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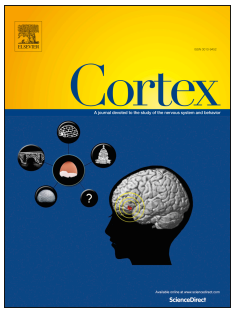


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# Validity of irritability in Huntington's disease: A scoping review

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# Validity of irritability in Huntington's disease: A scoping review


## Abstract

**Purpose:** To scope the literature concerning irritability in Huntington's disease to determine whether or not irritability is a valid and meaningful construct within this population.

**Method:** A scoping literature review was conducted based on findings from a search of five databases (Academic Search Ultimate, PsycINFO, CINAHL, Scopus and Web of Science) in November 2018. From an initial return of 453 papers, 40 were found suitable for review.

**Results:** Review of the 40 studies highlighted several aspects of irritability in people with HD which influence its validity as an independent construct in context of the disease. While various measures are used to assess irritability, a gold standard has yet to be identified and consequently irritability is assessed inconsistently across the literature. In addition, the results suggest that irritability may not reflect pathological disease processes in HD, but rather comprises a multidimensional construct which appears to be strongly associated with other psychological difficulties such as depression and anxiety.

**Conclusions:** The current concept of irritability in people with HD continues to lack a general consensus in the clinical literature, in terms of both operationalisation and assessment. Consequently, further research is warranted in order to determine the extent to which irritability is a valid construct within the context of HD, including its associated behavioural, cognitive and affective dimensions.


Key words: Huntington's disease; Irritability; Review; Scoping; Validity

It has been suggested that irritability is commonly experienced by people with neurological conditions such as Parkinson's disease (PD; Aarsland et al., 1999), dementia (Burns, Folstein, Brandt & Folstein, 1990) and progressive supranuclear palsy (PSP; Gerstenecker, Duff, Mast, Litvan & ENGENE-PSP Study Group, 2013). However, it is perhaps most notably discussed in people with Huntington's disease (HD; Wagle, Wagle, Markova & Berrios, 2000), where it is often reported as an important 'neuropsychiatric' symptom of the disease process (Klöppel et al., 2010). Nonetheless, while many studies have reported high rates of irritability in people with HD (Craufurd, Thompson & Snowden, 2001; van Duijn, Kingma & van der Mast, 2007), it has been argued that the current conceptualisations lack psychological rigour, suggesting that research on and measures of 'irritability' could in fact be potentially measuring different concepts, for example anger and aggression (Craig, Heitanen, Markova & Berrios, 2008).

**Introduction to Huntington's disease**

HD is an inherited neurodegenerative disease, caused by an autosomal-dominant mutation of a gene located on the short arm of chromosome 4, and characterised by a triad of progressive difficulties in motor, cognitive and behavioural domains (Craufurd et al., 2001). Formal diagnosis of HD is made when motor symptoms become apparent (Tabrizi et al., 2009), which usually occurs around the age of 40 with the disease subsequently progressing over 15-20 years (Novak & Tabrizi, 2010). However, psychological and cognitive difficulties are frequently experienced by people carrying the mutated gene (often referred to as 'gene positive' or 'presymptomatic HD') prior to motor symptom onset (Duff et al., 2007; Roos, 2014). Psychological distress associated with HD varies across disease stages, with

irritability, depression and anxiety argued to form the three core psychological difficulties experienced by people with HD (Klöppel et al., 2010).

**Conceptualising irritability**

Irritability is generally characterised as a readiness to react excessively to negative stimuli, often having both an affective component (anger) and behavioural component (aggression) (Buss & Durkee, 1957; Caprara et al., 1985). However, it is ill-defined and sometimes, as a concept, not effectively rooted in psychological theory. For example, Snaith and Taylor (1985) proposed a definition of irritability as a "feeling state characterised by reduced control over temper which usually results in irascible verbal or behavioural outbursts, although the mood may be present without observed manifestation" (p.128); likewise Paoli et al. (2017) defined irritability as "a temporary psychological state characterized by impatience, intolerance, and poorly controlled anger" (p.6). These definitions are inconsistent with psychological theory which differentiates between an emotion and a mood, seeing them as closely related yet distinct phenomena on the grounds of characteristics such as duration, apparent cause, intentionality, consequences and function (Beedie, Terry & Lane, 2005).

Craig et al. (2008) instead conceptualised irritability as a more prolonged mood state, differentiating it from emotions such as anger (which tend to be more reactive and short-lived). Snaith and Taylor (1985) examined irritability in clinical populations across four studies, including people experiencing depression, anxiety, mood disorder and obsessional neurosis, which also indicated that irritability should be understood as a mood state rather than a personality trait.

Conversely, irritability has also been conceptualised as a stable personality trait (Buss & Durkee, 1957). For example, early German psychopathologists referred to changes in behaviour, such as irritability, as part of personality change (Craufurd & Snowden, 2014). It is evident that there are opposing views as to whether irritability should be conceptualised as a state or trait (Burns et al., 1990), or a further possibility may be that it has elements of both.

Specifically in terms of people with HD, irritability has been conceptualised using the definitions applied to the general population. However, its occurrence within this population can be more difficult to determine due to the brain changes associated with the condition, potential differences in understandings of irritability and a lack of reliable methods of assessment (Craufurd & Snowden, 2014).

**Causes of irritability in people with HD**

Various explanations have been advanced regarding the cause of irritability in people with HD (Craufurd & Snowden, 2014). Irritability is commonly viewed as the result of the biological progressive neurodegenerative nature of the disease. Indeed, it has been suggested that higher levels of irritability in people with HD, compared with spouse controls in the same environment, "implicates a neurobiological, rather than psychological or reactive, basis for these behavioural signs" (Tabrizi et al., 2009, p.799). For example, it has been suggested that degeneration in brain regions that control socially appropriate behaviour, such as the prefrontal area, may result in irritability in the earlier stages of HD (Mega & Cummings, 1994). This is consistent with wider understandings that neurodegenerative changes in people with HD are important in the development of all psychological difficulties experienced by people with the condition, in which irritability and aggressiveness are at the forefront, alongside apathy (Teixeira, de Souza, Rocha, Furr-Stimming & Lauterbach, 2016).

However, while irritability is frequently identified as a primary difficulty experienced by people with HD, some authors theorise that it may be secondary to other psychological difficulties such as depression (Craufurd & Snowden, 2014; van Duijn., 2010). Furthermore, some affected individuals report experiencing suicidal ideation after episodes of heightened irritability (Craufurd & Snowden, 2002), indicating a potential association between irritability and suicidality. Irritability may, at least in part, also be a consequence of experiencing frustration with increasingly difficult communication and cognition (Craufurd & Snowden, 2014). Indeed, although the dominant understanding is biologically-based, behaviour in people with HD is also likely to reflect both intrinsic and reactive changes (Craufurd & Snowden, 2014).

**Validity of irritability**

Several types of assessment have been argued to be important in terms of establishing whether a construct is valid and therefore construct validity, which can be conceptualised as a superordinate level of validity, and is often seen as the most difficult type of validity to achieve. Indeed, it can also only be demonstrated when more specific elements of validity have been established, e.g., convergent validity which refers to the degree to which a construct is similar to another construct to which it should be similar (Kendal, 1975).

Due to the lack of consensus around the construct and validity of irritability as it specifically presents in people with HD, it is timely to review the empirical evidence. Irritability is one of the key psychological difficulties considered important to treat in people with HD, so it is essential that therapeutic approaches are enabled to target a construct which is clear, defined and widely understood to be the same across studies and measures. A scoping review approach (e.g., Mays, Roberts & Popay, 2001) was adopted to assess the key

findings from the research. This is suitable for the assessment of construct validity, which is a broader aim than would be typical for a conventional systematic review where the review is focused on a narrower and more specific question. Consequently, this review will answer the question: what is the current conceptualisation of irritability among people with HD? It will also be considered whether the current conceptualisation is valid and clinically meaningful.

**Previous reviews**

Three prior reviews have been conducted in this general area, although none focusing on this or a similar question. Ramos and Garrett (2017) reviewed symptoms specifically associated with the premotor phase, concluding that irritability is overall increased in this phase compared to non-carriers. Honrath et al. (2018) systematically reviewed evidence for a link between irritability and suicidal ideation, finding poor evidence of any connection from prior studies. Finally, Dale and van Duijn (2015) reviewed evidence for associations between anxiety and irritability in people with HD, finding that those with the condition who have higher levels of anxiety may be more prone to becoming irritable. Although there is therefore evidence pertaining to irritability in people with HD in existing reviews, no review has focused explicitly on the construct of irritability or its validity. This review will therefore be clinically useful and avoids replicating past work.

## Method

A scoping review approach was adopting, following the stages outlined by Arksey and O'Malley (2005). Studies appropriate for inclusion were selected and the relevant data collated and charted. The results were then summarised and reported. The papers selected for

inclusion met the following criteria: (i) published in English; (ii) published in a peer-reviewed journal; (iii) involved the investigation of irritability in people with a verified presence of the HD gene (both symptomatic and presymptomatic), including prevalence, associations with other variables, treatment options and aetiology. Papers investigating irritability in mixed samples of people with HD and other neurological conditions were excluded if the authors did not report findings for each condition separately.

Relevant papers were identified by searches of the databases Academic Search Ultimate (searchable from 2002, 'peer reviewed' and 'English' selected), PsycINFO (searchable from 1940, 'peer reviewed' and 'English' selected), CINAHL (searchable from 1999, 'peer reviewed' selected), Scopus (searchable from 2006, 'English' and 'Journals' selected), and Web of Science (searchable from 1990). The search was conducted in November 2018, and the search terms used to identify potential papers were "irritability" and "Huntington*". This database search returned 453 papers (Academic Search Ultimate = 50, PsycINFO = 78, CINAHL = 12, Scopus = 213 and Web of Science = 100). Duplicates were removed and the remaining papers were reviewed for suitability by screening titles and abstracts. Review papers, commentaries and case studies were excluded. For papers where eligibility was unclear, the full text was reviewed. References of included papers were also searched for relevant studies, although none were located which had not been identified on database search. Ultimately, 40 papers were identified as suitable for inclusion in the current review. Table 1 provides a summary of key characteristics of the included studies, and Figure 1 details the paper selection process. As quality appraisal is not considered a requirement for scoping reviews (Arksey & O'Malley, 2005), this was not conducted. Although some reviews in the field of HD (e.g. Crozier, Robertson & Dale, 2015; Dale & van Duijn, 2015) exclude papers published before 1993 due to the predictive test not being available until then (Huntington's Disease Collaborative Research Group, 1993), the search did not include date

parameters on the basis that this might exclude papers which did confirm genetic status on an individual study basis. However, only two papers were found which were published before 1993. In the Burns et al. (1990) paper, the HD sample is described as positive gene carriers, and in the Pflanz et al. (1991) paper as patients whom the clinician in charge was confident of their diagnosis of HD based on clinical presentation.

(<Insert Table 1 and Figure 1 here>)

## Results

Forty papers were included in the current scoping review; the relevant results are summarised in Table 2. Of the 40 papers, 12 compare irritability in people with HD to healthy controls, 12 examine changes in irritability across disease stage, two compare irritability in individuals with HD with those with other neurological conditions, 17 report associations with other psychological difficulties in people with HD, three describe interventions and four report potential neurological pathways for irritability in HD. In addition, the measures used to assess irritability are discussed.

(<Insert Table 2 here>)

### Measures of irritability

A wide range of measures were used in the reviewed studies to assess irritability in people with HD (see Table 3). Eleven studies used the behavioural component of the United Huntington's Disease Rating Scale (UHDRS; Anderson et al., 2016; Banaszkiewicz et al., 2012; Craufurd et al., 2001; Hubers et al., 2013; Reedeker et al., 2012; Rickards et al., 2010; Thompson et al., 2002; van Duijn et al., 2014; van Duijn et al., 2018; Vassos, Panas, Kladi & Vassilopoulos, 2007; Yang et al., 2016). Eight used the Problem Behaviours Assessment

(PBA; Craufurd et al., 2001; Gregory et al., 2015; Kingma et al., 2008; Reedeker et al., 2012; Thompson et al., 2002; Thompson et al., 2012; van Duijn et al., 2013; van den Stock et al., 2015), one its Dutch equivalent (NL-PBA; Bouwens et al., 2016), and four the PBA short-form (PBA-s; Fritz et al., 2018; Honrath et al., 2018; Martinez-Horta et al., 2016; Ruiz-Idiago et al., 2017). Three studies used the Irritability Scale (IS; Bouwens et al., 2015; Diago et al., 2018; Reedeker et al., 2012), four used the Snaith Irritability Scale (SIS; Berrios et al., 2001; 2002; Klöppel et al., 2010; Maltby et al., 2016) and two the Hospital Anxiety and Depression Scale combined with the SIS (HADS-SIS; Underwood et al., 2016; Vassos et al., 2007). Two used the Irritability, Depression, Anxiety Scale (Nimmagadda et al., 2011; Singh-Bains et al., 2016), two the John Hopkins Irritability Questionnaire (JHIQ; Chatterjee et al., 2005; Klöppel et al., 2010), two the abbreviated Minnesota Multiphasic Personality Inventory irritability scale (MMPI; Kirkwood et al., 2002a; 2002b), and two the Neuropsychiatric Inventory (NPI; Litvan, Paulsen, Mega and Cummings, 1998; Paulsen, Ready, Hamilton, Mega & Cummings, 2001). One study each used the Barratt Impulsiveness Scale (BIS; Nimmagadda et al., 2011), the Present State Examination (Pflanz et al., 1991), the Hostility & Direction of Hostility Questionnaire (HDHQ; Vassos et al., 2007), the Composite International Diagnostic Interview (CIDI; Julien et al., 2007) and Burns et al. (1990) developed a bespoke Irritability/Apathy Scale for their study.

The IDAS (Snaith et al., 1978) was initially developed to address the need for scales to assess irritability in clinical populations, and has been used in studies assessing irritability in people with HD (Berrios et al., 2001; Berrios et al., 2002; Nimmagadda, Agrawal, Worrall-Davies, Markova & Rickards, 2011). Snaith et al. described irritability as a two-dimensional construct, which led to an elaboration of the IDAS into two subscales measuring outwardly- and inwardly-expressed irritability (Snaith & Taylor, 1985); these may correspond to the "irritability" factor on the PBA-s, which comprises irritability and aggressiveness according

to Ruiz-Idiago et al. (2017). Snaith and Taylor's self-report measure assesses subjective irritability. Snaith and Taylor's interpretation was somewhat supported on factor analysis of the Snaith Irritability Scale by Maltby et al. (2016), who found two equally well-fitting bifactor models representing the data. Bifactor models explain data via joint explanations, a single general factor (in this case "irritability") which explains the shared variance of all items, and individual ("group") factors which each explain some of the variance too, but allow recognition of multidimensionality within the data. Maltby et al. found justification for Snaith and Taylor's interpretation (outwardly- and inward-expressed irritability, alongside the irritability general factor)) but also for another bifactor model in which "temper" and "self-harm" were the group factors. Importantly, both models showed higher loadings for items for the general factor, and the general factor explained more variance; the authors therefore recommended that the full-scale score should be used as the overall measure of irritability, rather than generating sub-scales. This may have implications for the validity of studies which rely on the sub-scales, such as Singh-Bains et al. (2016), who used the outward irritability component of the IDAS as a measure of irritability when exploring the role of globus pallidus degeneration in HD.

The PBA is a semi-structured interview used with both people with HD and close others such as family members. The scale comprises three factors (apathy, irritability and depression), all with individual sub-scale items (for example on obsessions/perseverative thinking and psychosis) and includes ratings from patients and informants, as well as observations from clinicians, thereby encompassing multiple perspectives. Irritability items include inflexibility, preoccupations, irritability, and verbal and physical aggression (Craufurd et al., 2001). Items are reported on five-point scales to assess both the frequency and severity of behavioural difficulties, and multiplied for an overall score (Gregory et al., 2015). The short-form PBA-s is more commonly used now, but retains similar apathy, irritability and affect factors to the

original PBA on principal components analysis, as well as equivalent good inter-rater agreement (Callaghan et al., 2015).

(<Insert Table 3 here>)

Further measures that have been used to assess irritability in people with HD include the behavioural section of the Unified Huntington's Disease Rating Scale (UHDRS-b) and informant-report measures such as the John Hopkins Irritability Scale and the Burns Irritability Scale (BIS; Burns et al., 1990). The Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996) is one of the most commonly-used measures, assessing motor, cognitive and behavioural aspects of HD as well as functional capacity; it was used in a number of studies included in the current review (Banaszkiewicz et al., 2012; Hubers et al., 2013; Reedeker et al., 2012; Rickards et al., 2011; Thompson, Snowden, Craufurd & Neary, 2002; van Duijn et al., 2014). The BIS also purports to allow an objective measure of irritability to be obtained from a carer or family member, aiming to measure a change in behaviour in the context of illness rather than objective irritability level, i.e. someone who has always been irritable would be unlikely to score highly for irritability using this scale.

The present results suggest that measures differ in their conceptualisation and measurement of irritability. Although multi-item irritability measures such as the Irritability Questionnaire have been shown to have good reliability and assess various thoughts, feelings and behaviours related to irritability, scales attempting to measure irritability also tap into constructs such as anger and hostility (Holtzman, O'Connor, Barata & Stewart, 2015). This may be problematic in the assessment of irritability since irritability, unlike anger, often occurs in the absence of a direct antecedent and lasts longer, suggesting that they are different constructs which require differentiation in assessments (Beedie et al., 2005; Craig et al.,

2008). Nonetheless, despite it being generally acknowledged that irritability is distinct from anger and aggression, this is not currently reflected in the measures used to assess it (Holtzman et al., 2015).

**Irritability in people with HD compared with healthy controls**

Thirteen studies have compared irritability in people with HD with healthy controls (Anderson et al., 2016; Berrios et al., 2001; Berrios et al., 2002; Diago et al., 2018; Julien et al., 2007; Kirkwood et al., 2002a; Kirkwood et al., 2002b; Kingma, van Duijn, Tinman, van der Mast & Roos, 2008; Klöppel et al., 2010; Martinez-Horta et al., 2016; Reedeker et al., 2012; van den Stock et al., 2015; Vassos et al., 2007). Seven of these studies found that irritability is significantly higher in people with HD compared with non-carrier controls (Berrios et al., 2001; Berrios et al., 2002; Julien et al., 2007; Kingma et al., 2008; Kirkwood et al., 2002a; Reedeker et al., 2012; van den Stock et al., 2015). Additionally, Martinez-Horta et al.'s (2016) examination included presymptomatic individuals not long prior to onset and found that both this group and those with early-stage HD had significantly higher irritability than non-carrier controls, indicating that changes in irritability pre-empt motor onset. In addition, Kirkwood et al. (2002a) observed an increase in irritability and clinical hostility over an average of 3.7 years in pre-symptomatic gene carriers compared with non-gene carriers. Similarly, Berrios et al. (2002) found that gene carriers had significantly higher inward and outward irritability than non-gene carriers measured by the SIS, which was suggested to be a possible result of irritability being part of a personality change occurring as a consequence of HD – importantly, the authors selected participants prior to genetic testing, eliminating the confound of psychological effects of diagnosis. These findings demonstrate

that irritability may develop/increase prior to the occurrence of clinical motor symptoms, and in general that irritability is a clinical feature across the disease course.

However, four of the 12 studies which compared people with HD to healthy controls failed to find a significant between-group difference in irritability (Diago et al., 2018; Kirkwood et al., 2002b; Klöppel et al., 2010; Vassos et al., 2007). Klöppel et al. (2010) also did not find a significant difference between pre-symptomatic gene carriers and non-gene carriers. Additionally, there was good agreement between pre-symptomatic gene carriers and their close companions regarding their level of irritability, suggesting that lowered insight into irritability as reported by Reedecker et al. (2012) may occur later in the disease process.

Similarly to Klöppel et al. (2010), Kirkwood et al. (2002b) did not find a difference in irritability between those with manifest HD, pre-symptomatic gene carriers and non-gene carriers as measured by the MMPI. However, although the MMPI measures personality traits and psychopathology, it may not be sensitive to changes in people with HD because it has never been standardised for this population. Nevertheless, the use of the SIS (which was constructed for use with clinical populations) was also unable to detect differences in irritability between pre-symptomatic gene carriers and non-gene carriers (Klöppel et al., 2010). The choice of measure is therefore likely to represent only one of several variables which may have contributed to the lack of significant results.

Finally, Vassos et al. (2007) investigated the psychological and behavioural features which differentiate people with HD from non-affected individuals, and did not find a significant difference in either inward or outward irritability as measured by the SIS. The authors reported a small effect size of $d = 0.20$ for inward irritability, which suggests an effect is potentially detectable, but reported $d = 0.06$ for outward irritability, suggesting there is no difference to find. However, they also reported that people with HD showed a

significantly higher level of extroverted hostility compared with healthy controls, describing hostility as a personality dimension rather than a behavioural aspect. Similarly, Berrios et al. (2002) found that both inward and outward irritability loaded onto a personality factor for people with HD within their derived factor structure (inward irritability did not load on any factor for non-carriers), suggesting a qualitative difference in the nature of irritability in people with HD.. Finally, Anderson et al. (2016) reported that for non-carriers, irritability was significantly predictive of suicidal ideation whereas in gene carriers it was not, suggesting that irritability may interact differently with other psychological variables in people with the HD gene compared to those without.

**Irritability across disease stage**

In addition to comparisons between gene carriers and healthy controls, studies have explored whether irritability varies across stage of disease. Of the 12 papers comparing irritability across disease stage, eight did not find significant differences (Bouwens et al., 2015; Craufurd et al., 2001; Julien et al., 2007; Kingma et al., 2008; Kirkwood et al., 2002b; Pflanz, Besson, Ebmeier & Simpson, 1991; Ruiz-Idiago et al., 2017; van Duijn et al., 2013). Six were cross-sectional studies, and two longitudinal. The latter found no significant increase in irritability between baseline and two-year follow-up (Bouwens et al., 2015; van Duijn et al., 2013). Bouwens et al. (2015) measured irritability at two time points using the Irritability Scale (Chatterjee, Anderson, Moskoqitz, Hauser & Marder, 2005) and found that of those who were irritable at baseline (33%), 70% remained irritable at follow-up two years later. Furthermore, of those who were not irritable at baseline, only 23% went on to report irritability at follow-up, so overall only minor differences were apparent over the two-year period. van Duijn et al. (2013) additionally reported no difference in irritability at two-year follow-up compared to baseline.

Interestingly, although Craufurd et al. (2001) also identified a lack of linear relationship between irritability and disease duration, they did find a less straightforward relationship. Across their cohort's disease duration span of 1-23 years, the authors found that difficulties defined under the factor 'irritability' (including irritability, verbal aggression, physical aggression, inflexibility and pathologic preoccupation) occurred more frequently in people with a disease duration of 6-11 years, suggesting that disease stage and irritability may indeed be related, but in a more complex manner. Collectively, however, these studies suggest that irritability does not appear to be directly associated with disease stage, and therefore may not be an underlying process associated with pathological manifestations of HD.

Conversely, however, three papers identified a difference in irritability across disease stage (Gregory et al., 2015; Thompson et al., 2012; van Duijn et al., 2014), although their findings were inconsistent. Gregory et al. (2015) found that irritability was significantly higher in those with clinically-diagnosed early HD compared with pre-manifest HD, although this research was not extended to those with more advanced HD. Martinez-Horta et al. (2016) also reported significantly increased risk and prevalence of irritability in groups less than 10.8 years prior to predicted onset or in the early stages of HD, in comparison to those further from predicted onset, although the very broad timespan reduces the generalisability of this information and the validity of describing those ten years from becoming symptomatic as "close to onset" might also be questioned. van Duijn et al. (2014) additionally found moderate to severe irritability (using the behavioural component of the UHDRS) increased by stage of disease from 10.4% at stage one (diagnosed, but remaining fully functional) to 19.6% at stages four and five (advanced stages); however, this increase at such advanced stages of the disease course could potentially be interpreted as an effect of psychological

distress due to the increasing impact of HD, and therefore a by-product of other symptoms of HD rather than a direct symptom.

In addition to studies finding a difference in irritability measures between disease stages, Honrath et al. (2018) found that irritability has predictive value regarding suicidal ideation in manifest but not premanifest groups, with premanifest groups more affected by functional changes in activities of daily living, whereas psychological difficulties such as irritability were of more relevance in the manifest group. This suggests a change in the impact and role of irritability as HD progresses.

Similarly, a longitudinal study by Thompson et al. (2012) showed an increase in the presence of irritability (determined as a score of two or greater for severity) over time as measured by the PBA-HD. However, this was limited to a significant linear effect in those who entered the study at stage one and two, and not in those who entered at stage three. The progression of irritability was therefore only evident in early-stage HD. There may, however, be a confound in their measurements; the authors note that irritability was common among their sample, describing poor temper control in 80% of participants and physical aggression in 50%. While temper and aggression are frequently measured independently of irritability, in this study they were assumed to be aspects of irritability as opposed to separate constructs. This may have influenced findings, and reduces comparability with other studies in the area.

Two final studies found decreases in irritability associated with markers of disease stage. Although they did not assess disease stage directly, Yang et al. (2016) evaluated correlations between irritability and CAG repeats (the extent of the genetic mutation, corresponding to the number of trinucleotide repeats on the chromosome)/age of onset in Chinese patients, finding that later onset and fewer CAG repeats correlated with lower irritability. In a similar vein, Singh-Bains et al. (2016) found that irritability decreased with

increasing years since onset despite cognitive and motor deterioration, possibly implying some stabilisation of irritability with advancing age. Therefore, the relationship between irritability and age or disease stage overall seems less than clear-cut.

When interpreting these findings, consideration should be given to studies in which participants were taking medication to manage their irritability and the impact this may have had on its assessment. Participants in Thompson et al.'s (2012) study had access to psychiatric input, and therefore may have been taking medication to manage their irritability; the increase in irritability only being seen in the early stages may therefore mean that people were prescribed medication when it started to impact on their quality of life. For example, Craufurd et al. (2001) reported 35% of participants to be taking medication to manage irritability. This might also explain the decrease in irritability as the disease progressed, reported by Yang et al (2016) and Singh-Bains et al. (2016). Consequently, differences in findings across studies may be influenced by current treatment options being accessed by participants.

**Comparing HD with other neurodegenerative conditions**

Since irritability has been reported to occur in neurological conditions other than HD, it is appropriate to compare irritability in this population with other neurodegenerative conditions. Burns et al. (1990) compared people with HD with people with Alzheimer's disease (AD) on irritability and apathy using an irritability/apathy scale developed specifically for their research, finding no significant difference in irritability between the two groups. However, the HD group showed significantly higher levels of aggressiveness than the AD group, and their aggressive outbursts lasted significantly longer. Importantly, in both groups, irritability, apathy and aggression appeared to be unrelated, suggesting that an

increase in one would not predict changes in the others. Interestingly, irritability correlated positively with bad temper in the HD group while there was no correlation in the AD group, implying that the presentation of irritability and related constructs may differ between neurodegenerative conditions. Thus, while there was no significant difference between the two groups, people with HD demonstrated higher levels of aggression and bad temper than those with AD.

In addition, Litvan et al. (1998) compared people with HD to people with progressive supranuclear palsy (PSP) using the Neuropsychiatric Inventory (NPI). Irritability was shown to influence the total NPI score in people with HD; additionally, the HD group scored significantly higher on agitation, irritability and anxiety, while those with PSP scored higher for apathy. In the HD group, agitation was positively correlated with anxiety, irritability, disinhibition and euphoria. Similarly, irritability was associated with anxiety, disinhibition, euphoria and depression. Logistic regressions indicated that people with HD were more likely to exhibit hyperactive behaviour (agitation, irritability) whereas people with PSP were more likely to exhibit hypoactive behaviour (apathy). These results are consistent with the findings of Burns et al. (1990), who reported that irritability and apathy can occur independently of each other. The research in this area is therefore limited, but there appear to be important differences in psychological presentation between HD and other neurodegenerative conditions.

**Association with other psychological difficulties**

Irritability has also often been investigated along with other psychological difficulties reported to be common in people with HD. Of the 17 studies comparing irritability with other psychological difficulties (Anderson et al., 2016; Banaszkiewicz et al., 2012; Bouwens et al.,

2015; Bouwens et al., 2016; Burns et al., 1990; Diago et al., 2018; Fritz et al., 2018; Honrath et al., 2018; Hubers et al., 2013; Litvan et al., 1998; Nimmagadda et al., 2011; Paulsen et al., 2001; Pflanz et al., 1991; Thompson et al., 2002; Underwood et al., 2016; van Duijn et al., 2014; van Duijn et al., 2018), nine reported correlations between irritability and other psychological difficulties, and one reported association via multiple regression. Nine of these studies reported significantly positive correlations with other psychological difficulties including apathy (Bouwens et al., 2015; Pflanz et al., 1991), anxiety (Litvan et al., 1998; Nimmagadda et al., 2011; Paulsen et al., 2001), depression (Litvan et al., 1998; Nimmagadda et al., 2011; van Duijn et al., 2014), bad temper (Burns et al., 1990) and suicidal ideation and/or behaviour (Anderson et al., 2016; van Duijn et al., 2018). Fritz et al. (2018) additionally identified that poorer behavioural scores (a composite score from the PBA-HD short form, covering ten behavioural problems including irritability, although not a specific measure of irritability in itself) were associated with higher apathy scores (large effect size: $R^2 = 0.30$), in line with research specifically examining irritability as a stand-alone variable. A single paper reported no correlation between irritability and cognitive impairment (Thompson et al., 2002).

In addition to the van Duijn et al. (2018) study of suicidal ideation and behaviour, which found moderate/severe irritability to be modestly predictive of both, Hubers et al. (2013) found irritability was significantly positively correlated with suicidal ideation at baseline. However, this was not maintained at four-year follow up and thus irritability was not considered an independent predictor of suicidal ideation. It should though be considered that since the cohort were all four years further into the disease course by follow-up, it should be considered that the predictive value of irritability may relate to disease stage. A further study by Honrath et al. (2018) found that irritability significantly predicted suicidal ideation for the manifest but not premanifest group. The evidence is therefore conflicted.

In a study of apathy and irritability, Bouwens et al.'s (2015) longitudinal analysis demonstrated that an increase in irritability was associated with an increase in apathy over a two-year period, an association which was maintained after confounds such as age, sex, motor function change and medication use had been controlled. Although the concomitant increase in apathy and irritability appears paradoxical, the authors suggested that while irritability is often linked to the outward expression of anger, it may also be expressed and experienced internally (similar to Snaith and Taylor's (1985) development of the IDA to examine both inward and outward irritability), and therefore some people with HD may experience inward irritability alongside external apathy. Consequently, apathy has the potential to mask irritability by limiting overt expression.

Furthermore, three studies found associations between irritability and anxiety. Both Litvan et al. (1998) and Paulsen et al. (2001) found irritability to be significantly positively correlated with anxiety ($r$ = 0.88 and $r$ = 0.43 respectively), as measured by the NPI. Similarly, Nimmagadda et al. (2011) found that participants' inward and outward irritability scores were both significantly positively associated with both their state and trait anxiety, as measured by the IDAS and State-Trait Anxiety Inventory. While a causal relationship cannot be determined, irritability could hypothetically occur in response to feelings of anxiety. Therefore, people with HD who have higher levels of anxiety may be more prone to becoming irritable.

In addition to apathy and anxiety, there were also associations between irritability and depression. Irritability was found to be positively correlated with depression in Litvan et al.'s (1998) study using the NPI, and Nimmagadda et al. (2011) found irritability (both IDAS-inward and IDAS-outward) to be significantly positively associated with depression as measured subjectively by the IDA-D and objectively by the Montgomery and Asberg

Depression Rating Scale (MADRS). However, these correlations did not persist when irritability was informant-reported on the Barratt Impulsiveness Scale. The authors suggest that this could be due to informants not recognising irritability in people with HD struggling with depression, which is supported by the IDA-inward irritability score showing a stronger correlation with the depression score on the MADRS, suggesting that people experiencing depression in HD may internalise irritability and thus hide it from those around them. Interestingly, evidence suggests that a history of depression (van Duijn et al., 2014) and bad temper (Burns et al., 1990) may increase the likelihood of people with HD experiencing irritability. In contradiction to the above studies, however, van Duijn et al. (2018) found only a weak correlation between depressed mood and irritability, although both were independently predictive of suicidal ideation/behaviour in their study.

In terms of associations between irritability and more functional HD symptoms and characteristics, Banaszkiewicz et al. (2012) found that irritability was not significantly related to functional disability, Bouwens et al. (2016) found no relation between plasma cytokine levels and irritability (although there was a significant association between plasma cytokine levels and executive function) and Diago et al. (2018) found that although markers of poor sleep quality moderately correlated with irritability, these trends were non-significant. Additionally, Underwood et al. (2016) noted that interviewer-rated irritability positively predicted likelihood of severe pain, although greater participant-rated irritability did not (despite participant-rated measures of anxiety and depression being significant predictors). This may demonstrate an important lack of insight specifically into irritability in people with HD.

**Treatment options for irritability in people with HD**

Three papers examined the treatment options for irritability in people with HD (Bouwens et al., 2015; Groves et al., 2011; van Duijn, 2010). Groves et al. (2011) used an HD irritability survey developed specifically for their research, which revealed use of various pharmacological treatments to reduce irritability with little general consensus, particularly with regards to treatment duration (although there was some agreement among expert clinicians regarding selective serotonin reuptake inhibitors (SSRIs) and antipsychotics (APDs) being the preferred medication). Additionally, when considering that people with HD may also experience other psychological difficulties, medication choice was affected by reported psychological comorbidities. SSRIs were preferred when irritability occurred with comorbid depression and anxiety, whereas APDs were often used when irritability occurred alongside aggression and impulsivity (suggesting that it may be used to treat these comorbid difficulties, not the irritability itself).

Given the difference in usage by clinicians, it is possible that the medication used may actually be affecting the comorbid psychological difficulty, e.g. depression, as opposed to irritability; the treatment of such co-occurring difficulties may in fact be more effective than targeting irritability. Consequently, it could be suggested that irritability occurs as part of these associated psychological difficulties, i.e. depression and anxiety, rather than representing a valid individual 'symptom' of HD.

Interestingly, Bouwens et al. (2015), in a longitudinal study, found that the use of APDs was associated with an increase in irritability over a two-year period. However, it cannot be ruled out that APDs were prescribed when irritability presented and were therefore an active treatment while irritability increased due to another process, rather than the medication being responsible for the increase.

It is also worth noting the general increased incidence of medication associated with irritability; Martinez-Horta et al. (2016) reported strong positive correlations between irritability and use of antidepressants, benzodiazepines and neuroleptics, although since reason for prescription or associated tracking of symptoms was not provided, this is not informative regarding the helpfulness of medication. It is clinically useful however to be aware of the apparent tendency towards prescription of medication in those with increased irritability, and to consider the justification and potential risks/benefits in patient care.

**Suggested neurological pathways for irritability in people with HD**

Little is known about the potential neurological changes associated with the psychological aspects of HD. Four relevant studies have been conducted (Gregory et al., 2015; Klöppel et al., 2010; Singh-Bains et al., 2016; van den Stock et al., 2015)

van den Stock et al. (2015) found evidence of striatal atrophy and increased irritability in the gene positive group compared to healthy controls. The authors evaluated the association between clinical irritability and experience of anger by correlating irritability scores on the PBA-HD with functional magnetic resonance imaging (fMRI) activation in people who were gene positive, but not showing motor symptoms. A significant positive correlation was identified between irritability and pulvinar activation, implying that the thalamic pulvinar plays a key role in irritability in HD. Additionally, anger experience was associated with hyper-activation of the emotion experience neurocircuitry. It is important to differentiate between brain activation relating to anger and irritability, as these appear to be at least partially separate. Importantly, research in other conditions have implicated striatal and orbitofrontal-subcortical circuit deterioration in the development of socially inappropriate behaviours including irritability (Salloway & Cummings, 1994), which Paoli et al. (2017)

argue may also be the case in people with HD; van den Stock's (2015) study of striatal atrophy may support this to a degree.

Klöppel et al. (2010) found higher levels of reported irritation were associated with stronger amygdala activation in controls compared to pre-symptomatic gene carriers, for whom equivalent correlational analyses were non-significant. The authors argue that inappropriate responses of the amygdala make pre-symptomatic gene carriers increasingly prone to psychological difficulties such as irritability. Additionally, the involvement of the amygdala has been highlighted in the experience of negative emotions such as irritability (e.g. Leibenluft, 2017), anger (e.g. Reuter, Weber, Fiebach, Elger & Montag, 2009) and frustration (e.g. Yu, Mobbs, Seymour, Rowe & Calder, 2014) more generally as opposed to being specific to irritability.

Furthermore, comparing people with early-stage HD with pre-manifest HD, Gregory et al. (2015) found a significant correlation between irritability (measured by the PBA-HD) and a decrease in white matter microstructure across the whole brain (identified via fractional anisotropy). These findings were reversed in those closer to onset, with results maintained following controlling for medication use. Additionally, the authors suggested that due to the dominant involvement of the posterior tracts and left hemisphere, it is possible that the increase in irritability could result from cognitive overload.

Finally, Singh-Bains et al. (2016) found that deterioration in the internal subsection of the globus pallidus was significantly correlated with decreasing irritability in their small-sample study relating post-mortem neurological findings to clinical symptom scores. The authors hypothesise that irritability occurs in the early stages of HD (as also found by Thompson et al. (2012)) and subsequently stabilises, either due to a natural change over the years (supported by Singh-Bains et al.'s finding that increasing years since onset were

associated with reduced irritability) or because medication or other management strategies mitigate irritability over time (Scher & Kocsis, 2012). However, no hypothesis relating specifically to neurodegeneration in this region was suggested. Overall, the evidence regarding how neural changes may relate to irritability in people with HD seems unclear, and potentially confounded by other psychological and cognitive factors.

## Discussion

One of the prime difficulties with research into irritability is measurement, as indicated by the wide range of prevalence reported in different studies. For example, van Duijn et al.'s (2007) review found reported rates of irritability in people with HD to range from 38% to 73% as measured by the PBA-HD and NPI. Indeed, considering that there is no gold standard for measuring irritability, cut-off scores between studies vary somewhat and are essentially arbitrary (Reedeker et al., 2012), leaving potential for different results. For example, three studies using the Irritability Scale (Chatterjee et al., 2005; Klöppel et al., 2010; Reedeker et al., 2012) used varying cut off scores of >15 and >14. Statistically, there is also a loss of sensitivity when assessments above and below cut-off are compared; it is preferable to use continuous variables where possible, which many studies did not (Altman & Royston, 2006). While efforts have been made to reduce the impact of varying cut-offs on findings, it seems that if irritability is to be considered a symptom of HD, standardised measures and scores specific for people with HD are essential. However, this highlights a vicious circle; difficulties with agreement regarding standardised measures and clinical cut-off scores are perpetuated by the lack of agreed definition, which inhibits the ability to designate clinically valid cut-off scores.

In addition, there remains no gold standard for assessing irritability (Bouwens, van Duijn, van der Mast, Roos & Guiltay, 2015). Various measures have been developed to

assess irritability both in non-HD and HD populations, for example, the Buss-Durkee Hostility Inventory (BDHI) and the Problem Behaviours Assessment for HD (PBA-HD), but there is no consensus on the most appropriate, reliable or valid measure. The only recommended scale from the existing literature is the Irritability Scale, which despite having high internal consistency has only moderate interrater reliability and so far little evidence of convergent validity (Mestre et al., 2016). Furthermore, the lack of a core and widely-understood construct means that different measures potentially measure different constructs. This can result in inconsistencies in research findings based on the choice of measure, as opposed to true differences between cohorts. It may also be important to consider whether a single measure of irritability is able to provide an accurate depiction of irritability (Klöppel et al., 2010).

Furthermore, irritability measures can rely on either self-report, caregiver-report, clinician-based assessment and in some cases a combination of the three, and it cannot be assumed that these are comparable given that differences have been highlighted between e.g. self- and informant-report, with self-report increasingly diverging from informant-report as the disease progresses (Chatterjee et al., 2005; Reedeker et al., 2012). Family- and clinician-rated measures are limited in that ratings can only be based on observable behaviour (Bogart, 2011). Self-report measures like the SIS are therefore important to measure the individuals' experience (e.g. of 'inward irritability'), and if irritability can be conceptualised as a "temporary psychological state" (Snaith et al., 1978, p.164) then self-report measures can play a pivotal role in the assessment process (Holtzman et al., 2015). However, self-report measures may become increasingly unsuitable as the disease progresses and self-awareness of mood or personality becomes more impaired, and more emphasis on objective or interviewer-rated measures may become appropriate, supplemented with clinician observations (Burns et al., 1990; Fisher, Sewell, Brown & Churchyard, 2014; Kirkwood et

al., 2002b). Measures such as the PBA-HD, which are conducted with the person with HD, a spouse or carer and additionally acknowledge interviewer observations (Callaghan et al., 2015; Craufurd et al., 2001), may be the best choices for holistic assessment.

Additionally, the lack of agreed definition may mean that individual participants have different understandings of irritability (Klöppel et al., 2010). Therefore, people's experience and understanding of what irritability comprises is likely to differ, as will the behaviours people attribute to irritability. For example, some people with HD may understand anger and aggression as a consequence of irritability whereas others may not. Such subjectivity is certain to affect the validity of both self- and informant-reported measures.

Indeed, it seems apparent that it is difficult to determine whether irritability is a separate construct from others such as anger, aggression and agitation. For example, Paulsen et al. (2001) found a high correlation between irritability and agitation ($r$ = 0.81), suggesting the same construct was being measured and so irritability may not be a valid independent symptom (as it is currently considered). Alternatively, they may comprise associated constructs; Siemer's (2009) dispositional theory of moods assumes that moods dispose people to appraise events/situations in an emotionally congruent manner. It may therefore be suggested that irritability predisposes an individual to become angry or make angry appraisals, consistent with how they are currently feeling. The theoretical difficulty in discriminating between irritability and anger becomes even more difficult when measurement problems are taken into account; for example, the NPI was used in several studies in the current review (Litvan et al., 1998; Paulsen et al., 2001; Ruiz-Idiago et al., 2017), in which the item for irritability is 'does the patient have sudden flashes of anger' (Cummings et al., 1994). Therefore, in Paulsen et al.'s (2001) study, a positive correlation between agitation and irritability becomes probable as a result of the measure used.

Additionally, irritability has been shown to correlate positively with anxiety (Litvan et al., 1998; Paulsen et al., 2001) and depression (Litvan et al., 1998; Nimmagadda et al., 2011). The findings indicate the potential for irritability to result from feelings of anxiety and depression or vice versa, as opposed to it being an independent construct. Certainly irritability research in young people have suggested that higher levels of irritability predict aggression, anxiety and depression in early adulthood (Leibenluft & Stoddard, 2013), suggesting an important association (although without determining its nature).

In contrast to this hypothesis, a factor analysis of the PBA-HD showed irritability to be an independent factor (Craufurd et al., 2001). However, aggression was located within this factor; this may again suggest that these two constructs are not independent and that aggression occurs as part of irritability, potentially as an external expression. Furthermore, it has been suggested that irritability be "viewed as a decreased threshold for experiencing frustration" (Deveney et al., 2013, p.1187). As irritability is often elicited through tasks which induce frustration, it is possible that irritability is the expression of multiple frustrations, which are likely to differ between people. Consequently, irritability may result from people struggling to regulate their emotions and behavioural responses; if frustrations become too much, anger and aggression follow (Zarotti, Fletcher & Simpson, 2018; Zarotti, Simpson, Fletcher, Squitieri & Migliore, 2018).

Additionally, from the research reviewed here, the concept of irritability has very limited predictive validity. It modestly predicted suicidal ideation in two studies (Honrath et al., 2018; van Duijin et al., 2018), although in Honrath et al.'s study this only applied to manifest (not premanifest) groups. Otherwise, no predictive value was reported. In addition, of the 12 papers that investigated irritability across disease stage, eight did not find a difference, three found an increase in irritability over time and two found a decrease, with the

majority therefore suggesting that irritability may not follow the disease course. Where changes in irritability were found, these still did not follow the course of degeneration, while other emotional difficulties such as apathy did (Kingma et al., 2008).. Equally importantly, this lack of consensus highlights the aforementioned difficulties incurred due to heterogeneity between study methodologies, measurement tools and definitions of irritability. At present, outcomes of studies of irritability in people with HD are affected by measures used, how irritability is defined and the stage of disease (van Duijn et al., 2013).

**Future research**

Future research should consider how irritability is understood in the context of HD. This may include further investigation into the neural pathways and circuitry associated with irritability and considering whether areas are, in fact, related to irritability or other potentially-associated constructs such as anger. Furthermore, consensus should be sought regarding the measures used to assess irritability in people with HD and their clinical cut-offs, particularly in relation to early-stage HD as earlier identification may help to mitigate the effects of irritability on maintenance of employment and the social/relational aspects of daily life (Sobreira, Ferreira & Alves, 2016). A number of psychological interventions are well-known to be effective for those with anger and aggression (see Glancy & Saini, 2005, for a review) and these might be appropriate for those with HD who are considered to experience irritability.

For irritability to be clinically meaningful, it will also be essential to disambiguate what is meant by the term, what this means in context of HD specifically, and whether different measures do actually assess this construct or variations of it. Finally, cross-cultural constructions of irritability remain unaddressed; only one study took place in a non-Western

country, China (Yang et al., 2016), and it cannot be assumed that Western-based study findings generalise across cultures.

## Conclusions

Considering the available literature, no satisfactory definition of irritability within the context of HD currently exists. Indeed, considering the correlates of irritability, including depression, apathy and anxiety, these may currently provide more meaningful information about a person's experience. Additionally, current treatment options appear designed to treat these associated psychological difficulties rather than specifically targeting irritability. Furthermore, the research remains unclear both in terms of the biological nature and aetiology of irritability, its associations with other psychological and emotional difficulties, and its relation to similar constructs (e.g. how a person feels when irritable may lead to the overt expression of irritability as anger). Therefore, measures need to capture the associated behavioural, cognitive and affective dimensions (Eckhardt, Norlander & Deffenbacher, 2004).

The evidence presented makes it difficult to conclude whether irritability in people with HD is a valid concept, with conflicting results being found. Such investigation does not, however, exclude or cast doubt on the reality of what we are describing as irritability for many individuals affected by HD and their clinicians. It does, however, suggest that if we are to provide effective help, we need to be much clearer on all aspects of this often extremely distressing experience.

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Note: * indicates inclusion in the review.

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**Table 1**

***Summary of studies of irritability in people with HD***

| Citation | Participants (N) | Gender (N) | Age (Mean) | HD stage | Irritability measures | Other measures |
|---|---|---|---|---|---|---|
| Anderson et al. (2016) | Mutation carriers (270)<br>Non carriers (531) | Female (559)<br>Male (242) | 45 | Various | UHDRS-b | BDI; BHS; BIS; UHDRS-m |
| Banaszkiewicz et al. (2012) | HD patient-caregiver dyads (80) | - | 47.7 | - | UHDRS-b | HAM-D |
| Berrios et al. (2001) | HD (26) | Female (10)<br>Male (16) | 37.8 | Various | IRR | PER, BDI, CFQ, SIGNAL, MOC, DIS, STAI & STAI2 |
| Berrios et al. (2002) | Gene carriers (32)<br>Non carriers (66) | Female (56)<br>Male (42) | 46.7 | Asymptomatic | IRR | PER, BDI, CFQ, SIGNAL, MOC, DIS |
| Bouwens et al. (2016) | Mutation carriers (124)<br>(90 by follow-up) | Female (53)<br>Male (71) | 50.7 | Premotor symptomatic and motor symptomatic mutation carriers. | NL-PBA | UHDRS<br>MMSE<br>Battery of executive functioning tests |
| Bouwens et al. (2015) | Mutation carriers (90) | Female (49)<br>Male (41) | 49 | Pre-motor symptomatic (25)<br>Motor symptomatic (64) | Irritability Scale (Chatterjee) | PBA<br>UHDRS |
| Burns et al. (1990) | Gene carriers (26)<br>Alzheimer's disease (31) | Female (29)<br>Male (28) | 48.3 (HD)<br>70.3 (AD) | - | Irritability/Apathy Scale (developed for this research) | Yudofsky Aggression Scale |
| Chatterjee et al. (2005) | Gene carriers (53)<br>Caregivers (53) | Female (21)<br>Male (32) | 48.2 | - | John Hopkins Irritability Questionnaire | BDI<br>Apathy Scale<br>MMSE |
| Craufurd et al. (2001) | Gene carriers (134) | Female (71)<br>Male (63) | 50 | Various | UHDRS, PBA-HD | |

| Citation | Participants (N) | Gender (N) | Age (Mean) | HD stage | Irritability measures | Other measures |
|---|---|---|---|---|---|---|
| Diago et al. (2018) | PHD (23)<br>EHD (15)<br>Family/staff controls (38) | PHD: female (15); male (8)<br>EHD: female (9); male (14)<br>Controls: female (24), male (14) | PHD: 37.9<br>EHD: 49.6<br>Controls: 40.4 | PHD (23)<br>EHD (15) | Irritability Scale | UHDRS, PSQI, ESS, HADS |
| Fritz et al. (2018) | PHD (193)<br>EHD (187)<br>LHD (91) | PHD: female (125); male (68)<br>EHD: female (104); male (83)<br>LHD: female (52); male (39) | PHD: 43.1<br>EHD: 51.5<br>LHD: 56.2 | PHD (193)<br>EHD (187)<br>LHD (91) | PBA-s | UHDRS<br>HRQOL measures (EQ-5D; RAND-12; WHODAS)<br>Neuro-QOL<br>HDQLIFE<br>PROMIS |
| Gregory et al. (2015) | Gene carriers (45)<br>PHD (39) | Female (49)<br>Male (35) | 46 | Pre-symptomatic (39)<br>Early symptomatic (45) | PBA | HADS |
| Groves et al. (2011) | Physician leaders from HD (55) speciality centres (55) | - | - | - | - | - |
| Honrath et al. (2018) | PHD (1220)<br>MHD (4489) | PHD: female (764); male (456)<br>MHD: female (2271); male (2218) | PHD: 37.4<br>MHD: 52.5 | PHD (1220)<br>MHD (4489) | PBA-s | - |
| Hubers et al. (2013) | Gene carriers (2106 at baseline, 945 at follow-up) | Female (1034)<br>Male (1072) | 50.3 | Motor symptomatic | UHDRS-b | - |
| Julien et al. (2007) | Gene carriers (89)<br>Non carriers (115) | Female (123)<br>Male (81) | 38 | - | CIDI | - |
| Kingma et al. (2008) | Non-carriers (56)<br>Gene carriers (152) | Female (114)<br>Male (94) | 45.3 | Pre-symptomatic gene carriers (55)<br>Early symptomatic | PBA | UHDRS-m |

| Citation | Participants (N) | Gender (N) | Age (Mean) | HD stage | Irritability measures | Other measures |
|---|---|---|---|---|---|---|
| | | | | (47)<br>Advanced symptomatic (50) | | |
| Kirkwood et al. (2002a) | Gene carriers (12)<br>Non-carriers (31) | Female (28)<br>Male (15) | 44 | Pre-symptomatic gene carriers (12)<br>Non-carriers (31) | Abbreviated MMPI (irritability scale) | - |
| Kirkwood et al. (2002b) | HD (175)<br>Non-carriers (363) | Female (384)<br>Male (154) | 41.4 | Pre-symptomatic (149)<br>Manifest HD (26) | Abbreviated MMPI Irritability scale (content analysis of MMPI items) | - |
| Klöppel et al. (2010) | Gene carriers (16)<br>Controls (15) | Female (16)<br>Male (15) | 39.3<br>40.4 | Pre-symptomatic | SIS, John Hopkins Irritability Questionnaire | BDI<br>BIS11<br>STAI |
| Litvan et al. (1998) | HD (29)<br>Progressive Supranuclear Palsy (34) | - | HD: 43.8<br>PSP: 66.6 | Various stages | NPI | UHDRS |
| Maltby et al. (2016) | Gene carriers (1264) | Female: 667<br>Male: 597 | 48.7 | Premanifest to Stage V | SIS | UHDRS |
| Martinez-Horta et al. (2016) | PHD far from onset (34)<br>PHD near onset (24)<br>EHD (70)<br>Non-carriers (101) | PHD far from onset: female (22); male 12<br>PHD near onset: female (12), male (13)<br>EHD: female (41), male (29)<br>Non-carriers: female (67), male (34) | PHD far from onset: 34.8<br>PHD near onset: 40.4<br>EHD: 47.2<br>Non-carriers: 43.3 | PHD judged 10.8< years from onset (34)<br>PHD judged ≤10.8 years from onset (24)<br>EHD (70) | PBA-s | UHDRS |
| Nimmagadda et al. (2011) | PwHD & their carers (30) | Female (14)<br>Male (16) | 49.17 | Genetically confirmed HD | IDAS<br>BIS | BADS<br>MADRS<br>UHDRS-m<br>STAI |
| Paulsen et al. (2001) | HD (52) | Female (27) | 45.5 | Various | NPI | UHDRS |

| Citation | Participants (N) | Gender (N) | Age (Mean) | HD stage | Irritability measures | Other measures |
|---|---|---|---|---|---|---|
| | Caregivers (52) | Male (25) | | | | |
| Pflanz et al. (1991) | HD (86) | HD:<br>Male (17)<br>Female (20)<br>Deceased:<br>Male (17)<br>Female (32) | | Various | Present State Examination (9th Ed.) | - |
| Reedeker et al. (2012) | Gene carriers (130)<br>Non carriers (43)<br>Informants (158) | - | - | - | IS<br>PBA<br>UHDRS-b | UHDRS-m<br>CIDI |
| Rickards et al. (2010) | People with HD (1690) | - | - | - | UHDRS-b | - |
| Ruiz-Idiago et al. (2017) | At risk of HD (9)<br>PMD (12)<br>MHD (77)<br>Control: expansion negative (6)<br>Control: no family history of HD (13) | At risk: female (3), male (6)<br>PMD: female (10), male (2)<br>MHD: female (39), male (38)<br>Control: expansion negative: female (3), male (3)<br>Control: no history: female (11), male (2) | At risk of HD: 37.0<br>PMD: 38.2<br>MHD: 51.1<br>Control: expansion negative: 44.1<br>Control: no family history of HD: 61.0 | At risk of HD (9)<br>PMD (12)<br>MHD (77) | PBA-s | UHDRS Total Functional Capacity<br>NPI |
| Singh-Bains et al. (2016) | People with HD (8)<br>Matched healthy controls (7) | HD: male (6); female (2)<br>Controls: male (5), female (2) | HD: 56.0<br>Controls: 66.4 | Deceased | IDAS | QNE<br>MMSE<br>HADS |
| Thompson et al. (2002) | People with HD (82) | Female (41)<br>Male (41) | 49 | Clinically diagnosed HD | PBA-HD<br>UHDRS-b | - |
| Thompson et al. (2012) | HD (111) | Female (68)<br>Male (43) | 48 | Clinically diagnosed HD | PBA-HD | - |
| Underwood et al. | Gene carriers (1474) | Female (787) | 49 | Various; 71% | HADS-SIS | UHDRS |

| Citation | Participants (N) | Gender (N) | Age (Mean) | HD stage | Irritability measures | Other measures |
|---|---|---|---|---|---|---|
| (2016) | | Male (687) | | between stages I-III | | SF-36 |
| van den Stock et al. (2015) | Gene carriers (20)<br>Non-carriers (20) | Female (23)<br>Male (17) | 37.5 | Pre-manifest | PBA-HD | UHDRS<br>BDI<br>STAI |
| van Duijn. (2010) | Review of treatment studies | - | - | - | - | - |
| van Duijn et al. (2013) | HD (121) | - | - | Pre-symptomatic = 46<br>Symptomatic = 75 | PBA | - |
| van Duijn et al. (2014) | Gene carriers (1993) | Female (977)<br>Male (1016) | 50.3 | Early and mid-stage | UHDRS-b | - |
| van Duijn et al. (2018) | Gene carriers (1451) | Female (795)<br>Male (656) | 48.4 | Five disease stages post-motor-onset | UHDRS-b | UHDRS-m<br>C-SSRS<br>PBA (suicidal ideation item severity score) |
| Vassos, Panas, Kladi & Vassilopoulos (2007) | Gene carriers (29)<br>Non-carriers (35) | Female (37)<br>Male (27) | 34.2 | - | UHDRS<br>SIS<br>HDHQ | MOC |
| Yang et al. (2016) | HD patients (58) | Female (33)<br>Male (25) | 46.1 | Clinically diagnosed HD | UHDRS-b | UHDRS-m |

Abbreviations: AD = Alzheimer's disease; BADS = Behavioural Assessment of Dysexecutive Syndrome; BDI = Beck Depression Inventory; BHS = Beck Hopelessness Scale; BIS/BIS11 = Barratt Impulsiveness Scale; CFQ = Cognitive Failures Questionnaire; CIDI = Composite International Diagnostic Interview; C-SSRS = Columbia Suicide Severity Rating Scale; DIS = Dissociation Questionnaire; EHD: early-stage Huntington's disease; ESS = Epworth Sleepiness Scale; HADS = Hospital Anxiety and Depression Scale; HADS-SIS = Hospital Anxiety and Depression Scale-Snaith Irritability Scale; HAM-D =

Hamilton Depression Rating Scale; HDHQ = Hostility & Direction of Hostility Questionnaire; HDQLIFE = Huntington Disease Quality of Life; HRQOL = health-related quality of life; IDAS = Irritability, Depression, and Anxiety Scale; IRR = Snaith's Irritability Scale; IS = Irritability Scale; LHD = late-stage Huntington's disease; MADRS = Montgomery & Asberg Depression Rating Scale; MHD: manifest Huntington's disease; MMPI = Minnesota Multiphasic Personality Inventory; MMSE = Mini-Mental State Exam; MOC = Maudsley Obsessive-Compulsive Questionnaire; Neuro-QOL = Quality of Life in Neurological Disorders; NL-PBA = Problem Behaviours Assessment – Dutch translation; NPI = Neuropsychiatric Inventory; PBA = Problem Behaviours Assessment; PBA-s = Problem Behaviours Assessment – short form; PER = Personality Deviance Scale; PMD = premanifest HD; PROMIS = Patient Reported Outcomes Measurement Information System; PSQI = Pittsburgh Sleep Quality Index; QNE = Quantified Neurological Examination; SF-36 = Medical Outcome Study 36-Item Short Form Health Survey; SIGNAL = Signal Detection Memory Test; SIS = Snaith Irritability Self-Assessment Scale; STAI & STAI2 = Spielberger Anxiety scales; UHDRS = Unified Huntington's Disease Rating Scale (-b = behaviour component; -m = motor component); WHODAS = World Health Organization Disability Assessment Schedule 2.0.

**Table 2**

***Results of studies of irritability in people with HD***

| Citation | Aim | Results related to irritability |
|---|---|---|
| Anderson et al. (2016) | Identify associations between neuropsychiatric symptoms and suicidal ideation. | No significant difference in suicidal ideation between gene carriers and non-carriers ($p = .2275$), and gene mutation presence did not significantly increase the chance of the participant reporting suicidal ideation. For gene carriers, only hopelessness significantly predicted suicidal ideation (for non-carriers, hopelessness, irritability and anxiety were all significantly predictive of suicidal ideation). |
| Banaszkiewicz et al. (2012) | Identify determinants of quality of life, functional disability and caregiver burden. | Irritability is not significantly associated with disability. |
| Berrios et al. (2001) | Investigate the relationship between psychiatric profile and CAG repeats. | Compared with available norms, participants showed increased levels of 'outward irritability'. No significant correlation with irritability and CAG repeat length. |
| Berrios et al. (2002) | Compare psychiatric profiles of gene carriers and non-carriers. | Significant difference in inward and outward irritability between GC and NGC, with irritability being higher in GC. Factor structure: inward and outward irritability were included within the 'personality' factor. |
| Bouwens et al. (2016) | Identify whether cytokine levels are associated with neuropsychiatric symptoms and cognitive dysfunction. | Plasma cytokine levels were inversely associated with executive functioning (IL-6: $\beta = -0.114$; $p = .01$) (IL-1ra: $\beta = -0.110$; $p = .02$), but not with any other neuropsychiatric symptom score including irritability. |
| Bouwens et al. (2015) | Investigate the course and temporal relationship between irritability and other psychological difficulties. | No significant increase in irritability from baseline to follow-up. At baseline 33% of people with HD were irritable, with 70% of those remaining irritable at 2-year follow-up. Of those who were not irritable at baseline 23% developed irritability at 2-year follow-up. Multivariate regression model showed an association between increase in apathy and an increase in irritability, when including confounds such as age, sex, motor function changes and medication use. Continuous use of antipsychotics associated with an increase in irritability. |
| Burns et al. (1990) | Compare irritability, aggression and apathy in people with HD with people with AD. | No significant difference in irritability or apathy between the HD and AD groups. HD group were significantly more aggressive than the AD group and aggressive outbursts lasted longer in the HD group. Irritability, apathy & aggression were independent of each other in both groups. Irritability correlated positively with bad temper in the HD group but there was no correlation in the AD group. |
| Chatterjee et al. | Examine agreement between | No significant difference in report of irritability between PwHD and caregivers. No difference in BDI |

| Citation | Aim | Results related to irritability |
|---|---|---|
| (2005) | people with HD and their caregivers regarding presence of irritability, apathy and depression. | scores. Difference in apathy scores between the two groups. |
| Craufurd et al. (2001) | Understand behavioural abnormalities in people with HD and develop a method of assessing these changes. | Irritability present in 44% of sample (severity rating of 2 or more). Three factors obtained from factor analysis: 1 - apathy; 2 - irritability; 3 - depression. Irritability difficulties occurred more frequently in people with HD with an illness duration of 6-11 years. Irritability factor showed no correlation with duration of illness or CAG repeat length. |
| Diago et al. (2018) | Investigate relationships between sleep quality and psychological factors in people with HD. | Irritability non-significantly higher in comparisons between controls and premanifest HD (mean difference: 1.65; p = .330) and early-stage HD (mean difference: 2.00; p = .412). No significant correlation between sleep quality (rho = .368; p = .023), sleep latency (rho = .224; p = .177), sleep disturbance (rho = .321, p = .0050), sleep dysfunction (rho = .193, p = .247) or sleepiness (rho = .277, p = .092). |
| Fritz et al. (2018) | Examine relationships between apathy and behaviour, cognition, physical function and health-related quality of life in people with HD. | Better clinician-reported behavioural scores (including irritability) associated with better apathy scores (p<.001, adjusted $R^2$ = .30 (large effect size)). Smaller (moderate) $R^2$ found for physical ability, functioning and cognition. |
| Gregory et al (2015) | Investigate structural connectivity and changes associated with depression, apathy and irritability in HD. | Significant difference in irritability between the two groups. Significant negative correlations between irritability score and fractional anisotropy which was dependent on cumulative probability to onset. |
| Groves et al. (2011) | Provide direction for the management of irritability in people with HD. | SSRIs were most frequently used to treat mild to moderate irritability in HD. Antipsychotics (APD) were more commonly used in Europe to treat mild to moderate irritability than in North America & Australia. SSRIs used when irritability occurred with comorbid depression and anxiety. APDs used when irritability occurred with aggression and impulsivity. |
| Honrath et al. (2018) | Assess neuropsychological risk factors for suicidal ideation. | Irritability was not associated with suicidal ideation in the premanifest group, but was a significant predictor of suicidal ideation for the manifest group (B = 0.039; SE = 0.012; OR = 1.040, [CI = 1.016-1.064], p = .001). |
| Hubers et al. (2013) | Investigates predictors and correlates of suicidal ideation in people with HD. | Baseline presence of irritability significantly correlated with suicidal ideation – those with suicidal ideation were more irritable than those without. Multivariate analyses indicated irritability was not an independent correlate of suicidal ideation. At follow-up, irritability was not a predictor of suicidal |

| Citation | Aim | Results related to irritability |
|---|---|---|
| | | ideation in people with HD. |
| Julien et al. (2007) | Compare the prevalence of psychological difficulties in pre-symptomatic gene carriers and non-carriers and to look at the relationship with proximity to onset. | Gene carriers reported a greater prevalence of 'manic' symptoms (11%) compared with NGC (4%) – in every case irritability was reported. Irritability was increased in gene carriers up to 10 years prior to clinical onset but not in those further from onset. No significant relationship between proximity to onset and irritability within the 10 year period. |
| Kingma et al. (2008) | Investigate behavioural difficulties in people with HD. | Factor analysis revealed 3 components: irritability, apathy and depression. All mutation carriers showed significantly more irritability, apathy & depression than non-carriers. No significant difference in irritability between advanced symptomatic GCs and other disease stages. No significant relationship between irritability and depression or apathy. |
| Kirkwood et al. (2002a) | Examine whether longitudinal changes in personality can be detected in pre-symptomatic gene carriers. | Greater increase irritability and clinical hostility observed over time in the pre-symptomatic GC group compared with NGC. No correlation between number of CAG repeats and irritability in both groups. |
| Kirkwood et al. (2002b) | Investigate whether psychological difficulties can be detected in pre-symptomatic HD. | No significant difference in MMPI scores across groups. No significant difference in irritability across the three groups and no association with proximity to onset. |
| Klöppel et al. (2010) | Examine the emotional neurocircuitry associated with irritation, | No significant difference in irritability between pre-symptomatic GCs and controls. Companions' ratings did not differ from those of the pre-symptomatic GCs. Ratings on the SIS were within the normal range, apart from 1 pre-symptomatic GC. Negative emotions positively correlated with SIS & BIS-11. |
| Litvan et al. (1998) | Compare neuropsychiatric aspects of HD compared with PSP. | Irritability influenced the total NPI score in PwHD. PwHD scored significantly higher on agitation, irritability and anxiety while those with PSP scored higher for apathy. In PwHD, agitation was correlated with anxiety, irritability, disinhibition and euphoria. Irritability was associated with anxiety, disinhibition, euphoria and depression. Logistic regression analysis indicated PwHD are more likely to exhibit hyperactive behaviour. People with PSP are more likely to exhibit hypoactive behaviour. |
| Maltby et al. (2016) | Analyse the factor structure of the irritability construct as reported via the SIS. | Confirmatory factor analysis found two bifactor models to offer the best fit of the data, both comprising a general irritability factor and two group factors: 1) outward irritability and inward irritability, as per the original conceptualisation of the SIS (general factor explained 64.2% of variance; inward irritability 13.7%; outward irritability 22.1%); 2) temper and self-harm, as generated by exploratory factor analysis (general factor explained 67.3%; temper 12.1%; self-harm 20.5%). Loadings for items were |

| Citation | Aim | Results related to irritability |
|---|---|---|
| | | higher on the general factor for both models. Recommendation is that the full scale score be used as an overall measure of irritability. |
| Martinez-Horta et al. (2016) | Explore relationships between neuropsychiatric symptoms and disease stage/controls, as well as medication use. | In the far from onset group, irritability was the most prevalent symptom (32%) along with depression (no increased risk of irritability by odds ratio). In the close to onset group, irritability (56%) was the second-most prevalent symptom after apathy (64%), with OR: 5.1. In the early-stage HD group, irritability was the third most prevalent symptom (47%) after depression (65%) and apathy (63%), with OR: 3.6. In the non-carrier controls, irritability was present in 20%. Significant difference on irritability prevalence between groups ($p < .001$); close to onset and early-stage HD had higher mean irritability than people far from onset and non-carrier controls. Strong correlation between irritability and use of antidepressants ($r^2 = .127$, $p = .001$), benzodiazepines ($r^2 = .127$, $p = .001$) and neuroleptics ($r^2 = .127$, $p = .01$). |
| Nimmagadda et al. (2011) | Investigate the association of irritability in people with HD with other psychological constructs and movement disorder. | Both inward and outward irritability were significantly positively associated with MADRS scores, STAI state and trait anxiety scores. BIS scores were positively associated with STAI trait scores and both outward and inward irritability scores on the IDA. Negative correlation between irritability scores and the UHDRS. |
| Paulsen et al. (2001) | Use the NPI to characterise neuropsychiatric symptoms in people with HD. | Irritability endorsed in 65.4% of sample. NPI. High correlation between irritability & agitation indicating two scales are measuring the same construct. Irritability also correlated with anxiety and disinhibition. |
| Pflanz et al. (1991) | Determine the range and frequency of psychological difficulties in people with HD. | Irritability present in 64% of cases and was the 2nd most common difficulty. Irritability occurred between 0-3 years prior to onset of motor symptoms. Loss of interest and concentration correlated with irritability. |
| Reedeker et al. (2012) | Investigate the psychometric properties of the Irritability Scale against the PBA irritability factor to establish a reliable cut off. | Irritability significantly higher in mutation carriers (35% irritable) than NC (9% irritable). 28% of mutation carriers considered irritable according to IS-self and informant scales. 50% considered not irritable according to both scales. For the remaining 23% there was disagreement between participants and informants (18/27 reported selves as not irritable but their informant did). Irritability independently correlated with benzodiazepine use. |
| Rickards et al. (2010) | Perform a factor analysis on completed UHDRS-b assessments. | Factor analysis indicated that irritability is a distinct 'psychiatric symptom' in HD. |
| Ruiz-Idiago et al. (2017) | To validate the Spanish PBA-s including internal consistency, inter- and intra-rater | Internal consistency was good (Cronbach's $\alpha = .79$) and NPI items assessing similar symptoms correlated strongly (for irritability, $r = .918$, $p<.01$). Inter- and intra-rater reliability were good (Cohen's weighted kappa: severity scores: 1.00 (intra-rater); .98-.92 (inter-rater); frequency scores: .97 (intra- |

| Citation | Aim | Results related to irritability |
|---|---|---|
| | reliability, exploratory factor analysis and convergent validity. | rater); .91-.93 (inter-rater)). A four-factor model accounted for 56% of the variance in outcomes, comprising irritability (18%), apathy (13%), depression (15%) and perseveration (10%); the irritability factor comprised items relating to irritability and aggressiveness. Irritability did not correlate with UHDRS Total Functional Change outcomes (r = .050, p = .597). |
| Singh-Bains et al. (2016) | Relate neurodegeneration in the globus pallidus to clinical symptomatology. | Relative to controls, in HD patients the external globus pallidus showed a 54% overall volume decline, 60% neuron loss and 34% reduced soma volume. The ventral pallidum was similarly affected, with a 31% reduction in volume, 48% neuron loss and 64% reduced soma volume. The internal globus pallidus was less affected (38% loss of overall volume only, without concurrent neuronal loss. Volume loss was greater at later stages of disease for all three subdivisions of the global pallidus. Decreasing internal globus pallidus volume was associated with decreasing irritability ($r_s$ = 0.90; p = .04). Decreasing volume in the external globus pallidus and ventral pallidus was not associated with irritability ($r_s$ = .50; p = .23 in both cases), but was associated with increasing cognitive and motor impairment. Increasing years since symptom onset was also associated with decreased irritability ($r_s$ = -.90; p = .04). |
| Thompson et al. (2002) | Investigate how behavioural change in people with HD relates to other indices of disease severity. | Depression & irritability subscales poorly correlated with functional capacity, motor impairment & cognition. Apathy was significantly correlated. UHDRS-b score significantly correlated with PBA-HD depression & irritability subscales. UHDRS irritability scale significantly correlated with irritability subscale of the PBA-HD. |
| Thompson et al. (2012) | Evaluate the prevalence of neuropsychiatric difficulties in people with HD over time. | Irritability common with a prevalence ranging from 49-83%. Longitudinal analysis showed an increase in irritability over time with a significant linear effect in those who entered the study at stage I and II but not in those who entered at stage III of HD. |
| Underwood et al. (2016) | Evaluate psychological indicators of pain in people with HD. | Interviewed-rated irritability was a significant predictor of pain severity (OR: 1.053, p = .002) after controlling for confounds (gender, age, disease stage, motor function and dementia). Higher participant-rated irritability score was not associated with an increase in the odds of greater pain severity (OR: 1.095, p = .056). |
| van den Stock et al. (2015) | Identify structural and functional brain changes underlying irritability in pre-manifest HD. | Irritability significantly higher in GC vs NC. |
| van Duijn. (2010) | Review the treatments of irritability. | Suggests use of an SSRI as a first-choice medication to manage irritability in people with HD or a mood stabiliser. An alternative would be an antipsychotic. Behavioural or other psychotherapeutic interventions should be considered. |
| van Duijn et al. | Investigate the progression of | 2-year follow-up: no significant change in irritability. Associations between PBA factor scores and |

| Citation | Aim | Results related to irritability |
|---|---|---|
| (2013) | irritability, depression and apathy in people with HD over a 2-year follow up. | UHDRS-m: as UHDRS-m score increased so did the PBA irritability factor. In pre-symptomatic group, strongest relationship was between an increased UHDRS-m score and increased irritability score. At follow-up 15 of the pre-symptomatic group were symptomatic. No significant increase in irritability compared with those who remained pre-symptomatic. |
| van Duijn et al. (2014) | Examine occurrence and correlates of neuropsychiatric symptoms in people with HD. | 61.4% of HD mutation carriers scored 'no irritability', 24.7% scored 'mild irritability' and 13.9% scored 'moderate/severe irritability'. The prevalence of moderate/ severe irritability increased by stage of disease from 10.4% at stage 1 to 19.6% at stages 4-5. Irritability independently correlated with male sex, younger age, a history of depression, psychosis and a previous suicide attempt. |
| van Duijn et al. (2018) | Examine correlates of suicidal ideation and suicidal behaviour in gene carriers. | HD gene carriers with moderate/severe irritability had significantly higher mean suicidal ideation score (0.83, SE 0.09) and suicidal behaviour score (0.24, SE 0.04) than those with no or mild irritability. Moderate/severe irritability significantly predicted suicidal ideation (b = 0.068, p - .01) and suicidal behaviour (b = 0.071, p - .01). Those with mild and no irritability differed only in passive suicidal ideation (higher for mild irritability, $p < .001$). Suicide attempts had occurred more frequently in those with moderate/severe irritability (10.4%) than those with no (5.6%) or mild (5.7%) irritability. There were no significant between-group differences for self-injurious behaviour. The correlation between depressed mood and irritability was weak ($r = .32$, $p < .001$), implying that these are separate constructs. |
| Vassos, Panas, Kladi & Vassilopoulos (2007) | Distinguish which behavioural and psychiatric features differentiate gene carriers with non-carriers. | No significant difference in irritability between GC and NC. Higher extroverted hostility in GC than in NC. Overlap between the two groups suggests extroverted hostility may not be pathologic in GC. |
| Yang et al. (2016) | Identify relationships between CAG repeats, age of onset and irritability in Chinese clinically-diagnosed HD patients. | Irritability was positively correlated with CAG repeats ($r = .449$; $p < .001$) and negatively correlated with age of onset ($r = -.391$, $p = .002$). There was no significant difference in prevalence ($p = .300$) or scores ($p = .403$) of behaviour symptoms between males and females. |

Abbreviations: AD = Alzheimer's disease; BDI = Beck Depression Inventory; BIS/BIS11 = Barratt Impulsiveness Scale; GC = gene carriers; HD = Huntington's disease; IDAS = Irritability, Depression, and Anxiety Scale; MADRS = Montgomery & Asberg Depression Rating Scale; MMPI = Minnesota Multiphasic Personality Inventory; NGC = non-gene carriers; NPI = Neuropsychiatric Inventory; OR = odds ratio; PBA = Problem Behaviours Assessment; PBA-s = Problem Behaviours Assessment – short form; PSP = progressive supranuclear palsy; SIS = Snaith Irritability Scale; SSRI = selective serotonin

reuptake inhibitors; STAI & STAI2 = Spielberger Anxiety scales; UHDRS = Unified Huntington's Disease Rating Scale (-b = behaviour component; -m = motor component).

**Table 3**

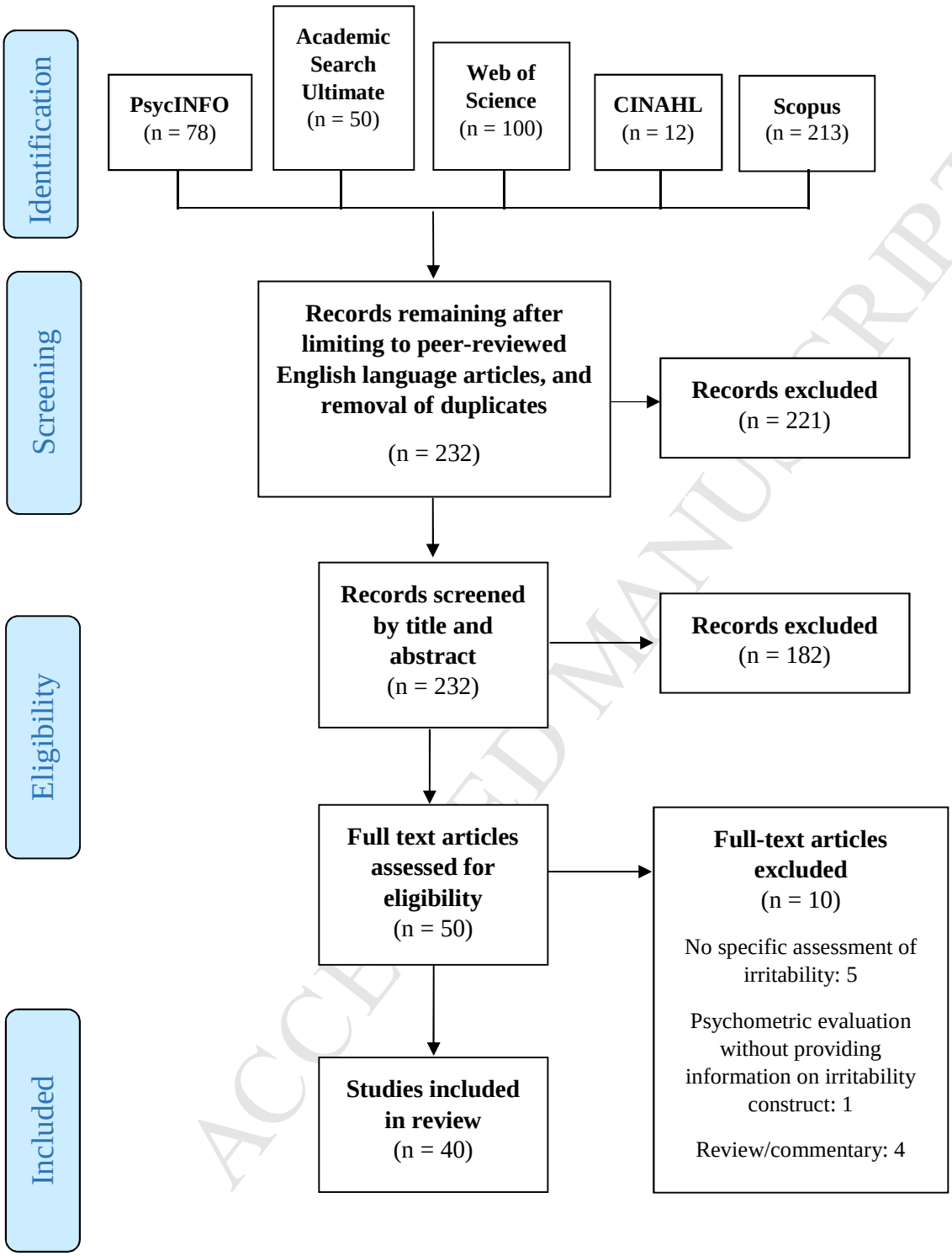
***Measures of irritability in HD***

| Measure | Description | Reliability | Validity |
|---|---|---|---|
| Burns Irritability Scale (BIS; Burns, Folstein, Brandt & Folstein, 1990) | Measures irritability and apathy according to carer's ratings and does not include subjective experience. It uses a 5-point scale assessing the presence of irritability ranging from "never" to "always". | Internal consistency:<br>- Irritability: α = 0.82<br>- Apathy: α = 0.78<br>Inter-rater[1]:<br>- Whole interview: κ = 0.98<br>- Irritability: κ = 1.00<br>- Apathy: κ = 0.85<br>Test-retest:<br>- Whole interview: κ = 0.88<br>- Irritability: κ = 0.81<br>- Apathy: κ = 0.76 | Convergent:<br>- Psychogeriatric Dependency Rating Scale: *r* = 0.87 |
| Irritability, depression, anxiety scale (IDA; Snaith, Constantopoulos, Jardine & McGuffin 1978) | Scale assessing irritability, depression and anxiety to be used within clinical context. Irritability understood as a temporary psychological state. Includes 8 irritability items | Inter-rater:<br>- Outward irritability: *r* = .87-.90<br>- Inward irritability: *r* = .74-.90<br>- Depression: *r* = .80-.90<br>- Anxiety: *r* = .75-.80<br>Split-half:<br>- Outward irritability: *r* = .77, .80, .88<br>- Inward irritability: *r* = .70, .92, .93<br>- Depression: *r* = .72, .77, .81<br>- Anxiety: *r* = .74, .80, .87 | |
| Irritability Questionnaire (IRQ; Craig, Hietenan, Markova & Berrios, 2008) | Subjective measure of irritability. Consists of 21 items assessing the frequency and severity of irritability with each individual item | Internal consistency:<br>- Global: α = 0.90<br>Split half = 0.78<br>- Frequency: α = 0.90<br>Split half = 0.77 | Convergent:<br>- Trait anger scale: *r* = 0.72<br>- State anger scale: *r* = 0.58<br>- IDA outward: *r* = 0.58<br>- IDA inward: *r* = 0.49 |

[1] Assessed the presence or absence of irritability.

| Measure | Description | Reliability | Validity |
|---|---|---|---|
| | score ranging from 0-3. | - Severity: α = 0.89<br>Split half = 0.58<br>Retest reliability: *r* = 0.82 | - BIS: *r* = 0.37 |
| John Hopkins Irritability Scale (Chatterjee, Anderson, Moskoqitz, Hauser & Marder, 2005) | Objective measure (informant-report) of irritability. Consists of 14 items pertaining to irritability with the range of all possible scores being 0-42 to assess the presence of irritability. | No data available | No data available |
| Problem Behaviours Assessment – Huntington's disease (PBA-HD; Craufurd, Thompson & Snowden, 2001) | Semi-structured interview measuring behavioural difficulties in HD including the presence, severity and frequency. | Inter-rater:<br>- Severity: *r* = 0.86<br>- Frequency: *r* = 0.84<br>Internal consistency: α = 0.67<br>Test-retest:<br>- Severity: *r* = 0.94<br>- Frequency: *r* = 0.92 | |
| Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996) | Assesses difficulties in motor, cognitive, functional and behavioural domains. The behavioural section measures the frequency and severity of difficulties related to affect, thought content and coping styles. | Internal Consistency:<br>- Behavioural: α = 0.83<br>- Motor: α = 0.95<br>- Cognitive: α = 0.90<br>- Functional: α = 0.95 | Divergent (Behavioural Total):<br>- Motor: *r* = -0.10<br>- Total Functional Capacity: *r* = -0.07 |

**Figure 1.** PRISMA flow diagram of studies excluded/included at each stage.



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