory tone frequencies participants reported the greatest degree of auditory irritation. Participants reported significantly more auditory irritation in response to the 4 kHz tone compared to the 0.5 kHz tone (Diff = 1.75, $p < .001$). Participants also reported significantly more auditory irritation in response to the 8 kHz tone compared to the 0.5 kHz tone (Diff = 1.71, $p < .001$). There was no significant difference in the auditory irritation scores between the 4 kHz and 8 kHz tones (Diff = 0.04, $p = .992$).

These findings indicate that participants reported the irritating 4 kHz and 8 kHz tones to be significantly more irritating than the non-irritating 0.5 kHz tone.

Appendix C

Table 11.

AVD Items and Descriptions

Experience	Definition
Visual Pain / Discomfort	The observer experiences a pain from viewing the grating.
Shadowy Shapes	There are dark illusory halos within the grating.
Flickering	The grating appears to flicker (on and off), sometimes rapidly.
Bending of lines	The lines in the grating appear to bend. The lines can either be seen to alternately bend and straighten (i.e. with an implied rhythmic motion) or merely appear to have a constant and stable curvature.
Shimmering	The shape appears to move or vibrate, as though being viewed through a haze on a hot day.
Colours: Red, Blue, Green, Yellow	Perceiving illusory colours from viewing the black / white gratings. Please note the exact colour you may have perceived. Some observers see one or two colours: others may see many.
Nausea	Where one may feel temporarily nauseous from viewing the grating.
Unease	The observer feels generally uneasy about viewing the grating.
Dizziness	The observer starts to feel dizzy and disorientated from viewing the grating. They may also start to feel they themselves are moving while viewing the grating.
Faint	The observer feels as if they may faint from viewing the grating.
Headache	Where the observer may feel some form of headache from viewing the grating.

Illusory stripes	Where the observer may experience illusory lines from viewing the grating
Zooming	The observer perceives the grating as growing/shrinking in size and moving away from / towards them. The movement may alternate in direction rhythmically.
Jitter	Where the grating may be seen to move, around a centre point in a number of directions. The surface of the grating remains flat to the observer, the jitter refers to a rapid displacement in the x,y co-ordinates.
Physical eye strain	A physical sensation of actual eye-strain from viewing a given grating.
Light-headedness	Where the observer may feel light-headed from viewing a grating.

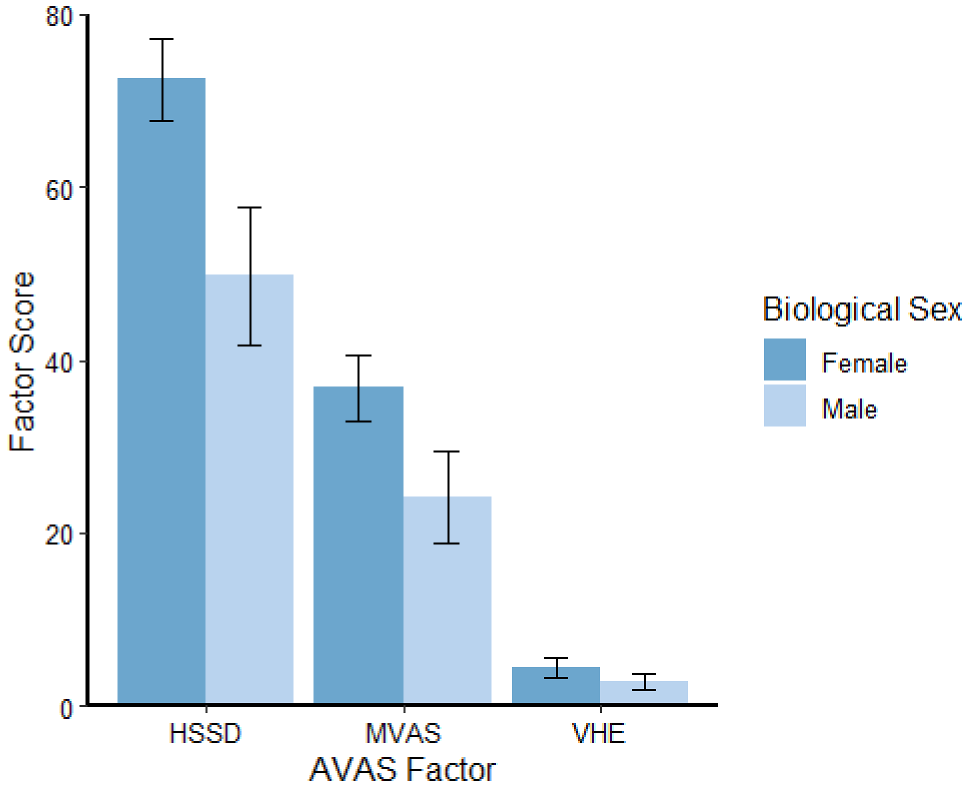
Appendix D

Biological Sex and Cortical Hyperexcitability

Biological sex differences have been observed in cortical hyperexcitability, with an increased susceptibility to related aberrant experiences observed in females versus males (Foutch & Peck, 2013; for review see - Vanston & Strother, 2017). A recent investigation by Jurokvičová et al. (2024) demonstrated that these sex differences in baseline cortical hyperexcitability are also associated with sex differences in predisposition to aberrant perceptual experiences. It was therefore deemed pertinent to conduct a post-hoc analysis to examine sex differences in both state-based and trait-based cortical hyperexcitability in this investigation, and to determine whether sex differences in sensory cross-talk occur. Biological sex differences can be observed in mean scores on the separate factors of the trait-based AVAS questionnaire within this sample (see Figure 8).

Figure 8.

Biological Sex Differences in AVAS Factor Scores



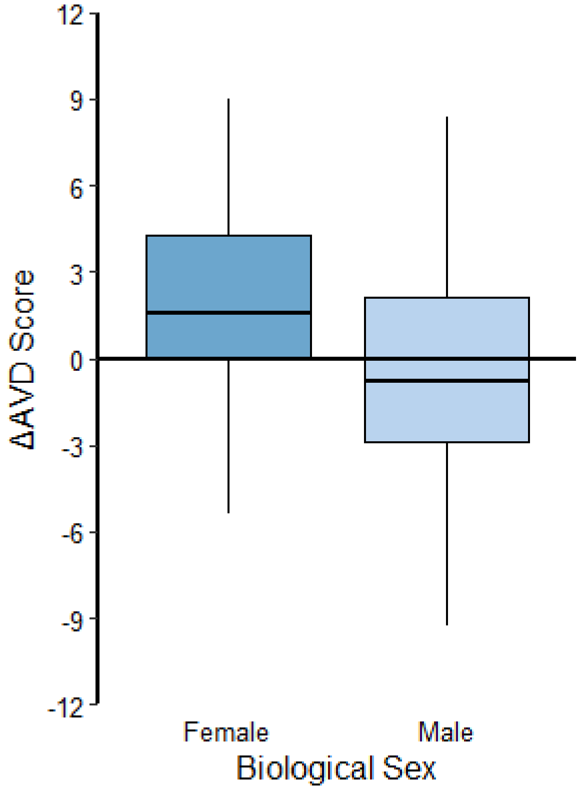
As biological sex differences are also thought to reflect cortical hyperexcitability, they would again be most notable in response to the medium frequency (3 cpd) grating, as well as the medium frequency – high frequency (ΔAVD) calculation. Therefore, AVDs and Visual Irritation across visual-only and audiovisual conditions in response to the medium frequency grating (3 cpd) will be examined to reveal biological sex differences when adding auditory stimuli, as well as biological sex differences in ΔAVD score.

Biological Sex and ΔAVDs

A visual illustration of migraineur group differences in ΔAVD scores is presented in Figure 9.

Figure 9.

Biological Sex Differences in ΔAVD Scores



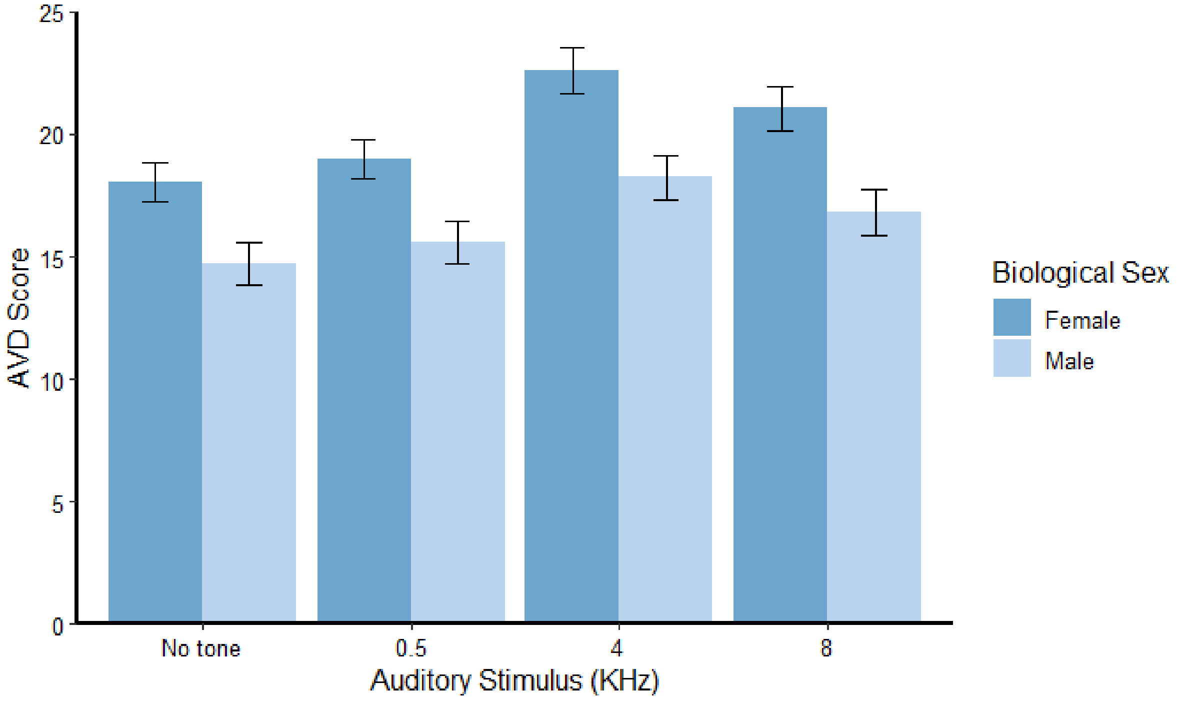
To examine biological sex differences further, ΔAVD scores were entered as an outcome variable into a one way between-subjects ANOVA with Biological Sex (Female, Male) as predictor variable. This revealed a significant effect of Biological Sex F (1, 69) = 6.09, $p = .016$, $\eta^2\rho = 0.081$, $BF_{10} = 3.18$. Post-hoc Tukey's HSD revealed female participants scored significantly higher than male participants, Diff = 3.47, 95 CI [0.66, 6.27], $p = .016$.

Biological Sex and AVDs

A visual illustration of biological sex differences in mean AVD scores in response to the medium frequency grating (3 cpd) across visual only (no tone) and audiovisual conditions is available in Figure 10.

Figure 10.

Biological Sex Differences in AVD Scores (3 cpd) by Auditory Stimulus



AVD Scores were entered as an outcome variable into a 2 (Biological Sex; Female, Male) x 4 (Auditory Stimulus; No tone, 0.5 KHz, 4 KHz, 8 KHz) ANOVA with interaction term. This revealed significant main effects of Biological Sex *F*(1, 8512) = 18.78, $p < .001$, $\eta^2\rho = 0.002$, $BF_{10} > 1000$; and Auditory Stimulus *F*(1, 8512) = 22.07, $p < .001$, $\eta^2\rho = 0.008$, $BF_{10} = 188.36$. There was no significant effect of the interaction term *F*(3, 8512) = 0.09, *p* =

0.97, $\eta^2\rho < 0.001$. Post-hoc Tukey's HSD showed Females reported significantly higher AVD scores than Males (Diff = 1.48, 95CI [0.81, 2.15], *p* <.001).

Together these results show significant and consistent biological sex differences in experiences of Pattern Glare. Female participants report significantly more intense AVD's across visual only (no tone) and audiovisual conditions. Female participants also scored significantly higher on the medium frequency – high frequency subtraction (ΔAVD).

Appendix E

This appendix features descriptions of AVD items which were not added or altered for this study (*i.e.* surviving AVD items) – see Table 10.

Table 10.

Surviving AVD Items and Descriptions

Experience	Description
Visual Pain / Discomfort	The observer experiences a pain from viewing the grating.
Shadowy Shapes	There are dark illusory halos within the grating.
Bending of lines	The lines in the grating appear to bend. The lines can either be seen to alternately bend and straighten (i.e., with an implied rhythmic motion) or merely appear to have a constant and stable curvature.
Colours: Red, Blue, Green, Yellow	Perceiving illusory colours from viewing the black / white gratings. Please note the exact colour you may have perceived. Some observers see one or two colours: others may see many.
Nausea	Where one may feel temporarily nauseous from viewing the grating.
Unease	The observer feels generally uneasy about viewing the grating.
Dizziness	The observer starts to feel dizzy and disorientated from viewing the grating. They may also start to feel they themselves are moving while viewing the grating.
Faint	The observer feels as if they may faint from viewing the grating.
Headache	Where the observer may feel some form of headache from viewing the grating.

Illusory stripes	Where the observer may experience illusory lines from viewing the grating
Zooming	The observer perceives the grating as growing/shrinking in size and moving away from / towards them. The movement may alternate in direction rhythmically.
Physical eye strain	A physical sensation of actual eye-strain from viewing a given grating.
Light-headedness	Where the observer may feel light-headed from viewing a grating.
Visual Pain / Discomfort	The observer experiences a pain from viewing the grating.

Appendix F

This appendix presents a more detailed summary of analyses in section 3.3 on trait-state associations between participants' overall AVD scores (state-based) and AVAS factor scores (trait-based) in visual-only trials. These are summarised in Table 11.

Table 11.

AVAS Factors × AVDs by Flicker Rate for Visual Only Trials, Medium Frequency Grating

		Frequentist				Bayesian		
AVAS Factor	Flicker	*r*	*p*	B&H	Sig?	BF_{10}	Hypothesis	Support
MVAS	10 Hz	.33	.009	.0056	Yes	6.77	Alternative	Substantial
MVAS	15 Hz	.32	.012	.0111	No	5.29	Alternative	Substantial
VHE	15 Hz	.29	.022	.0167	No	3.23	Alternative	Substantial
VHE	10 Hz	.27	.036	.0222	No	2.19	Alternative	Anecdotal

MVAS = Migrainesque Visual Aura Symptoms; VHE = Voice Hearing Symptoms. All comparisons not presented were not statistically significant under frequentist statistics prior to correction for multiple comparisons (*p* > .05).

Appendix G

This appendix presents a more detailed summary of analyses in section 3.4 on trait-state associations between participants' overall AVD scores (state-based) and AVAS factor scores (trait-based) in audiovisual trials. These are summarised in Table 12.

Table 12.

AVAS Factors × AVDs by Flicker Rate for Audiovisual Trials, Medium Frequency Grating

		Frequentist				Bayesian		
AVAS Factor	Flicker (Hz)	*r*	*p*	B&H	Sig?	BF_{10}	Hypothesis	Support
MVAS	15	.38	.003	.0056	Yes	18.02	Alternative	Very Strong
MVAS	10	.35	.006	.0111	Yes	9.61	Alternative	Substantial
VHE	10	.31	.014	.0167	Yes	4.69	Alternative	Substantial
HSSD	15	.21	.015	.0222	Yes	4.31	Alternative	Substantial
HSSD	10	.30	.018	.0278	Yes	3.79	Alternative	Substantial
VHE	15	.29	.023	.0333	Yes	3.13	Alternative	Substantial

MVAS = Migrainesque Visual Aura Symptoms; VHE = Voice Hearing Symptoms; HSSD = Heightened Sensory Sensitivity and Discomfort. All comparisons not presented were not statistically significant under frequentist statistics prior to correction for multiple comparisons ($p > .05$).