Subjective visual sensitivity in neurotypical adults: Insights from a magnetic resonance spectroscopy study

Excitability in subjective visual sensitivity

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2. Abstract

Introduction

Altered subjective visual sensitivity manifests as feelings of discomfort or overload elicited by intense and irritative visual stimuli. This can result in a host of visual aberrations including visual distortions, elementary visual hallucinations and visceral responses like dizziness and nausea, collectively referred to as "pattern glare". Current knowledge of the underlying neural mechanisms has focused on overall ~~visual cortex~~ excitability of the visual cortex, but the individual contribution of excitatory and inhibitory systems has not yet been quantified.

Methods

In this study, we focus on the role of glutamate and γ-aminobutyric acid (GABA) as potential mediators of individual differences in subjective visual sensitivity, measured by a

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computerized Pattern Glare Test – a series of monochromatic square-wave gratings with three different spatial frequencies, while controlling for psychological variables related to sensory sensitivity ~~response bias and predisposition towards anomalous experiences~~ with multiple questionnaires. Resting neurotransmitter concentrations in primary visual cortex (V1) and right anterior insula were studied in 160 healthy participants using magnetic resonance spectroscopy.

Results

Data showed significant differences in the perception of visual distortions (VD) and comfort scores between men and women, with women generally reporting more VD, and therefore the modulatory effect of sex was considered in a further examination. A general linear model analysis showed a negative effect of occipital glutamate on a number of reported visual distortions, but also a significant role of several background psychological traits. When assessing comfort scores in women, an important intervening variable was the menstrual cycle.

Discussion

Our findings do not support that baseline neurotransmitter levels have a significant role in overreactivity to aversive stimuli in neurotypical population, ~~and suggest that the V1 hyperexcitability hypothesis for visual discomfort remains supported only when the cortex is stimulated.~~ However, ~~W~~we demonstrated that biological sex can have a significant impact on subjective responses. Based on this additional finding, we suggest that future studies investigate aversive visual stimuli while examining the role of biological sex.

3. Keywords

Pattern Glare Test, visual discomfort, magnetic resonance spectroscopy, GABA, glutamate, cortical excitability

1. Introduction

Certain individuals are more sensitive to harsh lights or patterns than others – resulting in the experience of visual discomfort, sensory overload, irritation, and anxiety or anger. This subjective feeling is called subjective visual sensitivity and varies across individuals both within the neurotypical population and in association with certain disorders like autism or migraine (Braithwaite et al. 2013; Robertson and Simmons 2013; Braithwaite et al. 2015; Ward 2019; Wood et al. 2021). Proposed neural mechanisms for inter-individual differences involve

a change in the balance of excitatory and inhibitory systems, but direct evidence quantifying the individual contribution of these systems is lacking.

Individual differences in subjective sensory sensitivity can be studied with laboratory tasks that utilize aversive stimuli, such as the Pattern Glare Test (PGT, Wilkins et al. 1984; Evans and Stevenson 2008; Braithwaite et al. 2013), aiming at assessing particularly visual sensitivity and resultant visual distortions/aberrations. This visual task features stationary high-contrast horizontal achromatic gratings with different spatial frequencies that can elicit discomfort, induce phantom visual perceptions, and visual distortions (e.g. colorful halos, shadows and illusory movement) as well as visceral responses like nausea and dizziness. These experiences are a form of "visual stress", collectively referred to as *pattern glare*. Gratings with a spatial frequency of around 3 cycles-per-degree (cpd) are particularly potent at inducing pattern glare in observers (Wilkins et al. 1984; Braithwaite et al. 2013) and even more so in hypersensitive persons, e.g. those suffering from migraine (Huang et al. 2003; Fong et al. 2019; Fong et al. 2020). Multiple neural mechanisms for this effect have been proposed, ranging from pre-cortical mechanisms as early as at the retina (Szmajda and Devries 2011) to post-sensory centrally mediated processing including cognitive-affective responses (Green and Wood 2019).

Increased excitability of V1 has been considered a plausible mechanism of subjective visual sensitivity since early theories (Wilkins et al. 1984), supported by later research in migraine patients (Wilkins et al. 2004). Spatial frequencies around 3 cpd are rare in natural scenes (Conlon et al. 2001; Geisler 2008; Haigh et al. 2015), therefore V1 is not efficient in their encoding and responds with unnecessarily abundant activation (De Valois et al. 1974; Le et al. 2017). This makes these frequencies more likely to overstimulate the visual cortex; for example to trigger epileptic seizures (Radhakrishnan et al. 2005). This overall increase in neural activation (a kind of over-stimulation) might reflect increased excitation, decreased inhibition, or both. Excitation is primarily facilitated by glutamate and inhibition by γ-aminobutyric acid (GABA) (Badawy et al. 2012). The basic processing microcircuit in the cerebral cortex consists of excitatory glutamatergic projection neurons and inhibitory GABAergic interneurons (Douglas and Martin 2004). In case of intense stimulation of a single type of frequency-sensitive cells, the excitation might exceed the shared lateral inhibitory capacity of the microcircuit (Evans and Stevenson 2008). Therefore, uncomfortable striped patterns overstimulate the neurons and produce larger and less sparse activation in a computational model (Hibbard and O'Hare 2015), resembling the excessive activation of the brain during

sensory overload. As this occurs in the visual cortex, these processes manifest themselves as increased susceptibility to visual pattern glare experiences.

Direct evidence for the role of visual cortex excitability in subjective visual sensitivity comes from neuroimaging research. In functional magnetic resonance imaging (fMRI) studies, uncomfortable striped patterns evoke increased blood oxygenation response in V1 and visual association cortex (Huang et al. 2003; Huang et al. 2011). This has been corroborated by near infrared spectroscopy (Haigh et al. 2013), and electrophysiology (Adjamian et al. 2004; O'Hare et al. 2015; O'Hare 2017; Orekhova et al. 2019). Causal evidence for the role of cortical excitability comes from transcranial direct current stimulation (Braithwaite et al. 2015), where under excitatory (anodal) stimulation of V1, healthy subjects perceived more visual distortions on medium-frequency gratings and this effect was larger for observers screened for trait-based predisposition to anomalous perceptions. Although these findings point to the role of increased excitation-to-inhibition ratio in subjective visual sensitivity, the individual role of excitatory glutamatergic and inhibitory GABAergic systems awaits clarification. Currently, the only non-invasive method measuring GABA and glutamate concentrations in vivo is proton magnetic resonance spectroscopy (MRS) (Öz et al. 2020). MRS-quantified GABA and glutamate concentrations have been previously found to reflect change in the level of cortical excitability as measured (Stagg et al. 2011a) or manipulated (Gröhn et al. 2019) by transcranial magnetic stimulation and also to reflect the role of GABA in visual perception (Song et al. 2017).

Additional evidence on the role of cortical excitability, not limited only to V1, arises from studies in migraine patients where patients proved to be particularly susceptible to pattern glare (Wilkins and Evans 2010; Fong et al. 2020). Patients suffering from so-called complex auras show higher resting-state functional connectivity within the visual network and the right anterior insula (rAI) (Silvestro et al. 2022), which also shows heightened inter-ictal intrinsic connectivity with V1 in migraine without aura (Tso et al. 2015). The anterior insula, as a key node of the salience network, evaluates the impact of sensory stimuli on the body state (Downar et al., 2000; Cauda et al. 2011; Uddin 2015) and along with the visual and parietal brain areas, is involved in multisensory and cognitive-affective processing – including the generation of conscious feeling states (Saffin and Tohid 2016; Gogolla 2017; Campbell et al. 2018; Cebeiro and Rodríguez 2019). The rAI cortex has a role in bodily awareness and interoception (Craig 2009; Rahmani and Rahmani 2019; Fermin et al. 2021). Consequently, the insula may well be

important for mediating the visceral-body related experiences reported from viewing aversive gratings.

In the present study, we aim to expand the understanding about the role of cortical excitability in subjective visual sensitivity by quantifying the contribution of baseline GABA and glutamate, utilizing naturally occurring inter-individual differences in a neurotypical sample. To measure visual sensitivity, we used both measures of the PGT: aberrant visual experiences (visual distortions – VD) and subjective ratings of visual discomfort. We related these scales to glutamate and GABA concentrations measured with proton magnetic resonance spectroscopy in V1 and in the rAI, while controlling for response bias and predisposition towards anomalous experiences with multiple questionnaires. We predicted that: (1) the number of visual distortions elicited by aversive medium-frequency gratings would be negatively correlated to inhibitory GABA or (2) positively correlated to excitatory glutamate in V1; (3) subjectively reported feeling of comfort would be positively correlated to GABA or (4) negatively correlated to glutamate in V1. We aimed to also evaluate the role of rAI excitability in a context of subjective visual sensitivity and propose a model of the relationship between cortical excitability and subjective sensitivity. By applying the hyperexcitability hypothesis on young neurotypical adults, we attempt to bridge the explanatory gap between aberrant neural processes and anomalous conscious perceptions in neurotypical samples.

2. Materials and methods

185 healthy young adults (aged 18 to 39; mean = 24.28, SD = 4.762) with normal or corrected-to-normal vision and no neurological or psychiatric diagnosis were recruited via a database of volunteers and advertisements in university/social media. The volunteers were invited to participate in the research as a part of an international research project on consciousness research (COST Action CA18106 - The neural architecture of consciousness), for which the exclusion criteria were adapted. With respect to these criteria, we excluded individuals over 40 years of age, with current neurological or psychiatric medication intake, a history of ~~self-reported~~ migraine symptoms with aura or those not fulfilling MR safety criteria, as they self-reported in a screening questionnaire prior to study participation. In total, 182 subjects (self-reported 72 males and 110 females) gave written informed consent approved by the Research Ethics Committee of Masaryk University and underwent both the PGT and magnetic resonance spectroscopy. Participants were asked not to drink caffeinated beverages for at least 4 hours

before the first session (Wolde, 2014). After completing experiments, the subjects were debriefed and received a financial compensation of 1000 Czech crowns (~40 EUR).

2.1. Questionnaires

Validated psychological questionnaire measures were administered to provide an index of participants' trait-based predispositions to anomalous perceptions and subjective sensitivity that might influence the perception of visually aversive patterns. The questionnaires were selected to ascertain individual scores on various psychological aspects related to sensory sensitivity and with regard to the previous research on the topic (Braithwaite et al. 2013; Dance et al. 2021). This was supplemented by demography, sleep, and menstrual cycle.

2.1.1. Cardiff Anomalous Perceptions Scale

Cardiff Anomalous Perceptions Scale (CAPS) (Bell et al. 2006) is an instrument for measuring the propensity to report anomalous perceptual experiences, hallucinations in non-clinical populations. The questionnaire consists of 32 items of different forms (open-closed questions and Likert scales), divided into 3 components that can be interpreted as ‘‘clinical psychosis,’’ ‘‘chemosensation,’’ and ‘‘temporal lobe disturbance’’. Besides a total score that can be calculated by summing the number of endorsed items, it produces three separate subscale scores measuring distress, intrusiveness and frequency. Therefore, the possible range for the CAPS total was 0 (low) to 32 (high), and for each of the dimensions the possible range is 0 to 160.

2.1.2. Glasgow Sensory Questionnaire

Glasgow Sensory Questionnaire (GSQ) (Robertson and Simmons 2013) assesses self-rated hyper- and hypo-sensitivities across seven sensory modalities: visual, auditory, tactile, gustatory, olfactory, proprioceptive, and vestibular. The questionnaire consists of 42 items, six items targeting each sensory domain. Half of these items measure hypersensitivity, while the other half examine hyposensitivity. Each item can be answered using a scale of 0 (“Never”), 1 (“Rarely”), 2 (“Sometimes”), 3 (“Often”), and 4 (“Always”), the overall sensitivity score is calculated by summing all item scores (ranging 0 to 168). From the overall score, two separate scores can be derived for hyper- and hyposensitivity (ranging from 0 to 84), as well as one score for every sensory domain (ranging 0 to 24).

2.1.3. *NEO-FFI*

NEO Five-Factor Inventory (NEO-FFI; Costa 1989; Costa and McCrae 1992) is a revised, short version of NEO Personality Inventory (Costa and McCrae 1985). It consists of 60 items providing a concise measure of five personality factors: neuroticism, extraversion, openness, agreeableness, conscientiousness. Each of the factors is loaded with 12 items, some of which (N=28) are reverse-worded. The questionnaire uses a five-point Likert response format to indicate if participants (0) strongly agree, (1) agree, (2) are neutral, (3) disagree or (4) strongly disagree with a given proposition about themselves. Scores for each personality factor are calculated by summing 12 items with reverse-scored reversed items.

2.1.4. *Multidimensional Assessment of Interoceptive Awareness-2*

Multidimensional Assessment of Interoceptive Awareness-2 (MAIA-2) (Mehling et al. 2012) was designed as a multidimensional self-report measure to assess the main psychological aspects of the perception of body sensations. The 37 included items may be divided into eight subscales providing separate scores. The subscales are: noticing, trusting, body listening, emotional awareness, self-regulation, not worrying, not distracting and attention regulation. Participants assign 6-point Likert ratings from 0 (“Never”) to 5 (“Always”). Lower sum of scores (an overall or for the certain subscale) indicate more deficits in interoceptive awareness.

2.1.5. *Biological factors*

Studies have attempted to provide normative data for cortical excitability parameters, from which circadian regulation and menstrual/ ovarian cycle serve as potential bias factors in our study. Sleep deprivation increases cortical excitability significantly (Meisel et al. 2015). There is some evidence that there are no differences resulting from sex (Cueva et al. 2016), but studies focused on menstrual and ovarian cycle in women proved the effect of ovarian hormones to be an important factor affecting cortical excitability since menstrual cycle causes the fluctuations in the neurotransmitter concentrations (Smith et al. 1999; Smith et al. 2002; Inghilleri et al. 2004; Hattemer et al. 2007). Therefore, we decided to gather participants' data on the hours slept during the night before the experiment and the day of the menstrual cycle in women. A normal menstrual cycle is defined here as a standard 21-35 day cycle that is not regulated by hormonal contraceptives.

2.2. ***Pattern Glare Test***

With the aim to assess state-based subjective visual sensitivity, we used a modified computerized version of the Pattern Glare Test (Braithwaite et al. 2015), see Figure 1. The stimulation consisted of stationary horizontal square-wave achromatic gratings differing only in their spatial frequency. Three frequencies were presented: a control low-frequency grating (0.5 cpd – cycles pre degree) intended to screen for response bias, an aversive medium-frequency grating (3 cpd), and high-frequency grating (14 cpd). Each grating was presented 6 times in a randomized order. After every three trials with grating stimuli, a checkerboard of 0.5 cpd was presented instead to reduce the potential for lingering excessive neural activity to carry over onto subsequent stimuli. The task was administered in a shielded laboratory and the subject was seated at 80 cm distance from the presentation monitor (TFT-LCD display Philips 241S4L, refresh rate 60 Hz, 1920 × 1080 pixels, 533 × 300 mm). The gratings had dimensions 120 × 120 mm (432 × 432 pixels). The Michelson contrast of the gratings was 0.7, the background luminance 50 lux. The light in the room was kept on a stable dim setting (35 lux).

At the beginning of the experiment, participants were instructed on the definitions of visual distortions, and then to sit comfortably with one hand on the mouse and the other on the keyboard. Their basic task was to fixate a point at the center of the screen for the whole duration of its presence. If a stimulus turned out too uncomfortable, the participant could remove it by pressing the spacebar. Another spacebar press restored the stimulus. After each stimulus, participants were presented with three response screens: 1) select from a list all perceived visual distortions, 2) mark prevailing laterality of visual distortions (left/center/right) and 3) rate their comfort with viewing the stimulus on a 11-point scale (Figure 1). At the start of the experiment, two practice trials with checkerboard stimulus were included to ensure that participants understood the task. At the end, participants were debriefed and asked to report any visual distortions that did not fit the available alternatives. The whole task took approximately 15 minutes.

The number of visual distortions for each frequency (low-frequency gratings – VD-low, medium-frequency gratings – VD-med, high-frequency gratings – VD-high) was calculated as the average of the number of distortions reported after each presentation. We took into account the distortions of visual nature, i.e.: shadowy shapes amongst the lines, shimmering, flickering, bending, illusory stripes or colors, and overall discomfort such as nausea, unease, dizziness, and ocular pain. We also utilized a second measure of visual sensitivity - the comfort score,

which was calculated by averaging the comfort rating from each of the six stimulus presentations for each stimulus frequency (Comfort-low, Comfort-med, Comfort-high).

Data were examined for outliers and data from 12 participants who diverted from the instructions were excluded from further analysis. Seven participants did not pass the screening on the control VD-low for response bias by reporting over 2.64 distortions at average (>2.5 SD) and five by reporting more distortions on VD-low than to the aversive grating (Evans and Stevenson 2008).

2.3. MRI scan

To quantify the concentrations of individual neurotransmitters, we used the only currently available non-invasive method for measuring GABA and glutamate concentrations in vivo – magnetic resonance spectroscopy (MRS, Öz et al. 2020). MRS-quantified GABA and glutamate concentrations have been previously found to reflect change in the level of cortical excitability as measured (Stagg et al. 2011a) or manipulated (Gröhn et al. 2019) by transcranial magnetic stimulation and also to reflect the role of GABA in visual perception (Song et al. 2017). Participants underwent MRI scanning on the same day as PGT was performed.

Neuroimaging data were collected in a 3 Tesla MRI Scanner (MAGNETOM Prisma, Siemens Medical, Erlangen, Germany, Syngo VE11) using a 64-channel receive-array head/neck coil. Structural T1-weighted images were acquired during each measurement using a standard magnetization-prepared rapid gradient-echo (MPRAGE) sequence (T_R/T_E = 2300/2.34 ms, T_I = 900 ms, flip angle = 8°, slice thickness = 1 mm, 240 slices, field-of-view = 260 × 256 mm, resolution = 1 mm isotropic) for accurate placement of the MRS volume of interest (VOI) and within-VOI brain segmentation (Lin et al. 2021). MRS data were acquired using the SPECIAL sequence (Mekle et al. 2009; Near et al. 2013). The first voxel was placed in the primary visual cortex ~~centered along the calcarine sulcusplaced~~ placed to cover the calcarine sulcus bilaterally ~~(Figure 2-1)~~. The calcarine sulcus is a prominent anatomical landmark in the T1-weighted MPRAGE structural MRI scans, and a commonly used landmark for localization of the primary visual cortex. Thus, the V1 voxel was centered on this landmark, as shown in Figure 2-1.~~,~~ The voxel is placed as much as possible over the primary visual cortex without contaminating skull signals and includes V1 and a minimal part of the prestriate cortex. ~~t~~The second voxel was in the right anterior insula (Figure 2-2)~~,~~ focused to include the whole anterior insula and as minimal part of posterior insula as possible, given the inter-individual differences in brain

volume. Both voxels had these parameters: VOI = 30 x 15 x 25 mm, T_R/T_E = 3000/8.5 ms, 128 NEX, AT = ~6:36 min., VAPOR water suppression with 66° flip angle (Tkác et al. 1999). Unsuppressed water spectra (8 NEX) were acquired as the internal reference for metabolite quantification in absolute and relative units and correction of residual eddy currents. GRE brain SIEMENS shimming was used for shimming the MRS sequences. The straightforward MRS-VOI positioning secured its reproducible placement by a single operator (Park et al. 2016). MRS data were obtained with participants instructed to keep their eyes closed.

The advanced SPECIAL MRS method at 3T was used as it bears several advantages over the more conventional spectral editing techniques, such as superior localization performance, low sensitivity to B1 inhomogeneities and short echo time (Öz et al. 2020). Importantly, it allows reliable quantification of several metabolites simultaneously, including both GABA and glutamate as the main neurotransmitters of interest in this study, while maintaining reproducibility comparable to previously published reproducibility values for edited GABA measurements. The SPECIAL sequence was chosen for detection of GABA for the following reasons: 1) It uses a short echo time, this minimizing decay of the GABA resonances due to T2 relaxation and scalar evolution; 2) It maximizes GABA signal by preserving all three of the GABA resonances, compared to the difference editing approaches in which typically ~50% of the C4 and C2 GABA resonances is removed and ~100% of the C3 GABA resonance is removed due to the editing process; 3) It enables simultaneous detection and quantification of a large number of other metabolites, due to the short echo time. Moreover, LCModel has been shown to reliably estimate the concentration of GABA in synthetic SPECIAL MRS data with known GABA concentrations (Near et al. 2013). However, although the SPECIAL sequence demonstrates effective removal of macromolecule contamination (Near et al. 2011), it is acknowledged that the GABA concentration estimate may still contain some signal contributions from macromolecules and other sources (e.g., homocarnosine). ~~Despite the downside of imperfect lipid suppression, the SPECIAL sequence was preferred for the selective removal of the contribution of macromolecules by editing and modeling to obtain the raw GABA value, an important benefit for this study in contrast to this common limitation of conventional methods.~~

2.3.1. MRI/MRS data processing

MRS data were processed using the FID appliance (FID-A), an open-source MATLAB-based toolkit (Simpson et al. 2017). The FID-A processing pipeline had several steps including:

combination of multiple coils, alignment of SPECIAL subspectra, removal of motion-corrupted averages, and spectral registration for correction of frequency and phase drift. Brain metabolites were quantified with LCModel (Provencher 1993; Pfeuffer et al. 1999; Provencher 2001; Tkác et al. 2009) using a simulated basis set containing the following metabolites: Alanine (Ala), Aspartate (Asp), Phosphocholine (PCh), Creatine (Cr), Phosphocreatine (PCr), GABA, Glutamine (Gln), Glutamate (Glu), Glutathione (GSH), Glycine (Gly), Myo-inositol (mIns), Lactate (Lac), N-acetylaspartate (NAA), Scyllo-inositol (sIns), Taurine (Tau), Glucose (Glc), N-acetylaspartylglutamate (NAAG), Glycerophosphocholine (GPC), Phosphorylethanolamine (PE), Serine (Ser), and beta-hydroxybutyrate (bHB).~~of twenty-two brain metabolites~~. CSF, GM, WM fractions were calculated using GABA ANALYSIS TOOLKIT, Gannet 2.1 (Edden et al. 2014; Harris et al. 2015). Measured signal was corrected for the CSF-fraction of the voxel for 12 metabolites (Dhamala et al. 2019) including γ-aminobutyric acid (GABA) and glutamate (Glu), see descriptives in Table 1 and 2. Also~~,~~ a measured spectrum of fast-relaxing macromolecules (MM) was included in the basis set, based on an average metabolite-nulled brain macromolecular spectra acquired in six healthy volunteers. We excluded from the dataset 10 participants with low data quality: four in the V1 set and six in the set from insula. The inclusion criteria were signal-to-noise ratio (SNR) >= 30, w~~W~~ater linewidth <= 0,05 ppm, and good fit of LCModel (based on visual check of fit, baseline and residuals), see Figure 2-3 and Figure 2-4. The SNR and the FWHM (full width at half maximum) were determined by the program LCModel (Provencher, 1993). SNR is defined here as the ratio of the maximum in the spectrum minus baseline over the analysis window to twice the root mean square residuals. FWHM is a rough estimate of the linewidth in the in vivo spectrum. The maximum peak in the spectrum is NAA. ~~We excluded m~~Metabolites for which a single metabolite gives an average Cramèr-Rao lower bounds (CRLB) value > 20 % across all participants were excluded (Kreis 2016).

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 28.0.0.0 (190) and RStudio 2022.7.1.554. The normality, homoscedasticity and linearity of all variables were investigated using scatterplots. Correlations were computed by Spearman 's correlation coefficient and missing values were excluded in casewise fashion. Significance values are two-tailed and family-wise FDR corrected at α <0.05, unless stated otherwise. To investigate effects of biological sex on the main variables of interest Student~~Levene~~'s two-sample t-test was used

after testing the assumption of homogeneity of variances using Levene's test. Test statistics and p-values are also supplemented by Bayes factors reported in standard form as the ratio of evidence for the alternative hypothesis and for the null hypothesis (BF10). A default noninformative effect size prior was used: a Cauchy distribution with a scale parameter of $\sqrt{2}/2 \approx 0.707$.

To evaluate the relationship between responses on the aversive grating (VD-med) and neurotransmitter levels together with other psychological and biological variables, a backward stepwise regression, using the Bayesian~~Akaike~~ Information Criterion (BIC~~AIC~~; Schwarz 1978~~Csaki and Petrov 1973~~), was conducted in several phases. In backward stepwise regression, a full model including all candidate predictor variables is first constructed, after which regressors are removed one by one based on whether a measure of relative model quality (in this case BIC~~AIC~~) would be improved. Performing the model selection in phases allowed us to incorporate a priori assumptions into the process. For multiple linear regression, model coefficients are reported both in unstandardized (B) and standardized (beta) form to facilitate interpretation.

The first model included only the control low-frequency grating responses (VD-low ~~and VD-high~~) as a regressor~~s~~ to eliminate a broader underlying tendency to report sensory distortions and pre-cortical/ ocular processes independent of local cortical excitability. Backward stepwise regression was then computed with the effects of biological sex (women coded as 1, men as -1) and neurotransmitter levels, as well as their two-way interactions, using the first model as a lower limit on the included model terms. A third model was then constructed with all other biological and psychological variables (CAPS and GSQ total scores, five NEO-FFI factor scores, eight MAIA-2 subscale scores, and hours slept before experiment), ~~,~~ except those related to menstruation, using the second model as a lower limit on model terms.

After constructing the three models, a post hoc sensitivity analysis was conducted using G*Power version 3.1.9.7 (Faul et al., 2009) to determine the smallest increase in explained variance (R2) between the first and third models detectable with our sample size. Cohen's f2 was used as a standardized measure of effect size. Additionally, we calculated the smallest possible R2 of the full model, given the achieved R2 of the control-only (first) model, using the formula for f2 as a local effect size (Selya et al., 2012).

Additionally, the role of menstrual cycle in visual distortions and comfort during the perception of aversive grating (VD-med and Comfort-med) was examined using a basic cosine regression model to ensure that the number of days since menstruation is treated as a cyclical variable (Pewsey et al. 2013).

3. Results

The final sample included 160 young healthy volunteers (65 males, 95 females, age mean = 24.0, SD = 4.67). The main points of interest in spectroscopic analysis, GABA and glutamate, were ~~in accordance with previous spectroscopy research~~ correlated together positively in both occipital and insular voxel (Figure 3-1). In the occipital voxel, the average absolute concentrations were 3.3±0.55 [mM] for GABA, 10.1±0.83 [mM] for glutamate, and relative concentrations GABA/total creatine (tCr; phosphocreatine plus creatine) were 0.3±0.05 and glutamate/tCr were 0.93±0.07. ~~In the occipital voxel, the average absolute concentrations were 3.3±0.55 for GABA, 10.1±0.83 for glutamate, and concentrations relative to total creatine were 0.3±0.05 for GABA and 0.93±0.07 for glutamate (in mmol)~~; in the insular voxel, the average absolute concentrations were 3.89±0.6 [mM] for GABA, 14.44±1.34 [mM] for glutamate, and concentrations relative to total creatine were 0.32±0.05 for GABA and 1.18±0.09 for glutamate ~~(in mmol)~~. The average signal-to-noise ratio was 70.26±7.1 in V1 and 60.42±5.4 in insula, and full width at half maximum (FWHM) was 0.03±0.006 ppm (3.697±0.739 Hz) for both voxels.

Overall, there was not a significant difference between the sexes in both occipital and insular glutamate/tCr ~~and GABA/TCr~~ levels ~~concentration , as well as occipital GABA/tCr~~, as well as occipital GABA/tCr (Student's two-sample t-tests, ~~(~~all uncorrected $p > 0.05$ and $BF10 < 0.33$). However, men and women differed in insular GABA/tCr levels ($t = -3.411$, FDR corrected $p < 0.01$; $BF10 = 32.566$). Importantly, they also responded significantly differently to the key PGT variables, compared by the Student's two-sample t-test (FDR corrected): VD-med ($t = -3.795$, $p < 0.001$; $BF10 = 108.598$), VD-high ($t = -4.015$, $p < 0.001$; $BF10 = 228.127$), Comfort-med ($t = 3.131$, $p = 0.0042$) and Comfort-high ($t = 2.247$, $p = 0.04226$). Descriptives for the PGT scores are presented in Table 3~~1~~ and correlations between the PGT values in Figure 3-1 and Figure 3-2. The primary investigation focused on correlations between PGT scores and neurotransmitter levels ~~concentrations~~ in V1 and rAI (Figure 3 and Figure 4). Given the markedly different responses to the PGT scores in the two sexes, the general correlations are not truly relevant, and the correlations were calculated also for sample split by sex. Significant

differences between the sexes can be seen in the correlations of PGT scores and occipital and insular neurotransmitter levelsconcentrations. Therefore, as the next step, regression models accounting for the effect of sex were constructed to reveal the true role of neurotransmitters on PGT scores, with sex considered as an independent variable.

The coefficients of the three constructed linear models investigating the predictors of visual distortions on VD-med are graphically presented in Figure 5. Firstly, VD-med was regressed on thefor other two control gratings VD-low and VD-high to address the positive correlations between the variables (Model 1). In the second phase (Model 2), the model assessing the relationship with neurotransmitters selected only the occipital glutamate and its interaction with biological sex as a predictor contributing to the overall score. From the biological and psychological variables, only the GSQ overall score, and MAIA-2 Attention Regulation and Body Listening subscales remained in the final model (Model 3). Based on the model outcomes, CAPS questionnaire (mean = 6.32; SD = 4.949) and number of hours slept during the night before the experiment (mean = 6.84; SD = 1.521) did not predict subjectively perceived visual discomfort.

Outcomes of the third final model show that in the overall sample, there was a non-significant negative relationship between occipital glutamate and VD-med, with an increase of 0.1 mmol of Glu/tCr corresponding to -0.152 less distortions on average (B = -1.149; beta = -0.054). However, there was a significant ($p < 0.01$) interaction between occipital glutamate and sex, with women having a more negative relationship between glutamate and VD-med than men (B = -3.842.735; beta = -0.181229), while they generally reported more visual distortions on the aversive VD-med grating than men (B = 3.8522.613; beta = 0.186049). As the only included biological or and psychological variables, GSQ scores had a statistically significant ($p < 0.01$) positivethe strongest association with VD-med, as well as the only statistically significant ($p < 0.05$) regression coefficient (B = 0.02112; beta = 0.19822). Non-significant positive relationships with VD-med were also modeled for the Attention Regulation MAIA-2 subscale (B = 0.135; beta = 0.073). The only psychological variable to present a negative, though non-significant association with VD-med in the model was the MAIA-2 Body Listening subscale (B = -0.145; beta = -0.099). The first model (control-only) explained 21.84% of the variance in VD-med scores. The second model, which included occipital glutamate and its interaction with sex, accounted for 30.06% of the variance. The third model, which added GSQ, explained 33.87% of the variance in VD-med scores.

A post hoc sensitivity analysis was conducted to assess the difference in explained variance between Model 1 and Model 3 using the G*Power software. The analysis assumed an alpha level of 0.05, a power of 0.8, and a sample size of 160. The full model included five predictors, compared against a control-only model with one predictor. Under these assumptions, effect sizes larger than f2 = 0.077 can be reliably detected, which falls between Cohen's (1988) criteria for a small effect size (0.02) and a medium effect size (0.15). Given that Model 1 explains 21.84% of the variance in the dependent variable VD-med, this effect size corresponds to the full model needing to explain R2 = 27.42% or more.

Next, the cosine regression model evaluated the effect of the menstrual cycle on scores of aversive grating. Since the variables concerning menstruation were available only for a part of the sample, they could not be included in multivariate linear models. Their effects were therefore examined separately in a relevant subsample. Sixty-eight women reported having a normal menstrual cycle, while twenty-seven did not. There was no statistically significant difference (at $\alpha = 0.05$) between these groups in any of the PGT scores or neurotransmitter levels. Scores in VD-med were not predicted by the menstrual cycle ($F_{2,58} = 0.964$; $p = 0.388$). However, the cosine model of a cyclical relationship between the day of menstruation cycle and Comfort-med seemed to capture a non-significant trend ($F_{2,58} = 2.728$; $p = 0.074$), explaining 8.6 % of the variance in comfort ratings. The model is visualized using a scatterplot and a regression curve in Figure 6.

4. Discussion

4.1. Factors affecting perception of aversive spatial frequency

Despite being well-powered, our study did not confirm the hypothesis of a straightforward relationship between V1 occipital or insular neurotransmitter levels ~~concentrations~~ and the Pattern Glare Test as a selected proxy measure of visual sensitivity in neurotypical adults. However, a highly significant pattern of biological sex moderating this association emerged in our dataset. To our knowledge, this is the first work on cortical excitability and visual sensitivity to describe such an interaction. The differences between sexes' responses on the PGT were addressed and taken into consideration in further examination by correlations and linear regression modeling. Although both GABA and glutamate ~~concentrations~~ in the primary visual cortex were weakly negatively correlated with visual distortions on aversive medium-

frequency grating of 3 cpd in women, this correlation had a positive trend in men. When controlled for sex in the regression modeling, GABA was not included in the final model. On the contrary, our model revealed the predictive power of occipital glutamate, but only when an interaction with biological sex was modeled. This suggests that its role is more important in visual sensitivity than GABA. The role of insular neurotransmitters in the perception of aversive gratings was not supported by the model's outcomes.

As far as responses in the primary visual cortex are concerned, our findings do not uphold the assumption of a direct involvement of GABA and glutamate levels in subjective visual sensitivity, suggesting the hyperexcitability hypothesis requires refinement~~is not universally valid~~. Furthermore, although relatively weak, the direction of the relationship was opposite to what would be expected, both on the sample level and in the female subgroup, with larger resting glutamate levels in V1 corresponding to the experience of *fewer* visual distortions. These paradoxical findings might result partly from the neuroimaging method used. Magnetic resonance spectroscopy provides information on baseline neurochemical levels in subjects' neuronal cytoplasm, but does not quantify synaptic neurotransmitter activity (Stagg et al. 2011b; Duncan et al. 2014), which is more likely than total metabolite concentrations to be directly related to perceptual responses (Chan et al. 2022). In previous research that we built upon, significant results were achieved only after modulating basic cortical excitability through neurostimulation methods such as transcranial direct current stimulation (tDCS), or directly during the PGT. Our findings suggest that task-related visual sensitivity in neurotypical adults may be influenced by underlying cortical processes beyond simple quantification of neurotransmitter concentrations during resting state – individuals prone to pattern glare could show signs of elevated cortical excitability only after being exposed to aversive patterns and their baseline neurotransmitter levels measured in a separate MRS session do not play a critical role in their subjective PGT scores.

Another possible explanation lies within the examined test subjects. The imbalance between excitatory and inhibitory mechanisms in relation to sensory sensitivity was described in studies of wide range of neurological and neurodevelopmental disorders including migraine (Aurora and Wilkinson 2007; Nguyen et al. 2016), epilepsy (Wilkins et al. 2004), autism spectrum disorder (Dickinson et al. 2016; Wood et al. 2021), depression (Qi et al. 2019; Wang et al. 2022), or anxiety (Hui et al. 2023). However, the expected relationship between the Pattern Glare Test and neurotransmitter levels ~~concentrations~~ in V1 of the visual cortex may not be

sufficiently robust in the neurotypical individuals to reliably deduce GABA or glutamate ~~concentration~~ as a reliable indicator of visual discomfort. Additional factor possibly affecting the outcomes could be that our study sample generally scored low on the susceptibility to aberrant experiences, as shown by the CAPS questionnaire (mean = 6.32; SD = 4.95).

Apart from neurotransmitters, the modulatory role of only a single ~~several~~ psychological variable~~s~~ was revealed: trait-based sensory sensitivity (GSQ)~~, worse reading of and sustaining attention to physical signals (MAIA-2)~~. Other variables, including susceptibility to anomalous perceptions (CAPS), perception of body sensations (MAIA-2), personality factors (NEO-FFI), and sleep, were not included as relevant by the constructed models.

In women, the day of the menstrual cycle affected the comfort rating; the closer to ovulation, the higher the comfort, which then gradually decreased during the luteal phase and was the lowest at the beginning of the menstrual phase. This is in accordance with the progesterone-derived neurosteroids inhibitory effect during the follicular menstrual phase caused by the increase in the GABAergic inhibition (Smith et al. 2002), decrease in glutamate excitation and inhibition of pyramidal neurons (Stahl 2008), which can possibly reduce the feeling of subjective discomfort while observing the aversive patterns.

4.2. Sex differences in subjectively reported visual stress

Our findings make a novel and noteworthy contribution to examining individual predisposition to pattern glare effects of visual discomfort. However, the complexity of the relationship between neurotransmitters and reported visual stress by the two sexes is challenging. There was no statistical difference between the sexes in occipital ~~nor insular~~ neurotransmitter levels~~concentrations~~, the difference in means was only found for the PGT variables. We found no pattern in psychological traits examined in this work that explains these differences. A comprehensive investigation of the Pattern Glare Test carried out by Evans and Stevenson (2008) with the objective of establishing standard testing norms indicated that while pattern glare correlates with conditions such as migraines, which exhibit a higher prevalence in women, their study did not identify substantial gender disparities in behavioral responses. However, it is worth mentioning that their sample comprised 33 females and 33 males with notably broad age ranges in both groups (48 ± 21 years; range: 12–82 years; 48 ± 25 years; range: 10–90 years, respectively), which differ substantially from those in our study and also included children. The same study revealed that the effect of PGT decreases with age

significantly at both medium and high-frequency patterns. This leads us to speculate that sex differences might have been present in young adults in the age range used in our study but were statistically mitigated by age effects. Although there are a few studies that considered the potential influence of biological sex on the PGT scores in their study design by gender-matching the sample (e.g. Allen et al. 2010; Beasley and Davies, 2012; Qi et. al, 2019), no study known to us that utilized Pattern Glare Test as a proxy measure of visual stress considered sex as a possible covariate during the analysis. –Yet, an emerging number of recent studies propose the importance of control for sex in vision research (Shaqiri et al. 2018), whether the arguments arises from addressed differences in perception of color (Johansson et al. 2018; Abramov et al. 2012a; Fider and Komarova 2019), visual acuity (Abramov et al. 2012b), contrast sensitivity (Foutch and Peck 2013), or motion perception (Ruggeri et al. 2020). Considered together with the sex-contradictory results of this study, involvement of both sexes equally and inclusion of sex as a factor in the statistical analyses of future PGT studies could bring new insight into this area.

The present study has a few methodological limitations. First, the sex differences observed in subjective responses played a significant role in disentangling the actual role of neurotransmitters, thus the behavioral responses could not be easily explained by correlations. Although the study was performed on a very large sample, further research should be performed to replicate these results in a different neurotypical sample, given that previous studies did not identify the observed inter-sex differences in PGT scores. In addition, it would be useful to conduct a study on neurodiverse or neurological clinical samples that have been previously investigated in visual sensitivity research, as this could improve our understanding of the factors influencing the results of this study. The impact of sex differences should be considered in the study design, while controlling for the biological variables, such as menstrual cycle. Second, although this study was focused on the relationship between the pattern glare scores and the neurotransmitter levels, concentrations were not obtained directly during the visual task. There is evidence for differences in these levels during the different conditions, e.g. GABA ~~concentrations~~ decreases whereas Glx (glutamate + glutamine) levels increase with increasing visual input (Kurcyus et al. 2018). Our results showed that decreased glutamate levels correlate with increased number of visual distortions, but this could be claimed only for its resting state ~~concentration~~ with closed eyes. It would be useful to verify this relationship with spectroscopy measurement during the PGT. Moreover, based on previous literature, we believe that the SPECIAL sequence is capable of providing reliable GABA measurements.

However, it would be useful for future work to validate the current findings using more conventional GABA measurement techniques (i.e., MEGA-PRESS). Lastly, we suggest expanding the scope of investigation within the visual cortex to encompass the association cortex. Previous research on visual discomfort among migraine patients has indicated a notable decrease in cortical activation within areas V2-V4 when utilizing colored lenses, contrasting with findings in V1 (Huang et al. 2011). This implies that exploring the hyperexcitability of association visual cortex in neurotypical subjects could provide fresh insights into the underlying neural mechanisms influencing heightened reactions to aversive visual stimuli, as the visual association cortex may mediate such effects more than V1.

5. Code Accessibility

The R script for statistical analysis is available in the Zenodo repository at: https://doi.org/10.5281/zenodo.1220868~~10.5281/zenodo.10890416~~.

6. Abbreviations

GABA - γ-aminobutyric acid
MRS - magnetic resonance spectroscopy
PGT - Pattern Glare Test
cpd - cycles per degree (spatial frequency unit)
VD - visual distortion
rAI - right anterior insula

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8. References

Abramov, I., Gordon, J., Feldman, O. and Chavarga, A. (2012a). Sex and vision II: color appearance of monochromatic lights. *Biology of sex differences*, 3(1), p. 21, doi:10.1186/2042-6410-3-21.

Abramov, I., Gordon, J., Feldman, O. and Chavarga, A. (2012b). Sex and vision I: Spatio-temporal resolution. *Biology of sex differences*, 3(1), p. 20, doi:10.1186/2042-6410-3-20.

Adjamian, P., Holliday, I. E., Barnes, G. R., Hillebrand, A., Hadjipapas, A. and Singh, K. D. (2004). Induced visual illusions and gamma oscillations in human primary visual cortex. *The European journal of neuroscience*, 20(2), pp. 587–592, doi:10.1111/j.1460-9568.2004.03495.x.

Allen, P. M., Hussain, A., Usherwood, C., and Wilkins, A. J. (2010). Pattern-related visual stress, chromaticity, and accommodation. Investigative Ophthalmology and Visual Science, 51(12), 6843–6849. https://doi.org/10.1167/iovs.09-5086.

Aurora, S. K. and Wilkinson, F. (2007). The brain is hyperexcitable in migraine. *Cephalalgia: an international journal of headache*, 27(12), pp. 1442–1453, doi:10.1111/j.1468-2982.2007.01502.x.

Badawy, R. A. B., Loetscher, T., Macdonell, R. A. L. and Brodtmann, A. (2012). Cortical excitability and neurology: insights into the pathophysiology. *Functional neurology*, 27(3), pp. 131–145.

Beasley, I. G., and Davies, L. N. (2012). Susceptibility to pattern glare following stroke. Journal of Neurology, 259(9), 1832–1839. https://doi.org/10.1007/s00415-012-6418-5.

Bell, V., Halligan, P. W. and Ellis, H. D. (2006). The Cardiff Anomalous Perceptions Scale (CAPS): a new validated measure of anomalous perceptual experience. *Schizophrenia bulletin*, 32(2), pp. 366–377, doi:10.1093/schbul/sbj014.

Braithwaite, J. J., Broglia, E., Bagshaw, A. P. and Wilkins, A. J. (2013). Evidence for elevated cortical hyperexcitability and its association with out-of-body experiences in the non-clinical population: new findings from a pattern-glare task. *Cortex; a journal devoted to the study of the nervous system and behavior*, 49(3), pp. 793–805, doi:10.1016/j.cortex.2011.11.013.

614 Braithwaite, J. J., Mevorach, C. and Takahashi, C. (2015). Stimulating the aberrant brain:
615 Evidence for increased cortical hyperexcitability from a transcranial direct current
616 stimulation (tDCS) study of individuals predisposed to anomalous perceptions. *Cortex; a*
617 *journal devoted to the study of the nervous system and behavior*, 69, pp. 1–13,
618 doi:10.1016/j.cortex.2015.03.023.

619 Campbell, M. E. J., Mehrkanoon, S. and Cunnington, R. (2018). Intentionally not
620 imitating: Insula cortex engaged for top-down control of action mirroring.
621 *Neuropsychologia*, 111, pp. 241–251, doi:10.1016/j.neuropsychologia.2018.01.037.

622 Cauda, F., D'Agata, F., Sacco, K., Duca, S., Geminiani, G. and Vercelli, A. (2011).
623 Functional connectivity of the insula in the resting brain. *NeuroImage*, 55(1), pp. 8–23,
624 doi:10.1016/j.neuroimage.2010.11.049.

625 Cebeiro and Rodríguez (2019). Mirror neurons: A biological genesis of relational. *Papeles*
626 *del psicólogo*, 40(3), pp. 226–232, doi:10.23923/PAP.PSICOL2019.2900.

627 Chan, Y. M., Glarin, R., Moffat, B. A., Bode, S. and McKendrick, A. M. (2022). Relating
628 the cortical visual contrast gain response to spectroscopy-measured excitatory and
629 inhibitory metabolites in people who experience migraine. *PloS one*, 17(4), p. e0266130,
630 doi:10.1371/journal.pone.0266130.

631 Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences. Lawrence
632 Erlbaum Associates.

633 Conlon, E., Lovegrove, W., Barker, S. and Chekaluk, E. (2001). Visual discomfort: the
634 influence of spatial frequency. *Perception*, 30(5), pp. 571–581, doi:10.1068/p2954.

635 Costa, P. T. (1989). *NEO PI/FFI Manual Supplement for Use with the NEO Personality*
636 *Inventory and the NEO Five-Factor Inventory*. Psychological Assessment Resources.

637 Costa, P. T. and McCrae, R. R. (1985). *The NEO personality inventory: manual form S*
638 *and form R*. Psycholog. Assessment Resources.

639 Costa, P. T. and McCrae, R. R. (1992). *Revised NEO Personality Inventory (NEO PI-R)*
640 *and NEP Five-factor Inventory (NEO-FFI): Professional Manual*. Psychological
641 Assessment Resources.

Craig, A. D. B. (2009). How do you feel--now? The anterior insula and human awareness. *Nature reviews. Neuroscience*, 10(1), pp. 59–70, doi:10.1038/nrn2555.

~~Csaki, F. and Petrov, B. N. (1973). *Information Theory: Proceedings of the 2nd International Symposium*. Akadémiai Kiado.~~

Cueva, A. S., Galhardoni, R., Cury, R. G., Parravano, D. C., Correa, G., Araujo, H., Cecilio, S. B., Raicher, I., Toledo, D., Silva, V., Marcolin, M. A., Teixeira, M. J. and Ciampi de Andrade, D. (2016). Normative data of cortical excitability measurements obtained by transcranial magnetic stimulation in healthy subjects. *Neurophysiologie clinique = Clinical neurophysiology*, 46(1), pp. 43–51, doi:10.1016/j.neucli.2015.12.003.

Dance, C. J., Ward, J. and Simner, J. (2021). What is the Link Between Mental Imagery and Sensory Sensitivity? Insights from Aphantasia. *Perception*, 50(9), pp. 757–782, doi:10.1177/03010066211042186.

De Valois, R. L., Morgan, H. and Snodderly, D. M. (1974). Psychophysical studies of monkey vision. 3. Spatial luminance contrast sensitivity tests of macaque and human observers. *Vision research*, 14(1), pp. 75–81, doi:10.1016/0042-6989(74)90118-7.

Dhamala, E., Abdelkefi, I., Nguyen, M., Hennessy, T. J., Nadeau, H. and Near, J. (2019). Validation of in vivo MRS measures of metabolite concentrations in the human brain. *NMR in biomedicine*, 32(3), p. e4058, doi:10.1002/nbm.4058.

Dickinson, A., Jones, M. and Milne, E. (2016). Measuring neural excitation and inhibition in autism: Different approaches, different findings and different interpretations. *Brain research*, 1648(Pt A), pp. 277–289, doi:10.1016/j.brainres.2016.07.011.

Douglas, R. J. and Martin, K. A. C. (2004). NEURONAL CIRCUITS OF THE NEOCORTEX. *Annual Review of Neuroscience*.

Downar, J., Crawley, A. P., Mikulis, D. J. and Davis, K. D. (2000). A multimodal cortical network for the detection of changes in the sensory environment. *Nature neuroscience*, 3(3), pp. 277–283, doi:10.1038/72991.

Duncan, N. W., Wiebking, C., Muñoz-Torres, Z. and Northoff, G. (2014). How to investigate neuro-biochemical relationships on a regional level in humans? Methodological considerations for combining functional with biochemical imaging.

671 *Journal of neuroscience methods*, 221, pp. 183–188,
672 doi:10.1016/j.jneumeth.2013.10.011.

673 Edden, R. A. E., Puts, N. A. J., Harris, A. D., Barker, P. B. and Evans, C. J. (2014). Gannet:
674 A batch-processing tool for the quantitative analysis of gamma-aminobutyric acid–edited
675 MR spectroscopy spectra. *Journal of magnetic resonance imaging: JMRI*, 40(6), pp.
676 1445–1452, doi:10.1002/jmri.24478.

677 Evans, B. J. W. and Stevenson, S. J. (2008). The Pattern Glare Test: A review and
678 determination of normative values. *Ophthalmic and physiological optics: the journal of*
679 *the British College of Ophthalmic Opticians* , 28(4), pp. 295–309, doi:10.1111/j.1475-
680 1313.2008.00578.x.

681 Faul, F., Erdfelder, E., Buchner, A. and Lang, A.-E. (2009). Statistical power analyses
682 using G*Power 3.1: Tests for correlation and regression analyses. Behavior Research
683 Methods, 41(4), pp. 1149-1160, doi:10.3758/BRM.41.4.1149.

684 Fermin, A. S. R., Friston, K. and Yamawaki, S. (2021). Insula Interoception, Active
685 Inference and Feeling Representation. *arXiv [q-bio.NC]*.

686 Fider, N. A. and Komarova, N. L. (2019). Differences in color categorization manifested
687 by males and females: a quantitative World Color Survey study. *Palgrave*
688 *Communications*, 5(1), pp. 1–10, doi:10.1057/s41599-019-0341-7.

689 Fong, C. Y., Law, W. H. C., Braithwaite, J. J. and Mazaheri, A. (2020). Differences in
690 early and late pattern-onset visual-evoked potentials between self- reported migraineurs
691 and controls. *NeuroImage. Clinical*, 25, p. 102122, doi:10.1016/j.nicl.2019.102122.

692 Fong, C. Y., Takahashi, C. and Braithwaite, J. J. (2019). Evidence for distinct clusters of
693 diverse anomalous experiences and their selective association with signs of elevated
694 cortical hyperexcitability. *Consciousness and cognition*, 71, pp. 1–17,
695 doi:10.1016/j.concog.2019.03.003.

696 Foutch, B. K. and Peck, C. K. (2013). Gender differences in contrast thresholds to biased
697 stimuli. *JSM Ophthalmol*, 1, p. 1007.

698 Geisler, W. S. (2008). Visual Perception and the Statistical Properties of Natural Scenes.
699 *Annual Review of Psychology*.

Gogolla, N. (2017). The insular cortex. *Current biology: CB*, 27(12), pp. R580–R586, doi:10.1016/j.cub.2017.05.010.

Green, S. A. and Wood, E. T. (2019). The role of regulation and attention in atypical sensory processing. *Cognitive neuroscience*.

Gröhn, H., Gillick, B. T., Tkáč, I., Bednařík, P., Mascali, D., Deelchand, D. K., Michaeli, S., Meekins, G. D., Leffler-McCabe, M. J., MacKinnon, C. D., Eberly, L. E. and Mangia, S. (2019). Influence of Repetitive Transcranial Magnetic Stimulation on Human Neurochemistry and Functional Connectivity: A Pilot MRI/MRS Study at 7 T. *Frontiers in neuroscience*, 13, p. 1260, doi:10.3389/fnins.2019.01260.

Haigh, S. M., Barningham, L., Berntsen, M., Coutts, L. V., Hobbs, E. S. T., Irabor, J., Lever, E. M., Tang, P. and Wilkins, A. J. (2013). Discomfort and the cortical haemodynamic response to coloured gratings. *Vision research*, 89, pp. 47–53, doi:10.1016/j.visres.2013.07.003.

Haigh, S. M., Cooper, N. R. and Wilkins, A. J. (2015). Cortical excitability and the shape of the haemodynamic response. *NeuroImage*, 111, pp. 379–384, doi:10.1016/j.neuroimage.2015.02.034.

Harris, A. D., Puts, N. A. J. and Edden, R. A. E. (2015). Tissue correction for GABA-edited MRS: Considerations of voxel composition, tissue segmentation, and tissue relaxations. *Journal of magnetic resonance imaging: JMRI*, 42(5), pp. 1431–1440, doi:10.1002/jmri.24903.

Hattemer, K., Knake, S., Reis, J., Rochon, J., Oertel, W. H., Rosenow, F. and Hamer, H. M. (2007). Excitability of the motor cortex during ovulatory and anovulatory cycles: a transcranial magnetic stimulation study. *Clinical endocrinology*, 66(3), pp. 387–393, doi:10.1111/j.1365-2265.2007.02744.x.

Hibbard, P. B. and O'Hare, L. (2015). Uncomfortable images produce non-sparse responses in a model of primary visual cortex. *Royal Society open science*, 2(2), p. 140535, doi:10.1098/rsos.140535.

Huang, J., Cooper, T. G., Satana, B., Kaufman, D. I. and Cao, Y. (2003). Visual distortion provoked by a stimulus in migraine associated with hyperneuronal activity. *Headache*,

43(6), pp. 664–671, doi:10.1046/j.1526-4610.2003.03110.x.

Huang, J., Zong, X., Wilkins, A., Jenkins, B., Bozoki, A. and Cao, Y. (2011). fMRI evidence that precision ophthalmic tints reduce cortical hyperactivation in migraine. *Cephalalgia*.

Hui, C. L.-M., Wong, S. M.-Y., Yu, T. Y.-T., Lau, T. T.-Y., Choi, O., Tsang, S., Suen, Y.-N., Lam, B. Y.-H., Wong, C. S.-M., Lui, S. S.-Y., Chan, K.-T., Wong, M. T.-H., Wong, G. H.-Y., Chan, S. K.-W., Lee, E. H.-M., Chang, W.-C., Wilkins, A. and Chen, E. Y.-H. (2023). Visual-stress-related cortical excitability as a prospective marker for symptoms of depression and anxiety in young people. *European archives of psychiatry and clinical neuroscience*, 273(5), pp. 1051–1060, doi:10.1007/s00406-022-01469-7.

Inghilleri, M., Conte, A., Currà, A., Frasca, V., Lorenzano, C. and Berardelli, A. (2004). Ovarian hormones and cortical excitability. An rTMS study in humans. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, 115(5), pp. 1063–1068, doi:10.1016/j.clinph.2003.12.003.

Johansson, L. H., Skoog, I. and Zetterberg, M. (2018). Gender differences in objective and subjective visual function. *Investigative ophthalmology and visual science*, 59(9), pp. 1090–1090.

Kreis, R. (2016). The trouble with quality filtering based on relative Cramér-Rao lower bounds. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 75(1), pp. 15–18, doi:10.1002/mrm.25568.

Kurcyus, K., Annac, E., Hanning, N. M., Harris, A. D., Oeltzschner, G., Edden, R. and Riedl, V. (2018). Opposite Dynamics of GABA and Glutamate Levels in the Occipital Cortex during Visual Processing. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, 38(46), pp. 9967–9976, doi:10.1523/JNEUROSCI.1214-18.2018.

Le, A. T. D., Payne, J., Clarke, C., Kelly, M. A., Prudenziati, F., Armsby, E., Penacchio, O. and Wilkins, A. J. (2017). Discomfort from urban scenes: Metabolic consequences. *Landscape and urban planning*, 160, pp. 61–68, doi:10.1016/j.landurbplan.2016.12.003.

Lin A, Andronesi O, Bogner W, Choi IY, Coello E, Cudalbu C, Juchem C, Kemp GJ, Kreis R, Krššák M, Lee P, Maudsley AA, Meyerspeer M, Mlynarik V, Near J, Öz G, Peek AL, Puts NA, Ratai EM, Tkáč I, Mullins PG; Experts' Working Group on Reporting Standards for MR Spectroscopy. Minimum Reporting Standards for in vivo Magnetic Resonance Spectroscopy (MRSinMRS): Experts' consensus recommendations. NMR Biomed. 2021 May;34(5):e4484. doi: 10.1002/nbm.4484.

Mehling, W. E., Price, C., Daubenmier, J. J., Acree, M., Bartmess, E. and Stewart, A. (2012). The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PloS one*, 7(11), p. e48230, doi:10.1371/journal.pone.0048230.

Meisel, C., Schulze-Bonhage, A., Freestone, D., Cook, M. J., Achermann, P. and Plenz, D. (2015). Intrinsic excitability measures track antiepileptic drug action and uncover increasing/decreasing excitability over the wake/sleep cycle. *Proceedings of the National Academy of Sciences of the United States of America*, 112(47), pp. 14694–14699, doi:10.1073/pnas.1513716112.

Mekle, R., Mlynárik, V., Gambarota, G., Hergt, M., Krueger, G. and Gruetter, R. (2009). MR spectroscopy of the human brain with enhanced signal intensity at ultrashort echo times on a clinical platform at 3T and 7T. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 61(6), pp. 1279–1285, doi:10.1002/mrm.21961.

Near J, Simpson R, Cowen P, Jezzard P. Efficient γ-aminobutyric acid editing at 3T without macromolecule contamination: MEGA-SPECIAL. NMR Biomed. 2011 Dec;24(10):1277-85. doi: 10.1002/nbm.1688. Epub 2011 Mar 8. PMID: 21387450.

Near, J., Andersson, J., Maron, E., Mekle, R., Gruetter, R., Cowen, P. and Jezzard, P. (2013). Unedited in vivo detection and quantification of γ-aminobutyric acid in the occipital cortex using short-TE MRS at 3 T. *NMR in biomedicine*, 26(11), pp. 1353–1362, doi:10.1002/nbm.2960.

Nguyen, B. N., McKendrick, A. M. and Vingrys, A. J. (2016). Abnormal inhibition-excitation imbalance in migraine. *Cephalalgia: an international journal of headache*, 36(1), pp. 5–14, doi:10.1177/0333102415576725.

O'Hare, L. (2017). Steady-state VEP responses to uncomfortable stimuli. *The European*

journal of neuroscience, 45(3), pp. 410–422, doi:10.1111/ejn.13479.

O'Hare, L., Clarke, A. D. F. and Pollux, P. M. J. (2015). VEP Responses to Op-Art Stimuli. *PLOS ONE*.

Orekhova, E. V., Stroganova, T. A., Schneiderman, J. F., Lundström, S., Riaz, B., Sarovic, D., Sysoeva, O. V., Brant, G., Gillberg, C. and Hadjikhani, N. (2019). Neural gain control measured through cortical gamma oscillations is associated with sensory sensitivity. *Human brain mapping*, 40(5), pp. 1583–1593, doi:10.1002/hbm.24469.

Öz, G., Deelchand, D. K., Wijnen, J. P., Mlynárik, V., Xin, L., Mekle, R., Noeske, R., Scheenen, T. W. J., Tkáč, I. and Experts' Working Group on Advanced Single Voxel 1H MRS (2020). Advanced single voxel 1 H magnetic resonance spectroscopy techniques in humans: Experts' consensus recommendations. *NMR in biomedicine*, p. e4236, doi:10.1002/nbm.4236.

Park, Y. W., Deelchand, D. K., Joers, J. M., Soher, B. J., Barker, P. B., Park, H., Öz, G. and Lenglet, C. (2016). Fast automatic voxel positioning with non-rigid registrations for improved between-subject consistency in MRS. In: *Proc. Intl. Soc. Mag. Reson. Med*. p. 2343.

Pewsey, A., Neuhäuser, M. and Ruxton, G. D. (2013). *Circular Statistics in R*. OUP Oxford.

Pfeuffer, J., Tkác, I., Provencher, S. W. and Gruetter, R. (1999). Toward an in vivo neurochemical profile: quantification of 18 metabolites in short-echo-time (1)H NMR spectra of the rat brain. *Journal of magnetic resonance* , 141(1), pp. 104–120, doi:10.1006/jmre.1999.1895.

Provencher, S. W. (1993). Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 30(6), pp. 672–679, doi:10.1002/mrm.1910300604.

Provencher, S. W. (2001). Automatic quantitation of localized in vivo 1H spectra with LCModel. *NMR in biomedicine*, 14(4), pp. 260–264, doi:10.1002/nbm.698.

Qi, X., Fan, H., Yang, X., Chen, Y., Deng, W., Guo, W., Wang, Q., Chen, E., Li, T. and

817 Ma, X. (2019). High level of pattern glare in major depressive disorder. *BMC psychiatry*,
818 19(1), p. 415, doi:10.1186/s12888-019-2399-6.

819 Radhakrishnan, K., St Louis, E. K., Johnson, J. A., McClelland, R. L., Westmoreland, B.
820 F. and Klass, D. W. (2005). Pattern-sensitive epilepsy: electroclinical characteristics,
821 natural history, and delineation of the epileptic syndrome. *Epilepsia*, 46(1), pp. 48–58,
822 doi:10.1111/j.0013-9580.2005.26604.x.

823 Rahmani, M. and Rahmani, F. (2019). Cortex, Insula, and Interoception. In: Rezaei, N.
824 and Saghazadeh, A. (eds.) *Biophysics and Neurophysiology of the Sixth Sense*. Cham:
825 Springer International Publishing, pp. 59–68.

826 Robertson, A. E. and Simmons, D. R. (2013). The relationship between sensory sensitivity
827 and autistic traits in the general population. *Journal of autism and developmental*
828 *disorders*, 43(4), pp. 775–784, doi:10.1007/s10803-012-1608-7.

829 Ruggeri, P., Nguyen, N., Pegna, A. J. and Brandner, C. (2020). Interindividual differences
830 in brain dynamics of early visual processes: Impact on score accuracy in the mental
831 rotation task. *Psychophysiology*, 57(11), p. e13658, doi:10.1111/psyp.13658.

832 Saffin, J. M. and Tohid, H. (2016). Walk like me, talk like me. The connection between
833 mirror neurons and autism spectrum disorder. *Neurosciences* , 21(2), pp. 108–119,
834 doi:10.17712/nsj.2016.2.20150472.

835 Schwarz G (1978) Estimating the dimension of a model. The Annals of Statistics, 6(2),
836 pp. 461–464, doi:10.1214/aos/1176344136.

837 Selya, A. S., Rose, J. S., Dierker, L. C., Hedeker, D. and Mermelstein, R. J. (2012). A
838 practical guide to calculating Cohen's f2, a measure of local effect size, from PROC
839 MIXED. Frontiers in Psychology, 3, p. 111.

840 Shaqiri, A., Roinishvili, M., Grzeczkowski, L., Chkonia, E., Pilz, K., Mohr, C., Brand, A.,
841 Kunchulia, M. and Herzog, M. H. (2018). Sex-related differences in vision are
842 heterogeneous. *Scientific reports*, 8(1), p. 7521, doi:10.1038/s41598-018-25298-8.

843 Silvestro, M., Tessitore, A., Di Nardo, F., Scotto di Clemente, F., Trojsi, F., Cirillo, M.,
844 Esposito, F., Tedeschi, G. and Russo, A. (2022). Functional connectivity changes in
845 complex migraine aura: beyond the visual network. *European journal of neurology: the*

official journal of the European Federation of Neurological Societies, 29(1), pp. 295–304, doi:10.1111/ene.15061.

Simpson, R., Devenyi, G. A., Jezzard, P., Hennessy, T. J. and Near, J. (2017). Advanced processing and simulation of MRS data using the FID appliance (FID-A)-An open source, MATLAB-based toolkit. *Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 77(1), pp. 23–33, doi:10.1002/mrm.26091.

Smith, M. J., Adams, L. F., Schmidt, P. J., Rubinow, D. R. and Wassermann, E. M. (2002). Effects of ovarian hormones on human cortical excitability. *Annals of neurology*, 51(5), pp. 599–603, doi:10.1002/ana.10180.

Smith, M. J., Keel, J. C., Greenberg, B. D., Adams, L. F., Schmidt, P. J., Rubinow, D. A. and Wassermann, E. M. (1999). Menstrual cycle effects on cortical excitability. *Neurology*, 53(9), pp. 2069–2072, doi:10.1212/wnl.53.9.2069.

Song, C., Sandberg, K., Andersen, L. M., Blicher, J. U. and Rees, G. (2017). Human Occipital and Parietal GABA Selectively Influence Visual Perception of Orientation and Size. *The Journal of neuroscience: the official journal of the Society for Neuroscience*, 37(37), pp. 8929–8937, doi:10.1523/JNEUROSCI.3945-16.2017.

Stagg, C. J., Bachtiar, V. and Johansen-Berg, H. (2011a). What are we measuring with GABA magnetic resonance spectroscopy? *Communicative and integrative biology*, 4(5), pp. 573–575, doi:10.4161/cib.4.5.16213.

Stagg, C. J., Bestmann, S., Constantinescu, A. O., Moreno, L. M., Allman, C., Mekle, R., Woolrich, M., Near, J., Johansen-Berg, H. and Rothwell, J. C. (2011b). Relationship between physiological measures of excitability and levels of glutamate and GABA in the human motor cortex. *The Journal of physiology*, 589(Pt 23), pp. 5845–5855, doi:10.1113/jphysiol.2011.216978.

Stahl, S. M. (2008). *Depression and Bipolar Disorder: Stahl's Essential Psychopharmacology, 3rd Edition*. Cambridge University Press.

Szmajda, B. A. and Devries, S. H. (2011). Glutamate spillover between mammalian cone photoreceptors. *The Journal of neuroscience: the official journal of the Society for*

875 *Neuroscience*, 31(38), pp. 13431–13441, doi:10.1523/JNEUROSCI.2105-11.2011.

876 Thatcher, R. W., North, D. M., Neubrander, J., Biver, C. J., Cutler, S. and Defina, P.
877 (2009). Autism and EEG phase reset: deficient GABA mediated inhibition in thalamo-
878 cortical circuits. *Developmental neuropsychology*, 34(6), pp. 780–800,
879 doi:10.1080/87565640903265178.

880 Tkác, I., Oz, G., Adriany, G., Uğurbil, K. and Gruetter, R. (2009). In vivo 1H NMR
881 spectroscopy of the human brain at high magnetic fields: metabolite quantification at 4T
882 vs. 7T. *Magnetic resonance in medicine: official journal of the Society of Magnetic*
883 *Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 62(4), pp. 868–879,
884 doi:10.1002/mrm.22086.

885 Tkác, I., Starcuk, Z., Choi, I. Y. and Gruetter, R. (1999). In vivo 1H NMR spectroscopy
886 of rat brain at 1 ms echo time. *Magnetic resonance in medicine: official journal of the*
887 *Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*,
888 41(4), pp. 649–656, doi:10.1002/(sici)1522-2594(199904)41:4<649::aid-mrm2>3.0.co;2-
889 g.

890 Tso, A. R., Trujillo, A., Guo, C. C., Goadsby, P. J. and Seeley, W. W. (2015). The anterior
891 insula shows heightened interictal intrinsic connectivity in migraine without aura.
892 *Neurology*, 84(10), pp. 1043–1050, doi:10.1212/WNL.0000000000001330.

893 Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction.
894 *Nature reviews. Neuroscience*, 16(1), pp. 55–61, doi:10.1038/nrn3857.

895 Wang, M., Qi, X., Yang, X., Fan, H., Dou, Y., Guo, W., Wang, Q., Chen, E., Li, T. and
896 Ma, X. (2022). The pattern glare and visual memory are disrupted in patients with major
897 depressive disorder. *BMC psychiatry*, 22(1), p. 518, doi:10.1186/s12888-022-04167-9.

898 Ward, J. (2019). Individual differences in sensory sensitivity: A synthesizing framework
899 and evidence from normal variation and developmental conditions. *Cognitive*
900 *neuroscience*, 10(3), pp. 139–157, doi:10.1080/17588928.2018.1557131.

901 Wilkins, A., Huang, J. and Cao, Y. (2004). Visual stress theory and its application to
902 reading and reading tests. *Journal of research in reading*, 27(2), pp. 152–162,
903 doi:10.1111/j.1467-9817.2004.00223.x.

Wilkins, A. J. and Evans, B. J. W. (2010). Visual stress, its treatment with spectral filters, and its relationship to visually induced motion sickness. *Applied ergonomics*, 41(4), pp. 509–515, doi:10.1016/J.APERGO.2009.01.011.

Wilkins, A., Nimmo-Smith, I., Tait, A., McManus, C., Della Sala, S., Tilley, A., Arnold, K., Barrie, M. and Scott, S. (1984). A neurological basis for visual discomfort. *Brain: a journal of neurology*, 107 (Pt 4), pp. 989–1017, doi:10.1093/brain/107.4.989.

Wood, E. T., Cummings, K. K., Jung, J., Patterson, G., Okada, N., Guo, J., O'Neill, J., Dapretto, M., Bookheimer, S. Y. and Green, S. A. (2021). Sensory over-responsivity is related to GABAergic inhibition in thalamocortical circuits. *Translational psychiatry*, 11(1), p. 39, doi:10.1038/s41398-020-01154-0.

9. Captions

Figure 1. Pattern Glare Test trial. Fixation dot was followed by one of four stimuli and all three response screens: VD selection - What did you perceive when looking at the image? (shadowy shapes amongst the lines, shimmering, flickering, bending, illusory stripes, red, blue, yellow, green, nausea, dizziness, ocular pain; select as many as perceived). Laterality selection - the distortions were more prominent on: left side, both sides about the same, right side (select). Comfort rating - How comfortable was looking at the image? Rate on a scale: -5 = very uncomfortable, 0 = neither comfortable nor uncomfortable, 5 = very comfortable.

Figure 2. Representative example of magnetic resonance spectra from a single subject. (1) Occipital voxel placement. (2) Right anterior insula voxel placement. (3) ~~Example of LCModel fit quantifying metabolites values in V1~~Representative spectrum calculated by LCModel. The figure shows MRS fit, baseline and residuum for occipital voxel. (4) Representative spectrum calculated by LCModel. The figure shows MRS fit, baseline and residuum for insular voxel.

Figure 3. Pattern Glare Test~~GT~~ scores and neurotransmitter levels~~concentrations~~ (GABA/tCr and glutamate/tCr). Tables present non-parametric correlations for the (1) whole sample, (2) male (M) subsample and ~~(3)~~ female (F) subsample. All~~None of~~ the values marked with an asterisk are ~~survived~~ FDR correcte~~d~~i~~on~~ at p = 0.05.

Figure 4. Graphic presentation of behavioral scores for aversive gratings plotted against neurotransmitter levels~~concentrations~~ (GABA/tCr and glutamate/tCr), illustrating the trends

for separate biological sexes for (1) VD-med and (2) Comfort-med. ~~Statistical values reflect Pearson's correlation coefficient and 95% bootstrap confidence interval.~~ High visual sensitivity (visual distortions and discomfort) is hypothesized to be linked to high excitation (glutamate) and/or low inhibition (GABA). This expected pattern was not observed in either sex. Statistical values reflect Pearson's correlation coefficient and 95% bootstrap confidence interval.

Figure 5. The coefficients of the three constructed linear models predicting the response to VD-med (medium-frequency gratings). Note that to improve readability, the coefficients in the forest plot were computed after the standardization of all continuous variables, including the response variable (beta coefficients). VD-low – low-frequency gratings, ~~VD-high – high-frequency gratings,~~ GSQ – Glasgow sensory questionnaire score, ~~Attention Regulation and Body listening – MAIA-2 subscales.~~

Figure 6. Plot illustrating the outcome of the cosine regression model evaluating the effect of the menstrual cycle on Comfort-med.

Table 1. Average and standard deviation of metabolite concentrations and ratios to total creatine across all participants, with separate data for males and females, alongside average CRLB values, presented for the occipital voxel. GABA = Gamma-aminobutyric acid, Glu = Glutamate, Gln = Glutamine, Asp = Aspartate, GSH = Glutathione, Ins = Myo-inositol, Lac = Lactate, NAA = N-acetylaspartate, Scyllo = Scyllo-inositol, NAAG = N-acetylaspartylglutamate, tCh = Total choline (glycerophosphocholine and phosphocholine), tCr = Total creatine (creatine and phosphocreatine).

Table 2. Average and standard deviation of metabolite concentrations and ratios to total creatine across all participants, with separate data for males and females, alongside average CRLB values, presented for the insular voxel. GABA = Gamma-aminobutyric acid, Glu = Glutamate, Gln = Glutamine, Asp = Aspartate, GSH = Glutathione, Ins = Myo-inositol, Lac = Lactate, NAA = N-acetylaspartate, Scyllo = Scyllo-inositol, NAAG = N-acetylaspartylglutamate, tCh = Total choline (glycerophosphocholine and phosphocholine), tCr = Total creatine (creatine and phosphocreatine).

Table 3~~1~~. Behavioral PGT descriptives for the whole sample and separately for the two sexes.

961 Table 1.

V1	All sample, N = 160			Males, N = 65			Females, N = 95		
	Concentration (Mean ± SD)	Ratio to tCr (Mean ± SD)	Mean CRLB (%)	Concentration (Mean ± SD)	Ratio to tCr (Mean ± SD)	Mean CRLB (%)	Concentration (Mean ± SD)	Ratio to tCr (Mean ± SD)	Mean CRLB (%)
GABA	3,3 ± 0,55	0,3 ± 0,05	11,73	3,25 ± 0,54	0,3 ± 0,06	12,11	3,33 ± 0,56	0,31 ± 0,05	11,46
Glu	10,1 ± 0,83	0,93 ± 0,07	4,01	10,01 ±	0,92 ± 0,07	4,09	10,16 ±	0,93 ± 0,08	3,96
Gln	2,32 ± 0,45	0,21 ± 0,04	15,34	2,45 ± 0,43	0,23 ± 0,04	15,06	2,23 ± 0,46	0,21 ± 0,04	15,54
Asp	4,45 ± 0,49	0,41 ± 0,05	7,56	4,43 ± 0,42	0,41 ± 0,04	7,72	4,47 ± 0,54	0,41 ± 0,05	7,45
GSH	2,2 ± 0,19	0,2 ± 0,02	6,18	2,19 ± 0,2	0,2 ± 0,02	6,29	2,2 ± 0,18	0,2 ± 0,02	6,11
Ins	7,72 ± 0,89	0,71 ± 0,07	4,41	7,75 ± 0,89	0,71 ± 0,08	4,48	7,7 ± 0,89	0,7 ± 0,07	4,37
Lac	0,59 ± 0,25	0,05 ± 0,02	45,19	0,61 ± 0,26	0,06 ± 0,03	44,95	0,58 ± 0,24	0,05 ± 0,02	45,35
NAA	15,85 ±	1,46 ± 0,1	1,9	15,82 ±	1,46 ± 0,1	1,91	15,87 ±	1,46 ± 0,1	1,89
Scyllo	0,37 ± 0,11	0,03 ± 0,01	18,58	0,33 ± 0,1	0,03 ± 0,01	21,08	0,4 ± 0,12	0,04 ± 0,01	16,87
NAAG	1,46 ± 0,19	0,13 ± 0,02	10,83	1,45 ± 0,21	0,13 ± 0,02	11,22	1,48 ± 0,17	0,14 ± 0,02	10,56
tCh	1,33 ± 0,16	0,12 ± 0,01	3,93	1,31 ± 0,13	0,12 ± 0,01	4,03	1,35 ± 0,17	0,12 ± 0,01	3,85
tCr	10,91 ±	-	1,62	10,89 ±	-	1,63	10,93 ±	-	1,61

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963 Table 2.

Insula	All sample, N = 160			Males, N = 65			Females, N = 95		
	Concentration (Mean ± SD)	Ratio to tCr (Mean ± SD)	Mean CRLB (%)	Concentration (Mean ± SD)	Ratio to tCr (Mean ± SD)	Mean CRLB (%)	Concentration (Mean ± SD)	Ratio to tCr (Mean ± SD)	Mean CRLB (%)
GABA	3,.88 ± 0,.6	0,.32 ± 0,.05	11,.56	3,.7 ± 0,.54	0,.3 ± 0,.05	11,.89	4 ± 0,.61	0,.33 ± 0,.05	11,.33
Glu	14,.44 ± 1,.34	1,.18 ± 0,.09	3,.42	14,.51 ±	1,.17 ± 0,.09	3,.38	14,.38 ±	1,.18 ± 0,.09	3,.44
Gln	2,.91 ± 0,.65	0,.24 ± 0,.05	14,.22	3,.03 ± 0,.63	0,.24 ± 0,.05	13,.11	2,.83 ± 0,.65	0,.23 ± 0,.05	14,.98
Asp	3,.77 ± 0,.44	0,.31 ± 0,.03	10,.46	3,.86 ± 0,.47	0,.31 ± 0,.03	10,.14	3,.71 ± 0,.41	0,.31 ± 0,.03	10,.68
GSH	2,.65 ± 0,.23	0,.22 ± 0,.02	6,.22	2,.68 ± 0,.24	0,.22 ± 0,.02	6,.08	2,.63 ± 0,.22	0,.22 ± 0,.02	6,.32
Ins	8,.62 ± 0,.96	0,.7 ± 0,.07	4,.61	8,.89 ± 0,.95	0,.72 ± 0,.06	4,.37	8,.43 ± 0,.93	0,.69 ± 0,.07	4,.78
Lac	0,.87 ± 0,.32	0,.07 ± 0,.02	34,.91	0,.9 ± 0,.33	0,.07 ± 0,.02	31,.29	0,.85 ± 0,.31	0,.07 ± 0,.03	37,.4
NAA	16,.43 ± 1,.05	1,.34 ± 0,.1	1,.98	16,.28 ±	1,.32 ± 0,.1	1,.95	16,.53 ±	1,.36 ± 0,.09	2
Scyllo	0,.29 ± 0,.11	0,.02 ± 0,.01	30,.38	0,.26 ± 0,.1	0,.02 ± 0,.01	33,.35	0,.3 ± 0,.12	0,.03 ± 0,.01	28,.32
NAAG	1,.46 ± 0,.38	0,.12 ± 0,.03	18,.91	1,.49 ± 0,.32	0,.12 ± 0,.03	12,.98	1,.44 ± 0,.42	0,.12 ± 0,.04	23,.04
tCh	2,.76 ± 0,.38	0,.23 ± 0,.03	2,.98	2,.8 ± 0,.36	0,.23 ± 0,.03	2,.92	2,.73 ± 0,.39	0,.22 ± 0,.03	3,.01
tCr	12,.26 ± 0,.89	-	1,.86	12,.4 ± 1,.06	-	1,.8	12,.16 ±	-	1,.89

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966 Table 3.

	Mean	SD	Minimum	Maximum	Skewness	Kurtosis
All sample, N = 160						
VD-low	0,729	0,609	0,000	2,500	0,687	-0,221
VD-med	2,717	1,579	0,000	7,833	0,594	0,210
VD-high	2,608	1,439	0,000	7,167	0,725	0,232
Comfort-low	0,637	1,311	-1,667	5,000	1,523	1,667
Comfort-med	-0,196	1,553	-3,833	5,000	0,564	1,054
Comfort-high	-0,290	1,642	-4,500	5,000	0,498	1,003
Males, N = 65						
VD-low	0,589	0,507	0,000	2,000	0,821	0,086
VD-med	2,167	1,365	0,000	5,500	0,650	-0,507
VD-high	2,080	1,197	0,000	5,833	0,727	0,228
Comfort-low	0,653	1,253	-0,833	5,000	1,739	2,441
Comfort-med	0,256	1,426	-3,333	5,000	0,785	1,568
Comfort-high	0,058	1,558	-3,833	4,667	0,548	1,322
Females, N = 95						
VD-low	0,825	0,656	0,000	2,500	0,506	-0,530
VD-med	3,093	1,612	0,000	7,833	0,497	0,402
VD-high	2,968	1,484	0,333	7,167	0,625	0,001
Comfort-low	0,626	1,356	-1,667	5,000	1,429	1,383
Comfort-med	-0,505	1,567	-3,833	5,000	0,636	1,136
Comfort-high	-0,528	1,663	-4,500	5,000	0,567	1,098

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