# THE PSYCHIATRIC PHENOTYPE IN HUNTINGTON'S DISEASE

by

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# ABSTRACT

Psychiatric symptoms are more prevalent in Huntington's disease (HD) than the general population, but reasons for this are unknown. The primary aim of this research was to investigate possible familial influences on the psychiatric phenotype in HD.

96 gene positive and 5 gene negative siblings were recruited from 50 HD families throughout the UK and underwent a lifetime psychiatric history assessment using semi-structured interview and case-note review.

Gene positive index individuals had high lifetime rates of depressive (56%) and anxiety (38%) disorders. Their depressive episodes were less severe and more frequent with an older age of onset and fewer biological symptoms than individuals with depression without HD. Within gene positive sibling-pairs (n=53), there was significant familial aggregation of the presence ($\kappa$=0.46, $p$=0.004) and course (ICC=0.47, $p$=0.002) of depressive disorders and the presence of irritability ($\kappa$=0.357, $p$=0.024) and aggression ($\kappa$=0.384, $p$=0.016). Two gene negative siblings had lifetime psychiatric diagnoses.

The high prevalence of psychiatric co-morbidity in HD cannot be entirely explained by the HD gene. Familial factors, most likely other genetic factors, are likely to play a role. Further research into the contribution of biological and environmental factors to the psychiatric phenotype in large samples of individuals with HD is warranted.

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| | |
|---|---|
| **ABI** | Acquired Brain Injury |
| **APMS** | Adult Psychiatric Morbidity Survey |
| **ASOs** | Anti-sense oligonucleotides |
| **AUC** | Area under the curve |
| **BADDS** | Bipolar Affective Disorder Dimensional Scale |
| **BADDS-D** | Bipolar Affective Disorder Dimensional Scale – Depression subscale |
| **BDI** | Beck Depression Inventory |
| **BDI-II** | Beck Depression Inventory-II |
| **BDNF** | Brain-derived neurotrophic factor |
| **CAG repeat** | Cytosine-Adenine-Guanine repeat |
| **CI** | Confidence Interval |
| **DISCs** | Depression Intensity Scale Circles |
| **DSM** | Diagnostic and Statistical Manual of Mental Disorders |
| **ESEMeD** | European Study of the Epidemiology of Mental Disorders |
| **fMRI** | Functional Magnetic Resonance Imaging |
| **FuRST-pHD** | Functional Rating Scale Taskforce for pre-Huntington's disease |
| **GAD** | Generalised Anxiety Disorder |
| **GAS** | Global Assessment Scale |
| **GWAS** | Genome-wide association studies |
| **HADS** | Hospital Anxiety and Depression Scale |
| **HADS-D** | Hospital Anxiety and Depression Scale – depression subscale |
| **HD** | Huntington's disease |
| **HDA** | Huntington's Disease Association |
| **HPA axis** | Hypothalamic Pituitary Adrenal axis |
| ***HTT* gene** | *Huntingtin* gene |
| **ICC** | Intra-class Correlation Coefficients |
| **ICD-10** | International Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research, 10$^{th}$ Edition |
| **IQR** | Inter Quartile Range |
| **IS** | Irritability Scale |
| **LCSPT circuit** | Limbic-cortical-striatal-pallidal-thalamic circuit |
| **LTC circuit** | Limbic-thalamic-cortical circuit |
| **MDDR** | Major Depressive Disorder - recurrent |
| **MDDS** | Major Depressive Disorder – single episode |
| **MDRG** | Mood Disorders Research Group |
| **MS** | Multiple Sclerosis |
| **NCS-R** | National Comorbidity Survey-Replication |
| **NOS** | Not Otherwise Specified |
| **NPI** | Neuropsychiatric Inventory |
| **NPV** | Negative Predictive Value |
| **OCD** | Obsessive Compulsive Disorder |
| **O/Cs** | Obsessive/Compulsive Symptoms |

| | |
|---|---|
| **OPCRIT** | Operational Criteria diagnostic system |
| **PBA-s** | Problem Behaviours Assessment for Huntington's disease – short version |
| **PD** | Panic Disorder |
| **PPV** | Positive Predictive Value |
| **R&D** | Research and Development |
| **RNAi** | RNA interference |
| **ROC Curves** | Receiver Operating Characteristic curves |
| **SCAN** | Schedules for Clinical Assessment in Neuropsychiatry |
| **SD** | Standard Deviation |
| **SDMT** | Symbol Digit Modalities Test |
| **SPSS** | Statistical Package for the Social Sciences |
| **TFC** | Total Functional Capacity |
| **UHDRS** | Unified Huntington's Disease Rating Scale |
| **UHDRS-b** | Unified Huntington's Disease Rating Scale – behaviour section |
| **WHO** | World Health Organisation |
| **YBOCS** | Yale-Brown Obsessive Compulsive Scale |
| **5-HT** | Serotonin |

# CHAPTER 1: HUNTINGTON'S DISEASE

This chapter will provide an introduction to Huntington's disease (HD). It will outline the history of HD, epidemiology of HD, genetics of HD as well as a clinical description of the disease, the neuropathology and management of HD.

## *1.1 History of Huntington's Disease*

George Huntington's seminal paper in 1872 titled "On Chorea" described an unusual hereditary disease that has subsequently borne his name. His striking description emphasising three distinctive features of the disease, including: i) its hereditary nature, ii) a tendency to insanity and suicide, and iii) its manifesting itself as a grave disease only in adult life, remains highly relevant today. Although recognised and described before 1872, Huntington's account of HD was widely accepted from publication and knowledge of hereditary chorea spread rapidly. This was perhaps due to an increasing interest in heredity at this time but also due to the detailed clinical description of George Huntington's paper that comprised not only his observations but also those of his father and grandfather, all family doctors on Long Island, New York (Harper, 2014).

This publication by Huntington provided the foundation for all successive work on HD (see Table 1.1). Several papers on the genetics of HD were published in the early twentieth century but the true major advances came in the 1980s with the development of molecular genetic techniques (Petersen et al., 1999). The most exciting and perhaps most important of these advances being the identification of the causal *HD* gene in 1993 (Huntington's Disease

Collaborative Research Group, 1993), which has opened the door to more extensive approaches to better understand this highly complex disorder.

**Table 1.1: The main landmarks in the study of HD** (adapted from Walker, 2007 and Harper, 2014, p. 19).

| Year | Event |
|---|---|
| 1686 | Thomas Sydenham describes post-infectious chorea |
| 1832 | John Elliston identifies inherited form of chorea |
| 1841 | First definite description of HD (Charles Waters) |
| 1872 | George Huntington characterises HD |
| 1888 | Hoffman clearly describes Juvenile HD |
| 1908 | Mendelian dominant inheritance is recognised |
| 1953 | DNA structure is elucidated |
| 1955 | HD is described in Lake Maracaibo region of Venezuela |
| 1967 | World Federation of Neurology research group formed |
| 1976 | First animal model (kainic acid) of HD described |
| 1983 | Localisation of HD gene on chromosome 4 |
| 1993 | Identification of HD gene and of mutation as expanded cytosine-adenine-guanine (CAG) trinucleotide repeat |
| 1996 | Transgenic mouse with expanded HD repeat developed |
| 1997 | Neuronal inclusions recognised in transgenic mouse and human HD brain |
| 2000 | Drugs screened for effectiveness in transgenic animal models |
| 2001 | PREDICT-HD: to study healthy individuals at risk for HD |
| 2003 | REGISTRY study: European observational study of HD >10 000 participants |
| 2006 | COHORT-HD: large-scale observational study of HD in United States and Australia, 3500 participants. |
| 2009 | TRACK-HD: observational biomarker study of pre-manifest and early-stage HD |
| 2012 | ENROLL study: worldwide observational study of HD, foundation for clinical trials in HD |

## *1.2 Epidemiology of HD*

HD is a rare neuropsychiatric disorder with a similar prevalence for men and women.

Although the estimated worldwide prevalence of HD is 2.71 per 100 000 (Pringsheim et al., 2012), it's prevalence between and even within countries is variable due to population

differences in the normal distribution of predisposing alleles (Squitieri et al., 1994). The prevalence rate is highest in people of Western European descent (where it is thought the *HD* gene originated) with estimates of 5-10 cases per 100 000 (Roos, 2010; Pringsheim et al., 2012) and lower in the rest of the world with Japan for example, having a much lower prevalence of approximately one-tenth that of most populations of European descent (Nakashima et al., 1996). However, it is thought that the actual prevalence rates are much higher than those reported. One recent UK study using patients' electronic medical records found that the estimated prevalence rate rose from 5.4 per 100 000 in 1990 to 12.3 per 100 000 in 2010 (Evans et al., 2013).

Unusually high local concentrations of HD are also known to exist in particular populations, owing to large individual kindreds (Harper, 2014). Examples of these local foci of HD include: Gwent, South Wales (Walker et al., 1981); Moray Firth, Scotland (Lyon, 1962); and, Tasmania, Australia (Pridmore, 1990). The most well known of such kindreds is the Venezuelan isolate by the shores of Lake Maracaibo. This unique community consisting of over 100 affected individuals with the occurrence of probable homozygotes became a focus of study for the Hereditary Disease Foundation (Wexler et al., 1987). Annual visits from 1981 led to the creation of the pedigree of this kindred and blood samples taken for analysis culminated in the major breakthrough of locating and then isolating the *HD* gene in 1993.

### *1.3 Genetics of HD*

Since George Huntington's initial description in 1872, it has been known that HD is hereditary in nature. More specifically, HD shows a form of autosomal dominant inheritance

characterised by: (1) an equal incidence in both sexes; (2) equal transmission by both sexes; (3) 50% of offspring of an affected parent also being affected by the time they reach old age, and; (4) no transmission of the disorder by an unaffected offspring (Cazeneuve and Durr, 2014).

After an arduous search for the genetic basis of HD, in 1983 the *HD* gene was mapped to chromosome 4p16.3 using haplotype linkage analysis (molecular genetic testing to identify a set of closely linked segments of DNA) and by linkage disequilibrium (the non-random association of two genes on the same chromosome) (Gusella et al., 1983). However, it was still not until a decade later that it was discovered the HD causing mutation is an expanded CAG repeat in the first exon of the *interesting transcript gene 15, IT-15* (Huntington's Disease Collaborative Research Group, 1993). The gene contains 67 exons and encodes the cytoplasmic protein, huntingtin (Huntington's Disease Collaborative Research Group, 1993).

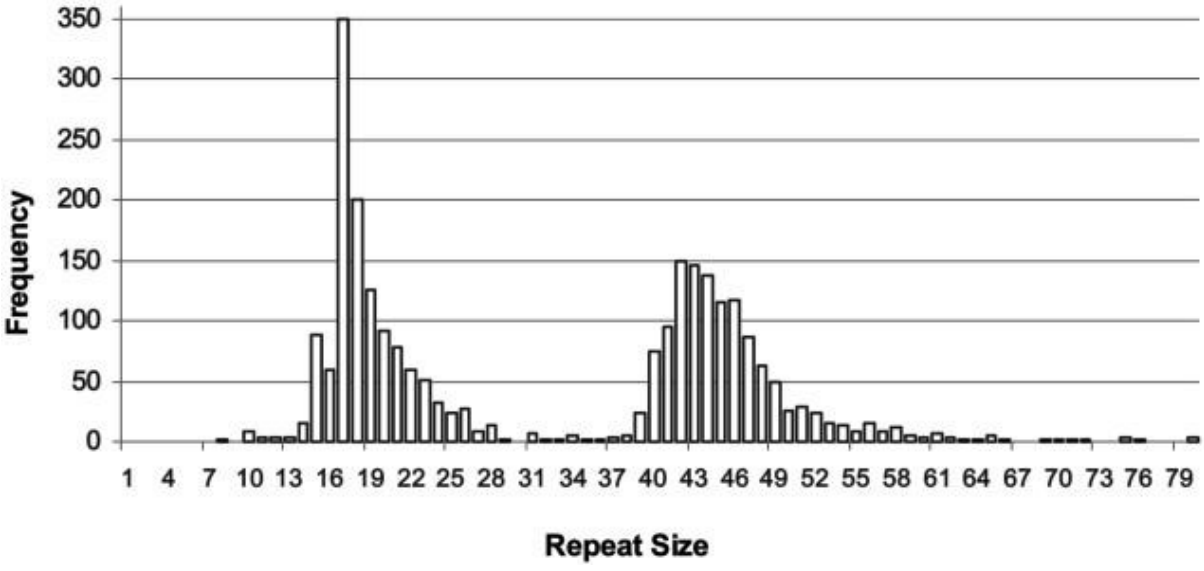



**Figure 1.1 The distribution of normal and expanded HD repeat sizes** (Myers et al., 2004, p.256).

At this site, normal alleles contain CAG repeat sizes between 9 and 35 (Snell et al., 1993). However, when this trinucleotide repeat length expands to 40 or more CAGs, the disease becomes fully penetrant (Rubinsztein et al., 1996). The HD and normal range have quite distinct peaks with the tails of both curves very close to each other and no gap between the normal and disease ranges (see Figure 1.1) (Myers, 2004).

CAG repeat lengths of 36-39 are not always associated with an HD phenotype, suggesting incomplete penetrance of the gene in this range. A repeat size of 35 CAGs or less has not been associated with manifest HD (Goldberg et al., 1995). However, an intermediate repeat size of between 27 and 35 has been shown to demonstrate instability on replication and expansion of the repeat length into the pathological range (Maat-Kievit et al., 2001). This instability could account for new onset cases of HD where there appears to be a negative family history. Expansion of the repeat length occurs much more frequently than contraction (73% versus 23%) and is also greater in spermatogenesis than oogenesis (Ranen et al., 1995). These findings can explain the known phenomenon of anticipation in HD, whereby the age of onset of the disease decreases with successive generations. Large expansions of the allele size (i.e. an expansion of more than 7 CAG repeats) happen almost exclusively in males and consequently paternal transmission accounts for the majority of cases of juvenile-onset disease (Ranen et al., 1995).

Identification of the *HD* gene has fuelled a wealth of research into the genotype-phenotype correlation in HD. Numerous studies have confirmed the existence of a significant inverse relationship between the number of CAG repeats and the age of onset of the disease (see

Figure 1.2) (Snell et al., 1993; Duyao et al., 1993; Andrew et al., 1993; Langbehn et al., 2010). This correlation is particularly strong for juvenile-onset cases, where individuals often have an allele size greater than 60 CAG repeats (Quarrell et al., 2013). It is important to recognise that although there is a clear inverse correlation (with the repeat length determining about 70% of the variance in age at onset), for each repeat number, there is a considerable range in the age at onset (Brinkman et al., 1997; Langbehn et al., 2010).

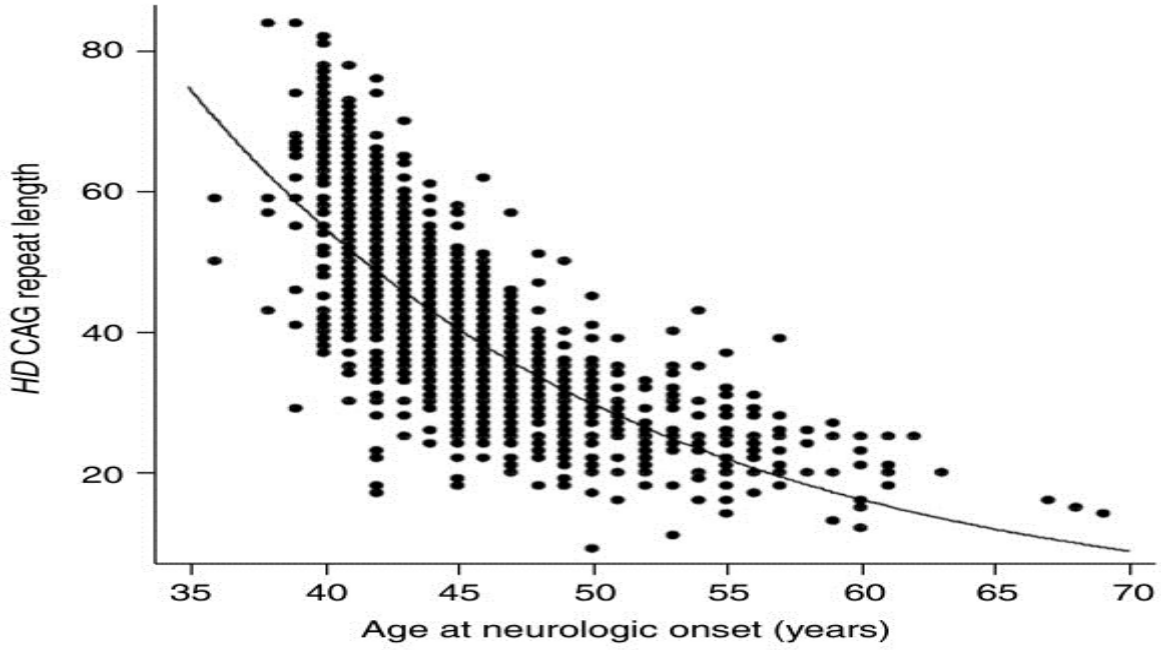



**Figure 1.2 Inverse correlation of age at neurologic onset and *HD* CAG repeat length for 1,200 HD subjects of known age at neurologic onset** (Gusella and McDonald, 2009, p. 80.2)

The CAG repeat length does not provide any indication as to the presenting symptom, the course or the duration of illness (Roos, 2010). However, a longer CAG repeat has been associated with faster weight loss (Aziz et al., 2008). Additionally, a positive correlation has been found between CAG repeat number and severity of brain pathology including degree of atrophy (Penney et al., 1997), loss of striatal dopamine 2 receptors (Antonini et al., 1998) and density of intranuclear inclusions (Becher et al., 1998).

## *1.4 Clinical description of HD*

HD is a progressive disorder characterised by motor, cognitive and psychiatric disturbances. Other prevalent but less well-known features of HD include autonomic nervous system dysfunction, sleep- and circadian rhythm disturbances and unintended weight loss (Roos, 2010). The mean age of onset is 35 to 44 years; however the disease may manifest itself from the age of 2 years up to the mid-80s (Huntington Disease Collaborative Research Group, 1993). Juvenile HD, whereby onset of symptoms is at or before the age of 20 years, accounts for approximately 5-10% of all HD cases (Quarrell, 2012). The duration of the illness also varies considerably but is typically about 15 to 20 years from motor onset to death with no difference between the sexes (Foroud et al., 1999). As the disease progresses, symptoms vary considerably and disability increases to the point where patients are no longer able to live independently. Common causes of death in HD patients are pneumonia, choking, heart disease, nutritional deficiencies and suicide (Lanska et al., 1988; Sørensen and Fenger, 1992). Although HD is caused by a single gene mutation, it gives rise to a wide array of phenotypic symptoms that vary from one individual to the next. Although it is the motor abnormalities that are most evident, it is the non-motor symptoms that are often most distressing to the patient and family (Craufurd and Snowden, 2014).

### 1.4.1. Motor abnormalities

Disturbances of both involuntary and voluntary motor functions occur in individuals with HD. Chorea, from the Greek word meaning ‘dance’, is the classical feature of the disease, hence the former name, Huntington’s chorea. The World Federation of Neurology defines chorea as, “a state of excessive, spontaneous movements, irregularly timed, randomly distributed

and abrupt. Severity may vary from restlessness with mild, intermittent exaggeration of gesture and expression, fidgeting movements of the hands and unstable dance-like gait to a continuous flow of disabling, violent movements" (Barbeau et al., 1981). Initially the choreatic movements are in the distal extremities such as the fingers and toes, spreading to all other muscles from distal to more proximal and axial (Roos, 2010). These movements cannot be suppressed voluntarily, are continuously present during waking hours and typically worsen with stress.

As the disease progresses, other abnormalities of movement appear gradually including bradykinesia, rigidity and dystonia (abnormal postures with increased muscle tone) and tend to dominate the latter stages of the disease (Kremer, 2002). Disturbances in voluntary motor function are early indicators of disease presence. Clumsiness is commonly reported by patients with motor speed, fine motor control and gait all affected. Oculomotor abnormalities are also frequent and manifest early in the disease and worsen with disease progression (Lasker and Zee, 1997). Specific difficulties include the initiation of saccadic movements, which are slower and unco-ordinated, an inability to suppress blinking or head movements and smooth pursuits are often interrupted by saccadic intrusions (Lasker and Zee, 1997).

Impairments of speech (dysarthria) typically occur early in the illness and swallowing difficulties (dysphagia) tend to present later in the course of disease and can significantly impact both intake of fluids and solids. As the motor disorder progresses, it interferes

increasingly with walking and standing as well as daily activities such as getting out of bed, showering, dressing and toileting.

### 1.4.2 Cognitive abnormalities

Cognitive decline is characteristic of HD but the rate of progression as well as the severity of these cognitive changes can vary considerably between individuals. Cognitive deficits have been demonstrated at least 15 years prior to a motor diagnosis of HD (Paulsen et al., 2006a; Paulsen et al., 2008; Stout et al., 2011) and are highly associated with disease-specific volume loss on MRI (Aylward et al., 2011).

The earliest cognitive deficits to be detected in pre-manifest individuals who are up to 15 years from their predicted motor onset are emotional recognition (Stout et al., 2011), deficits to the speed of cognitive and motor skills (Bechtel et al., 2010; Stout et al., 2011), difficulties with estimating time (Rowe et al., 2010; Tabrizi et al., 2011), and learning and memory problems (notably the implicit learning and memory system) (Montoya et al., 2006; Say et al., 2011). Cognitive abnormalities that can be detected in individuals with less than ten years to motor diagnosis include: smell identification (Stout et al., 2011; Tabrizi et al., 2011), attentional deficits (Nehl et al., 2001) and impairment of executive functions such as planning, the organisation of sequential events and mental flexibility (Duff et al., 2010; Stout et al., 2011). In contrast to cortical degenerative disorders such as Alzheimer's Disease, language skills, localisation skills, spatial orientation and semantic memory are generally well preserved in HD patients (Craufurd and Snowden, 2014).

### 1.4.3 Psychiatric symptoms

Psychiatric symptoms have been recognised as common features of Huntington's Disease since George Huntington's original description of the disease in 1872 when he wrote "The tendency to insanity, and sometimes that form of insanity which leads to suicide, is marked." Indeed, a wide range of psychopathology and behavioural abnormalities are seen in HD and include depression, anxiety, apathy, irritability, obsessive-compulsive disorders, aggression, sexual dysfunction and psychotic symptoms (Chatterjee et al., 2005).

Psychiatric disorders/symptoms are evident throughout the disease course with prevalence rates of between 33% and 76% being reported (van Duijn et al., 2007). Psychopathology may also present in the prodromal phase of HD (the phase prior to motor diagnosis) in many patients (Folstein et al., 1983; Duff et al., 2007; Julien et al., 2007). However, the psychiatric symptoms do not seem to follow the same progressive course as the motor and cognitive changes. Of all the commonly observed neuropsychiatric symptoms in HD, only apathy appears intrinsic to disease progression (Craufurd et al., 2001; Thompson et al., 2012).

Factor analyses of scales designed to assess the severity and frequency of behavioural problems in the HD population reveal similar factor structures. Craufurd et al (2001) and Kingma et al (2008) who both used the Problem Behaviours Assessment for Huntington's Disease (PBA-HD) found three factor solutions reflecting apathy, depression and irritability. Rickards et al (2011) using the Unified Huntington's Disease Rating Scale – Behaviour Section (UHDRS-BS) found four factors for depression, executive function, irritability/aggression and

psychosis. These results suggest that specific clusters of psychiatric symptoms exist in HD. The psychopathology of HD will be discussed in further detail in Chapter 2.

### *1.5 Neuropathology of HD*

It has been long recognised that the pathology of HD is distinctly brain specific (although, pathology is also seen in peripheral tissues, Björkvist et al., 2008) and primarily a disease of the basal ganglia. The basal ganglia are subcortical structures located beneath the anterior portion of the lateral ventricles in the forebrain and classically refers to the caudate-putamen (or striatum) and the globus pallidus (one of the striatum's main projection areas) (Vonsattel et al., 2011). Other structures considered an integral part of the basal ganglia core are the subthalamic nucleus and the substantia nigra.

Although post-mortem studies indicate that the pattern of pathological change in the brains of HD patients can vary, overall, the neuropathologic hallmark of HD is atrophy of the caudate nucleus, putamen and external segment of the globus pallidus (Vonsattel et al., 2011). Additionally, there is atrophy of the cerebral cortex, subcortical white matter, thalamus, specific hypothalamic nuceli and other brain regions (Ross and Tabrizi, 2011). Neuroimaging techniques have demonstrated structural brain changes in individuals who are over 15 years from predicted age of motor onset (Tabrizi et al., 2009). The earliest changes appear to be reductions in caudate and putamen volumes, however, progressive abnormailities in both grey and white matter, involving both cortical and subcortical regions have been evidenced (Tabrizi et al., 2009). By the later stages of the disease, the weight of the brain is often reduced by as much as 25-30% (see Figure 1.3) (Vonsattel et al., 1985).

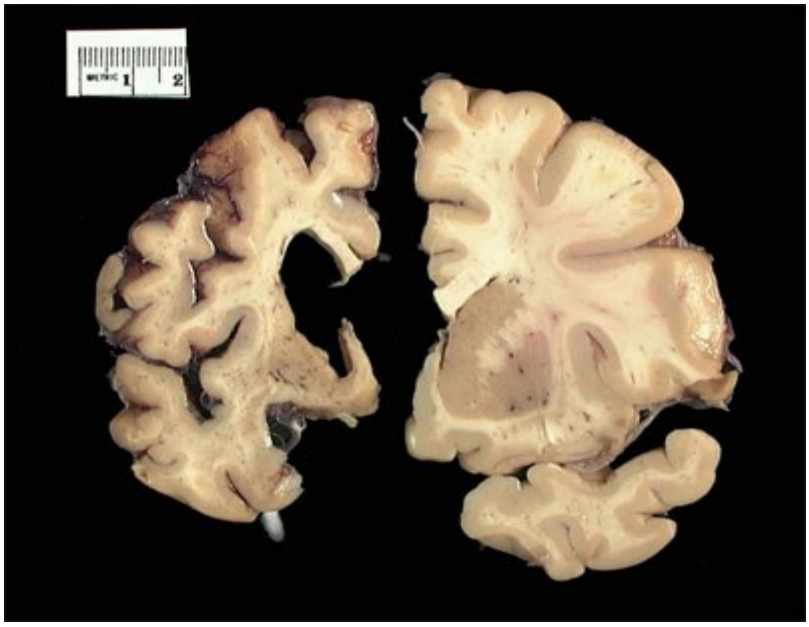


**Figure 1.3 Macroscopic image in which a slice of Huntington's brain (left) is put next to a slice from a normal control (right).** Harvard Brain Tissue Resource Center (2014)

The preferential loss of up to 95% of the GABAergic medium-spiny projection neurons of the indirect pathway concerned with motor control in the basal ganglia results in a reduced basal ganglia inhibitory output to the thalamus (Ross and Tabrizi, 2011). This in turn causes overactivation of thalamocortical projection systems, which manifests itself as chorea (Hedreen and Folstein, 1995).

Aside from the basal ganglia's involvement in motor function (namely skeletomotor and oculomotor), they are also involved in three other cortical-thalamic circuits that are concerned with non-motor aspects of behaviour (Cummings, 1993). These include the dorsolateral pre-frontal circuit, the lateral orbitofrontal circuit and the anterior cingulate circuit. The dorsolateral pre-frontal circuit appears to be involved in executive functions and damage to this circuit produces various behavioural abnormalities related to these cognitive

functions such as planning, organising and problem solving (Bonelli and Cummings, 2007). The lateral orbitofrontal circuit has been implicated in mediating empathetic and socially appropriate responses (Bonelli and Cummings, 2007). Damage to this circuit is associated with irritability, lack of empathy, emotional lability and is also thought to be involved in the neuropsychiatric disturbance, obsessive-compulsive disorder. The anterior cingulate circuit is believed to be involved in motivated behaviour and damage to this circuit may result in akinetic mutism, a significant impairment of movement initiation (Bonelli and Cummings, 2007).

The pathogenic mechanism(s) whereby mutant huntingtin induces neuronal dysfunction and death has yet to be satisfactorily elucidated. However, with the creation of accurate transgenic models of HD has come much greater understanding of the pathogenic process at molecular and cellular levels. Some of the most consistently described mechanisms that have been implicated in mediating HD pathogenesis include: abnormal protein aggregation and degradation (Davies et al., 1997; Young, 2003; Ravikumar et al., 2004); proteolytic cleavage (Goldberg et al., 1996; Wellington et al., 2002) transcriptional dysregulation (Li et al., 2002; Sugars and Rubenzstein, 2003); synaptic dysfunction (van Dellen and Hannan, 2004); excitotoxicity (Tabrizi et al., 1999; Li et al., 2003); neurotrophins (Zuccato and Cattaneo, 1997; Ferrer et al., 2000); cytoskeletal defects and axonal transport (Gunawardena and Goldstein, 2005); microglia activation (Sapp et al., 2001); apoptosis (Portera-Cailliau et al., 1995) and, mitochondrial abnormalities and impaired energy metabolism (Beal et al., 1993; Turner and Schapira, 2010). As the pathogenic pathways of HD are increasingly understood, some of these mechanisms may provide suitable targets for treatments.

### *1.6 Management of HD*

Currently, there is no preventive or curative treatment for HD. Due to the very nature of HD, as a progressive disorder of long duration, the management of the disease to maximise patients' quality of life and functional capabilities is of upmost importance. The great variation in clinical presentation between individuals also necessitates management and care that is specific to each patient's personal needs. A multi-disciplinary approach using non-pharmacologic as well as pharmacologic treatments is particularly beneficial to HD families due to the wide range of presenting symptoms and social problems.

Specialist input is required from neurologists, psychiatrists, neuropsychologists, genetic counsellors, occupational therapists, speech therapists, dieticians, physiotherapists, social services and HD support teams. It is important that symptoms are treated as and when they arise, whilst weighing up the many side effects associated with available pharmacologic treatments, for which there is little evidence available about which drug or dosage to prescribe. In order to address this, three recent international surveys of clinicians regarded as experts in the treatment of HD have led to the publication of algorithms to help inform clinical decision-making in the pharamacologic treatment of chorea (Burgunder et al., 2011), irritability (Groves et al., 2011) and obsessive –compulsive behaviours (Anderson et al., 2011). An example of the algorithm for the pharmacologic treatment of irritability in HD is outlined in figure 1.4.

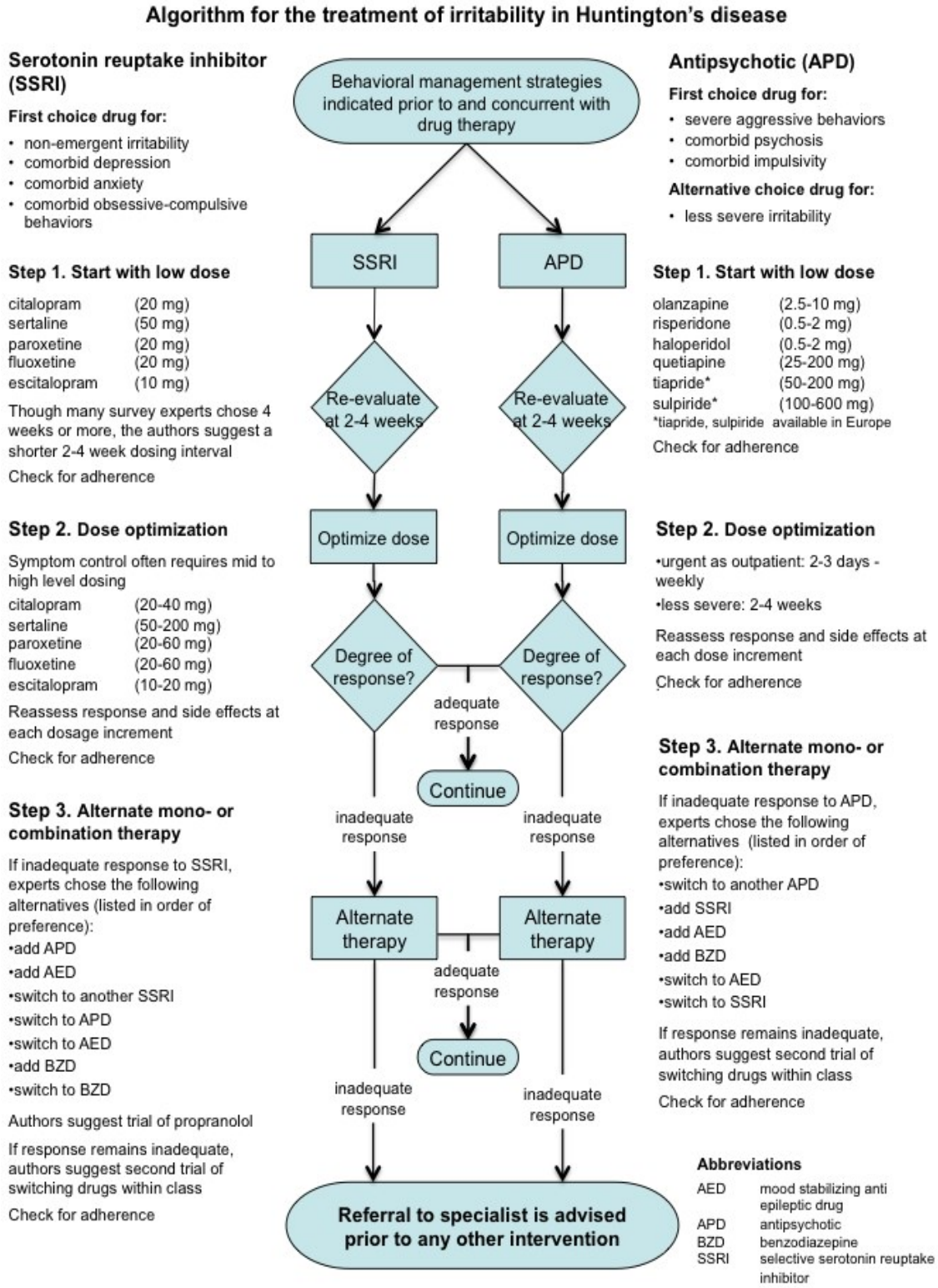



**Figure 1.4** Algorithm for the treatment of irritability in Huntington's disease (Groves et al., 2011).

Whereas chorea and psychiatric disturbances can be relatively well addressed by pharmacologic intervention, there are currently no medications available to either reduce or halt the progression of dementia in HD. However, attention must also focus on the general health of the patients, including diet and nutrition and sleep. Marked weight loss is commonly observed in HD, even when the calorie intake is adequate (Trejo et al., 2004; Robbins et al., 2006). Given that a higher premorbid body mass index has been associated with slower progression of disease (Myers et al., 1991), it is particularly important that dysphagia and appropriate changes in food texture as well as nutritional requirements receive continued attention. Sleep disturbances in HD are common and have been associated with reduced quality of life and depression as well as lower cognitive and functional performance (Aziz et al., 2010). Although there have been no efficacy studies of pharmaceuticals used to treat sleep deficits (Morton, 2013), hypnotics are considered useful at treating insomnia as well as subclinical cases of sleep disturbance (Morton et al., 2005).

The high diagnostic precision in HD, the ability to track individuals in the prodrome to detect the earliest biological changes in HD, the development of transgenic mouse models and an increasing understanding of the pathogenic mechanisms involved, provides a great opportunity for developing therapeutic interventions. Many of the possible lines of treatment that are in development are aimed at interfering with the pathological process with the hope of slowing down, delaying or even preventing the onset of HD (Roos, 2010). Some examples include: gene silencing drugs that prevent cells from making the huntingtin protein e.g. anti-sense oligonucleotides (ASOs) (Southwell et al., 2014) and RNA interference (RNAi)(Yu et al., 2012); interventions to increase the amount of neurotrophic support

(Gharami et al., 2008); compounds that enhance mitochondrial function such as coenzyme $Q_{10}$ and creatine (Galpern and Cudkowicz, 2007; Rosas et al., 2014); and, agents that promote autophagy and lysosomal clearance e.g. rapamycin (Renna et al., 2010).

Research and clinical emphases are often biased towards the motor and cognitive changes in HD. However, psychiatric symptoms deserve increased attention, owing to the fact that in HD, behavioural abnormalities have been associated with functional decline (Marder et al., 2000; Hamilton et al., 2003) and reduced quality of life (Ho et al., 2009). Moreover, they place the greatest burden on families (Paulsen, 2011) and can be predicitive of institutionalisation (Wheelock et al., 2003). The psychiatric phenotype in HD will be the focus of this thesis and an overview of the psychopathology of HD will be discussed in the following chapter (Chapter 2).

# CHAPTER 2: THE PSYCHOPATHOLOGY OF HUNTINGTON'S DISEASE

This chapter will provide an overview of existing research on the psychopathology of Huntington's disease (HD). For both formal psychiatric disorders (mood disorders, anxiety disorders, obsessive-compulsive disorder, alcohol abuse and psychotic disorders) and frequently observed neuropsychiatric symptoms in HD (irritability, aggression and apathy), the reported prevalence rates and their relationship to the disease course of HD will be discussed. Finally, the possible aetiology of the psychiatric disorders/symptoms will be reviewed.

## *2.1 Introduction*

In addition to the motor and cognitive deterioration observed in individuals with HD, neuropsychiatric symptoms comprise a significant component of the HD phenotype. Estimated prevalence rates of psychiatric disorders and symptoms in HD vary greatly, largely due to methodological differences including the assessment measures used, where the study sample was ascertained from and varying definitions of the neuropsychiatric phenomena. However, prevalence rates are undoubtedly high with one study finding that 98% of a sample of 52 individuals with HD reported experiencing at least one neuropsychiatric symptom in the last month (Paulsen et al., 2001). A literature review of the psychopathology in verified Huntington's disease gene carriers found that the most frequently reported neuropsychiatric symptoms were depressed mood, anxiety, irritability and apathy (each with prevalence rates of between 33% and 76%), followed by obsessive and compulsive symptoms (reported prevalence rates of 10% to 52%) and that psychotic

symptoms occurred least frequently (prevalence rates of between 3% and 11%) (van Duijn et al., 2007).

The neuropsychiatric symptoms of HD often cause considerably more distress to both the patients and their caregivers than the motor and cognitive aspects of the disease (Craufurd and Snowden, 2014). Such behavioural symptoms are also more likely to impact on daily functioning (Hamilton et al., 2003) and result in nursing home placement (Wheelock et al., 2003). Additionally, evidence suggests that psychopathology may predate motor symptom onset in many individuals with HD (Folstein et al., 1983; Di Maio et al., 1993; Duff et al., 2007). Together, these findings suggest that further understanding of the psychopathology of HD is warranted.

### *2.2 Depression in Huntington's Disease*

Neurological diseases have long been associated with higher than expected rates of depression (Rickards, 2005) and HD is no exception. Indeed, George Huntington noted the high prevalence of depression in HD in his seminal 19$^{th}$ Century paper on the disease (Huntington, 1872). Depression has been associated with reduced cognitive performance in HD gene carriers (Nehl et al., 2001; Smith et al., 2012), functional decline (Hamilton et al., 2003) and has been rated by HD patients as having the greatest impact on perceived quality of life (Ho et al., 2009). Depression has been described in HD both in terms of a formal psychiatric disorder and as the symptom "depressed mood" and consequently the prevalence rates reported vary greatly.

### 2.2.1 Prevalence of depression in HD

Lifetime Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2000) prevalence rates for depressive disorders in the motor manifest HD population have been reported at around 30% to 40% (Folstein et al., 1983,1987; Leroi et al., 2002; Rosenblatt, 2007). In a study of 89 pre-motor manifest individuals, 20% of the sample had a lifetime DSM-III diagnosis of major depression (Julien et al., 2007). Other studies using DSM criteria have looked at point or period prevalence rates only, which are likely to underestimate the lifetime prevalence of depression in HD. Van Duijn and colleagues (2008) found 12-month prevalence rates of DSM-IV depressive disorders of 17.9% in a sample of 140 mutation carriers. Caine and Shoulson (1983) used DSM-III classification to determine point-prevalence of depression or dysthymia and reported 5 (20.8%) and 6 (25%) affected individuals respectively out of 24.

Studies using scales that assess the symptom of depressed mood have found high prevalence rates. Studies using the behavioural section of the Unified Huntington's Disease Rating Scale (UHDRS-b; Huntington Study Group, 1996) and the Problem Behaviour Assessment Scale for Huntington's Disease (PBA-HD; Craufurd et al., 2001), which rate the frequency and severity of the symptom in question over the previous month have reported prevalence rates of 33% (Craufurd et al., 2001) and 40.5% (Paulsen et al., 2005a). Studies using the Neuropsychiatric Inventory (NPI) have reported prevelance rates of dysphoria of 41% (Kulisevsky et al., 2001) and 69% (Paulsen et al., 2001). However, these studies could be underestimating the lifetime prevalence of depressive symptoms given that they only report its presence or absence over the previous month. Indeed, a study that assessed the

prevalence of neuropsychiatric symptoms in HD at baseline and longitudinally clearly demonstrated that the prevalence of symptoms was considerably higher when the longitudinal assessments were taken into account (Thompson et al., 2012). For example, at baseline, the percentage of HD patients endorsing the symptom of depressed mood was 33% but this figure rose to 60% over the follow-up period, which was on average 5.2 years (based on a mean of 5 assessments with a mean inter-assessment duration of 1.3 years) (Thompson et al., 2012).

### 2.2.2 Age at onset of depression in HD

There has been little research into the age at onset of depression in HD, although it has been recognised for many years that onset of depression may precede motor symptom onset by up to 20 years (Folstein et al., 1983). A retrospective study by Folstein and colleagues found that for 23 HD patients for whom accurate onset data was available, depressive symptoms preceded motor onset by an average of 5.1 years (Folstein et al., 1983). Leroi et al. 2002 reported an average age at onset of first psychiatric symptom of 42.3 years in their HD sample (N=21), which was significantly higher than the average age at first psychiatric symptom onset reported by the neurologically healthy comparison participants (33.8 years). A significant negative correlation has also been reported between the age of onset of psychiatric disorders and the length of the CAG repeat in HD (Vassos et al., 2008). This finding suggests that the age of onset of psychiatric disorders is related to the age at clinical diagnosis of HD given that the CAG repeat length is also strongly associated with the age at onset of diagnostic motor symptoms (Lee et al., 2012). The development of the presymptomatic genetic test for HD in 1993 has enabled the study of individuals during the

illness prodrome (the period before manifestation of motor symptoms). Results from such studies strongly suggest that behavioural problems including depression are among the first disease symptoms in HD (Julien et al., 2007; Kingma et al., 2008; van Duijn et al., 2008; Epping and Paulsen, 2011).

### 2.2.3 Depression and the HD disease process

Depressive symptoms do not have a clear relationship with the progression of HD (Thompson et al., 2002; Kingma et al., 2008; Thompson et al., 2012). Evidence to date suggests they are most common in the mild-moderate stages of the illness (Paulsen et al., 2005a, Thompson et al., 2012) with a study using a sample of 2835 individuals finding that depressive symptoms were most frequently reported in stage 2 of the disease (see Section 3.4.4.2.3)(Paulsen et al., 2005a). It is also thought that the prevalence of depressive symptoms may then decline during the latter stages of the disease (Paulsen et al., 2005a; Thompson et al., 2012). This finding could be due to impaired insight, which means patients are less aware of their disability (Paulsen et al., 2005a), blunted affect, which increases with disease progression (Thompson et al., 2012) and/or better adaptation over time to their illness and prognosis. Alternatively (or additionally), patients in the latter stages of the disease are less likely to be assessed for depression and included in studies due to cognitive and communicative deficits making it more difficult for self-report of such depressive symptoms (Craufurd et al., 2001; Paulsen et al., 2005a).

It has also been reported that prevalence rates of depression in the illness prodrome may differ based on proximity to motor onset of HD (Julien et al., 2007). After an initial

psychiatric assessment where both interviewers and participants were blinded to genetic status, 51 gene carriers (for whom HD motor onset dates were subsequently available) were followed up for a number of years. The results showed that prevalence rates for current DSM-III affective disorder were significantly higher in those individuals who were closer to motor onset at the time of the psychiatric interview (Julien et al., 2007). Together, this evidence suggests that critical periods for depression in HD are close to the onset of motor symptoms and in the mild-moderate stage of the disease.

### 2.2.4 Suicide in HD

Individuals with HD have a marked increased risk for suicide or attempted suicide (Paulsen et al., 2005b). Reported prevalence rates of completed suicide among HD patients range from 4% (Schoenfeld et al., 1984) to 13% (Cummings, 1995), which are much higher than the completed suicide rate of 1.16% observed in the UK general population (Office for National Statistics, 2012). Additionally, one study reported that 27.6% of HD affected individuals had attempted suicide at least once previously (Farrer, 1986). In a study of 1941 motor manifest individuals, 26.5% had a history of suicidal ideation (current suicidality rate was 19%) and 9.5% of the sample had a history of at least one suicide attempt (Wetzel et al., 2011).

Studies have demonstrated an increased incidence of suicide and heightened suicide risk shortly prior to receiving a clinical diagnosis of HD (Schoenfeld et al., 1984; Paulsen et al., 2005b) and in Stage 2 of the disease (see Section 3.4.4.2.3) when functional loss is apparent such as termination of employment and driving (Lam et al., 1988; Paulsen et al., 2005). Other risk factors that have been associated with increased rates of suicidal ideation and suicide in

HD include: male gender (Schoenfeld et al., 1984; Di Maio et al.,1993), having no offspring (Lipe et al., 1993), being unemployed (Almqvist et al., 1999), the presence of a depressed mood (Wetzel et al., 2011; Hubers et al., 2012, 2013), taking anti-depressants (Hubers et al., 2012) and the presence of other neuropsychiatric symptoms such as anxiety, aggression and alcohol abuse (Wetzel et al., 2012; Hubers et al., 2013).

Like in other populations (Epping and Paulsen, 2011), the most consistent predictor for suicidality in HD is depressed mood (Hubers et al., 2012, 2013). Therefore, given the high prevalence of depression in HD (see section 2.2.1), it is perhaps not surprising that suicidality in HD is also high. Although published studies suggest that individuals with HD are more likely to commit suicide than the general population, this is in keeping with the well-established association between suicidality and general medical illness (Harris and Barraclough, 1997; Druss and Pincuss, 2000). However, the presence of the neuropsychiatric symptoms impulsivity and emotional lability, which are commonly observed in HD, may increase an individual's risk for suicide by reducing their ability to inhibit emotionally-driven behaviour (Wetzel et al., 2011).

### *2.3 Bipolar Disorder*

The prevalence of bipolar disorder in HD is controversial. Older reports suggest that hypomania and/or bipolar disorder is more prevalent in the HD population than expected by chance, with estimated prevalence rates of 5% to 10% (Heathfield, 1967; Folstein et al, 1987). However, although many individuals with HD experience manic symptoms such as prolonged periods of irritable mood, emotional lability and disinhibition, elevated mood and

other core symptoms of mania are rarely observed suggesting that operationally defined episodes of mania/hypomania are uncommon in the HD population (Julien et al., 2007; Rosenblatt, 2007; Craufurd and Snowden, 2014). Previous authors may have been describing symptoms that are more likely the result of the organic brain changes and cognitive impairment associated with HD than mania (Craufurd and Snowden, 2014). More recent research using DSM criteria have reported bipolar disorder prevalence rates of 2.1% (van Duijn et al., 2008), 4.8% (Leroi et al., 2002) and in a sample of 89 pre-motor symptomatic HD patients, no individuals had sufficient manic symptoms that fulfilled DSM-III diagnostic criteria for bipolar disorder (Julien et al, 2007).

### *2.4 Anxiety Disorders*

Anxiety in HD is thought to often be concerned with worries about the disease itself (Planz et al., 1991), which has maybe led to anxiety disorders in HD being dismissed as an understandable reaction to having a terminal, degenerative illness. Indeed, there is little literature on anxiety disorders in HD even though estimated prevalence rates of anxiety symptoms and "worrying" have been reported between 34% (Kulisevsky et al., 2001) and 61% (Murgod et al., 2001).

A study which determined 12-month prevalence rates of DSM-IV psychiatric disorders found a prevalence rate for all anxiety disorders of 14.5% in the presymptomatic mutation carriers and 16.5% in the symptomatic mutation carriers (van Duijn et al., 2008). The most common of the anxiety disorders reported for all the gene carriers was social phobia (5.7%) then generalised anxiety disorder (5.0%), panic disorder (4.3%) and obsessive compulsive disorder

(4.3%) (van Duijn et al., 2008). A further study investigating lifetime prevalence of DSM-III psychiatric disorders in pre-symptomatic gene carriers who were unaware of their genetic status found a lifetime prevalence of 17% for any anxiety disorder, with the most common diagnoses being generalised anxiety disorder (11%), agoraphobia (9%), panic disorder (8%) and simple phobia (8%) (Julien et al., 2007). A lifetime prevalence of 23.8% for any anxiety disorder (including generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, phobia and posttraumatic stress disorder) has been reported in a sample of 21 early to mid-stage Huntington's patients (Leroi et al., 2002).

### 2.4.1 Obsessive Compulsive Disorder, Obsessive Compulsive Symptoms and Perseverative thinking/behaviours

The prevalence of obsessive-compulsive disorder (OCD) in HD, like mania, is a contentious issue. Individuals with HD commonly experience cognitive inflexibility, which can manifest as repetitive thoughts and behaviours where individuals are unable to shift to a different topic of conversation or action (Craufurd and Snowden, 2014). However, unlike obsessive and compulsive symptoms, these perseverative thoughts and/or behaviours do not typically cause any distress to the patient, are not perceived as abnormal and the individual does not try to resist them. Nevertheless, some studies have reported that obsessive and compulsive symptoms (O/Cs) are commonly observed in HD. For example, Anderson et al. (2010) reported in their sample of 1642 individuals with a clinical diagnosis of HD that 27.2% endorsed current O/Cs on the UHDRS-b. Also using the UHDRS-b, Marder and colleagues (2000) found that 22.3% of HD patients reported O/Cs at their first clinic visit and a further study in a smaller sample of 27 HD patients found that 14 (52%) of the individuals endorsed at least one obsessive symptom on the Yale-Brown Obsessive Compulsive Scale

(YBOCS)(Anderson et al., 2001). However, the UHDRS-b measures perseverative thinking and obsessional thinking as the same item and in the study using the YBOCS, only the checklist part of the scale was used, which does not assess severity. Therefore, it is difficult to interpret exactly what phenomena these studies are measuring.

Prevalence rates of OCD according to DSM criteria in HD patients appear less common than the reported rates of O/Cs. A lifetime prevalence of 5% for OCD according to DSM-III criteria was found in a sample of 89 presymptomatic mutation carriers (Julien et al., 2007). Van Duijn and colleagues (2008) found an increased 12 month prevalence of OCD in HD mutation carriers relative to the general population (4.3% versus 0.5%). Case reports have also detailed HD patients with OCD (Cummings and Cunningham, 1992; Molano-Eslava et al., 2008), including a 72-year old man with late-onset HD and OCD (Scicutella et al., 2000).

Although O/Cs may predate motor onset (Duff et al., 2010), age at onset of OCD according to DSM is thought to be later in HD patients (Cummings and Cunningham, 1992; Scicutella, 2000) than in non-HD individuals with OCD (Kessler et al., 2005).

### *2.5 Alcohol Abuse*

Alcohol has well-known short term effects on cognition and behaviour including: impaired memory and concentration, slowed reaction times, difficulties with balance, slurred speech and a decrease in inhibition. In symptomatic HD individuals, alcohol can exacerbate these already present difficulties (Mattoo and Khurana, 1999) and possibly accounts for the finding that consumption of alcohol decreases after the motor onset of HD (Di Maio et al., 1993). A

small study of 42 HD patients in Baltimore, USA found a DSM-III prevalence rate for current or past alcohol abuse of 16.7% (24% for males and 5.9% for females) (King, 1985). This rate was comparable to that of the local Baltimore community (King, 1985). Another study using DSM-III criteria found a lifetime prevalence rate for alcohol dependence of 3% (Julien et al., 2007). A more recent study of 136 individuals with motor symptomatic HD used DSM-IV criteria to determine a lifetime alcohol abuse prevalence rate of 30.9% (43% for males and 19% for females) (Byars et al., 2012).

One study found the average age at onset of alcohol abuse in HD to be 16.9 years (standard deviation 4.6) (Byars et al., 2012) and alcohol abuse has been associated with an earlier age at HD onset (Ehret et al., 2007; Byars et al., 2012), notably in women (Byars et al., 2012). Alcohol abuse in Huntington's disease has been linked to increased rates of criminal convictions (Jensen et al., 1998) as well as more psychiatric symptoms (Ehret et al., 2007) and more severe suicidal ideation (Wetzel et al., 2013).

### *2.6 Psychotic disorders*

Early reports suggested that schizophrenia was a predominant feature of the psychiatric presentation of Huntington's disease. In a sample of 80 patients with HD, Dewhurst and colleagues (1967) reported that six of the individuals had paranoid schizophrenia and three had a diagnosis of schizophrenia simplex. Assessment of the clinical features of a sample of 334 HD patients living in the West of Scotland revealed that paranoid ideas, often poorly systematised, were found in 109 of the patients (32.6%), visual or auditory hallucinations were found in 12 individuals (3.6%), grandiose ideas in 11 (3.3%) and religiosity in 4

individuals (1.2%) (Bolt, 1970). However, well-defined delusional and schizophrenia-like disorders are less common than these older research reports would suggest. More accurate and earlier diagnoses of HD as well as a shift in the focus of research from in-patient to out-patient populations likely account for these changes in prevalence rates (van Duijn et al., 2007).

Recent research using DSM criteria found a lifetime prevalence of 1% for schizophrenia (Julien et al., 2007) and a 12-month prevalence rate of 1.4% for non-affective psychosis (van Duijn et al., 2007) in individuals gene positive for HD. However, the prevalence of schizophrenia-like symptoms (delusions and hallucinations) in HD may be higher and studies using dimensional rating scales such as the NPI and PBA-HD have found cross-sectional prevalence rates of between 3% (Craufurd et al., 2001) and 11% (Paulsen et al., 2001).

### *2.7 Irritability and Aggression*

Irritability, in the context of psychopathology, is defined as a mood state characterised by a reduction in control over temper, which may result in verbal or behavioural outbursts (Snaith and Taylor, 1985). In individuals with HD, irritability often presents as poor temper control, verbal outbursts and behavioural inflexibility (Thompson et al., 2012). It is a common neuropsychiatric symptom in HD and can be the cause of great distress to the HD patients and their families and may determine admittance to a nursing home (Wheelock, 2003). Various instruments have been used to assess the current prevalence of irritability in HD such as the PBA-HD (Craufurd et al., 2001; Kingma et al., 2008; Thompson et al., 2012), the UHDRS-b (Murgod et al., 2001); the NPI (Paulsen et al., 2001; Kulisevsky et al., 2010) and

the Irritability Scale (IS) (Chaterjee et al., 2005; Klöppel et al., 2010; Reedeker et al., 2012). The reported prevalence rates from these studies have ranged from 35% (Reedeker et al., 2012) to 73% (Murgod et al., 2001).

Increased levels of irritability have been found in pre-motor symptomatic gene carriers (Kirkwood et al., 2002) who were unaware of their genetic status and were up to 10 years from their estimated motor onset (Julien et al., 2007). The use of psychiatric medication may hide the true prevalence of irritability throughout the disease course but there is evidence that it may increase through the early stages of the illness, peaking (or reaching a plateau) by Stage 3 (see Section 3.4.4.2.3) and then decreasing again (perhaps when apathy and abulia become more apparent) (Craufurd et al., 2001; Thompson et al., 2012).

Alternatively, given that irritability/aggression may result in an individual no longer being able to be cared for in the community (Wheelock et al., 2003), it is possible that the previous studies using out-patient populations have under-reported the prevalence of irritability/aggression in the later stages of the disease. A study of 27 HD patients in a nursing home reported a significant relationship between aggression and functional impairment (Shiwach and Patel, 1993). One third of the sample was reported to be at least mildly aggressive during the 3-day observation period (Shiwach and Patel, 1993).

### *2.8 Apathy*

Apathy in HD, although difficult to conceptualise and therefore define, is often thought of as a disorder of motivation characterised by diminished goal-oriented behaviour, cognition and emotion (Starkstein and Leentjens, 2008). Apathy can of course be a symptom of a mood disorder but often manifests as a syndrome distinct from depression (Levy et al., 1998; Naarding et al., 2009). A factor analysis of the PBA-HD revealed an "apathy" factor consisting of the following seven symptoms: reduced energy and activity, self-neglect, blunting of affect, loss of initiative, lack of perseverance, impaired work performance, and poor judgment (Craufurd et al., 2001).

Apathy is one of the most frequently observed neuropsychiatric features of HD with most patients succumbing to some degree of apathy by the latter stages of the illness (Thompson et al., 2012). Estimated prevalence rates from cross-sectional studies have varied from 34% (Kulisevsky et al., 2001) to 76% (Craufurd et al., 2001), with a longitudinal study showing that 99% of a sample of 111 individuals with a genetic and clinical diagnosis of HD endorsed symptoms of reduced activity/energy at some point during the follow-up period (Thompson et al., 2012). Independent correlates of apathy (after the exclusion of HD mutation carriers with depression) have been found to be male sex, worse total functioning, higher use of neuroleptics and higher use of benzodiazapines (van Duijn et al., 2010). Apathy appears to correlate with duration of illness as well as motor, cognitive and functional measures of disease severity (Craufurd et al., 2001; Thompson et al., 2002; Reedeker et al., 2011; Thompson et al., 2012).

## *2.9 Aetiology of psychiatric disorders/symptoms in HD*

The aetiology of psychiatric disorders/symptoms in HD is most likely complex and multifactorial. As summarised in Table 2.1, although there are great differences in the reported prevalence rates of psychiatric disorders/symptoms in HD, in general, these prevalence rates are higher than those observed in the general population (van Duijn et al., 2007). Reasons for this overrepresentation in HD are unknown, however, a number of possibilities have been proposed, including: pleiotropic effects of the HD gene (*HTT gene)*, genetic linkage disequlibrium, overlapping biological pathways, organic brain changes as a result of HD and psychosocial effects.

### 2.9.1 The *HTT gene*

The *HTT* gene may itself increase the risk of individuals developing psychiatric symptoms through pleiotropic effects in the brain. The *HTT* gene codes for the protein *huntingtin* and although the exact function of this protein is unknown, it plays an important role in nerve cells and is thought to be involved in cell signalling, transporting materials, binding to proteins and other structures and protecting cells from apoptosis. Given the likely multiple roles of the huntingtin protein, it is possible that the HD mutation has wide-ranging effects (particularly in the brain where it is mainly expressed) and may predispose individuals to the development of psychiatric symptoms. However, studies to date have found no correlation between the length of the CAG repeat and the presence or severity of psychiatric symptoms (Zappacosta et al., 1996; Weigell-Weber et al., 1996; Berrios et al., 2001; Vassos et al., 2008).

**Table 2.1 Summary of the estimated prevalence rates of the most common psychiatric syndromes/symptoms in HD compared to the general population**

| Syndrome/Symptom | Lifetime DSM prevalence rates in the HD population (%)* | Current prevalence rates in the HD population using standardised instruments (%)* | General population lifetime prevalence rates (%) (NCS-R) |
|---|---|---|---|
| Major depression | 20[a]-32[b] | 33[c]-69[d] | 16.9 |
| Completed suicide | 4[e]-13[f] | N/A | 0.012** |
| Suicidal ideation | 26.5[g] | 19[g] | 13.7† |
| Bipolar Disorder | 0[a]-9[b] | N/A | 4.4 |
| Irritability/Aggression | N/A | 35[h]-73[i] | N/A |
| Anxiety Disorders | 17[a]-23.8[j] | 34[k]-61[i] | 31.2 |
| Obsessive Compulsive Disorder | 5[a] | 5[c]-52[l] | 2.3 |
| Alcohol Abuse | 3[a]-30.9[m] | N/A | 13.2 |
| Psychotic disorders | 1[a]-11.3[n] | 3[c]-11[d] | N/A |
| Apathy | N/A | 34[j]-76[c] | N/A |

[a]Julien et al., 2007; [b]Folstein et al., 1983; [c]Craufurd et al., 2001; [d]Paulsen et al., 2001; [e]Schoenfeld et al., 1884; [f]Cummings, 1995; [g]Wetzel et al., 2011; [h]Reedeker et al., 2012; [i]Murgod et al., 2001; [j]Leroi et al., 2002; [k]Kulisevsky et al., 2001; [l]Anderson et al., 2001; [m]Byars et al., 2012; [n]Dewhurst et al., 1967.

**NCS-R**; National Comorbidity Survey-Replication (updated data as of July 19, 2007) (Kessler *et al.,* 2005).

*The range is stated where applicable, otherwise, single prevalence rates are reported.

** Completed suicide data taken from the Office of National Statistics, UK, 2012

†Suicidal ideation data taken from the APMS; The Adult Psychiatric Morbidity Survey, 2007

### 2.9.2 Linkage disequilibrium

An alternative hypothesis is that a gene predisposing for psychiatric disorders/symptoms is in linkage disequilibrium with the HD gene and therefore inherited together during meiosis. As yet, there are no known genes that are thought to increase the risk for psychiatric disorders/symptoms in close proximity to the *HTT gene* on chromosome 4p16.3 (Lohoff et al., 2010).

### 2.9.3 Overlapping biological pathways

Dysfunction of specific molecular and cellular mechanisms that have been evidenced in HD pathogenesis and in individuals with psychiatric disorders/symptoms without HD may provide common biological pathways to explain the high prevalence of psychiatric disorders/symptoms in HD. For example, possible overlapping pathways associated with major depression include; dysregulation of the serotonin (5-HT) signalling system; hyperactivity of the hypothalamic pituitary adrenal (HPA) axis; reduced expression of brain derived neurotrophic factor (BDNF), and activation of the immune system (Du et al., 2013). Alterations in the dopamine system have been implicated in cognitive inflexibility, which has been associated with irritability and perseverative thinking/behaviour (Chen et al., 2013). A role for the serotonergic system in irritability and aggression has also been suggested given that selective serotonin reuptake inhibitors may be useful for treating irritability in HD (Ranen et al., 1996).

### 2.9.4 Organic brain changes

The high prevalence of psychiatric disorders/symptoms may be secondary to the organic brain changes that occur as a result of the HD gene.

#### 2.9.4.1 Depression

HD is associated with gross atrophy of the caudate nucleus (see Chapter 1.5) and major depression has been correlated with a decrease in caudate nucleus volume (Krishnan et al., 1992). Cummings (1995) postulated that neuronal loss in the ventral striatum as seen in individuals with HD may reduce the effectiveness of reward-mediated pathways thus increasing vulnerability to anhedonia and depression. However, even in the pre-motor manifest HD population, atrophy is not confined to the striatum (Tabrizi et al., 2009) and other important structural changes that occur in the brain as a result of HD are worth consideration as possibly aetiologically relevant in the psychopathology associated with HD.

Dysfunction of the frontal-subcortical circuits (more specifically the limbic-thalamic-cortical (LTC) circuit and the limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit) have been identified as being of critical importance in mood disorders (Carlson et al., 2006) and lesions in these areas are also common to HD pathology (Bonelli and Cummings, 2007). Dysfunction of the frontal lobes has also been hypothesised as contributing to depression in HD and has been shown to occur in the early stages of the disease even before the onset of motor symptoms (Jason et al., 1988). Hypometabolism in the orbital inferior prefrontal cortex has been evidenced in depressed HD patients (Mayberg et al., 1992) and reduced activity in the dorsal and ventral sectors of the prefrontal lobes were found in individuals with HD compared to healthy controls when dysphoric mood was induced in the participants using pictorial stimuli (Paradiso et al., 2008).

#### 2.9.4.2 Obsessive Compulsive Disorder/Obsessive Compulsive symptoms

Huntington's patients may be more prone to obsessive and compulsive symptoms than the general population due to shared frontostriatal pathology between HD and OCD (Anderson et al., 2001). Abnormal metabolic activity in the orbitofrontal cortex , the anterior cingulate/caudal medial prefrontal cortex, the basal ganglia and thalamus has been reported in functional imaging studies of individuals with OCD (Baxter et al., 1987; Nordahl et al., 1989; Saxena et al., 2001), which can then be normalised following successful treatment (Graybiel and Rauch, 2000). Intuitively, these results suggest that the striatal pathology and disruption of frontostriatal circuitry (in particular the orbitofrontal circuit) seen in HD gene carriers is related to the increased frequency of obsessive/compulsive symptoms seen in this population.

#### 2.9.4.3 Alcohol abuse

Alcohol abuse in HD could arise due to common cortical-striatal circuit involvement in both HD and substance use disorders (Ehret et al., 2007). Dysfunction of these circuits in HD, which have been implicated in reward mediated pathways (Cummings, 1993) may increase vulnerability to alcohol abuse.

#### 2.9.4.4 Psychotic symptoms

Psychotic symptoms in HD are thought to mainly occur in those patients who already have dementia (Shiwach and Norbury, 1994) and therefore, the underlying neuropathology of HD may contribute given that organic brain disorders have long been associated with symptoms including auditory hallucinations and delusions (Lyketsos, 2006). Deficits in neurocircuitry

that are common to both HD and schizophrenia may account for the increased prevalence of psychotic symptoms in the HD population (Bonelli and Cummings, 2007). The psychotic presentation in HD has been described as most often consisting of poorly systematised paranoia and overvalued ideas, often accompanied by irritability, aggression and poor impulse control (Guttman et al., 2003), which may result from disturbance of the dorsolateral prefrontal circuit, which contributes to the executive dysfunction seen in both HD and schizophrenia (Bonelli and Cummings, 2007).

#### 2.9.4.5 Irritability and Aggression

Irritability in HD is thought to be associated with HD pathology (Bonelli and Cummings, 2007; van Duijn et al., 2007; Reedeker et al., 2012; Thompson et al., 2012). Dysfunction of the orbitofrontal-subcortical circuit, as observed in HD patients, is thought to disconnect frontal monitoring systems from limbic input, resulting in inappropriate behavioural responses (Bonelli and Cummings, 2007). This can manifest as emotional lability (including irritability and aggression), disinhibition and a loss of socially appropriate behaviour (Bonelli and Cunnings, 2007). Disrupted emotional circuitry including the medial orbitofrontal cortex and amygdala has also been identifed using functional magnetic imaging (fMRI), in pre-symptomatic HD gene carriers completing tasks that induced irritation (Klöppel et al., 2010).

#### 2.9.4.6 Apathy

The correlation between apathy and measures of the HD disease course suggest that it is associated with the underlying neuropathology of HD (Craufurd et al., 2001; Thompson et al., 2002; Reedeker et al., 2011; Thompson et al., 2012). Apathy, in general, has been

associated with dysfunction of the anterior cingulate circuit given its role in motivated behaviour (Mega and Cummings, 1994; Bonelli and Cummings, 2007).

More specifically, Levy and Dubois (2006) refer to three subtypes of disrupted processing when describing the underlying mechanisms of apathy, including: emotional-affective, cognitive and auto-activation. Emotional-affective apathy is displayed as emotional blunting and a loss of interest in daily activities previously considered as motivating and is thought to be associated with dysfunction of the orbital and medial prefrontal cortex. Apathy due to disrupted cognitive processing is expressed as impaired executive functioning, including difficulties with: rule generation, set-shifting, planning and maintaining information in working memory. It is associated with damage to the lateral prefrontal cortex and the dorsal territories of the basal ganglia (notably the dorsal part of the head of the caudate nucleus). Deficits in auto-activation processing leads to the most severe form of apathy characterised by difficulties in self-generated thoughts and actions and are associated with damage to the dorsal-medial prefrontal cortex and the internal segment of the globus pallidus.

#### 2.9.4.7 Cognitive impairment

Cognitive deficits (including impairments in memory, attention and executive skills) in HD may also account for the high prevalence of particular neuropsychiatric symptoms in HD. Apathy (not in the context of depression) in particular has been associated with cognitive dysfunction (Thompson et al., 2002; Baudic et al., 2006). Difficulties in planning and organising, as evidenced by poor performance on cognitive tasks that require individuals to plan a sequence of actions such as the Tower of London task (Lange et al., 1995; Lawrence et

al., 1996; Watkins et al., 2000) and picture-ordering tasks (Snowden et al., 2001), likely contribute to the passive, amotivational states frequently seen in HD patients.

Impaired performance on specific cognitive tasks, including the Wisconsin Card Sorting Test and attentional set-shifting tasks, demonstrates reduced cognitive flexibility in HD patients (Owen et al., 1993; Paulsen et al., 1995; Lawrence et al., 1996). In the real world, a lack of cognitive flexibility is likely to impair an individual's ability to adapt to new situations or altered circumstances, which could lead to feelings of agitation and irritability when faced with unexpected changes. However, the direction of this relationship is unknown given that it is also possible that the presence of psychiatric symptoms leads to cognitive impairment.

### 2.9.5 Psychosocial factors

Psychosocial factors are likely to play a role in the development of psychiatric disorders/symptoms in HD. Specific stressors associated with HD including: growing up in a dysfunctional family, undergoing genetic testing; having to adjust to living with a hereditary, terminal illness and increasing disability are likely to contribute to the development of psychiatric disorders/symptoms. For example, a positive correlation has been found between stressful life events (measured using the Perceived Stress Scale) and depression in a pre-motor manifest HD sample (Downing et al., 2012). Anxiety is a feasible result of a gene positive individual wondering whether they are showing symptoms of HD yet or a symptomatic individual no longer coping at work and worrying about financial issues. Some individuals with HD may choose to self-medicate with alcohol as a way of coping with

stressful life events, especially if they are experiencing other psychiatric symptoms such as depressed mood and anxiety.

Environmental factors, including frustration and particular socio-demographic characteristics, may contribute to the increased irritability observed in HD gene carriers. Frustration is thought to augment aggression in certain situations (Buss and Arnold, 1963) and it is highly likely that individuals with HD can become frustrated with having a disabling illness and the loss of independence that comes with it as well as through experiencing reduced mental flexibility. Irritable behaviour exhibited by HD gene carriers can often be targeted at a specific household member closely involved in the individual's care (Craufurd and Snowden, 2014). Indeed, to date, being married/living together has been the only socio-demographic characteristic found to correlate with self-reported levels of irritability in HD (Reedeker et al., 2012). The authors of the study suggested that this could be due to the fact that intimate relationships may comprise more potential triggers of irritability (Reedeker et al., 2012).

### 2.9.6 Familiality studies in HD

Studies investigating the genotype-phenotype correlation in HD have focused on the CAG repeat length in the huntingtin gene. However, evidence to date strongly suggests that the presence and severity of psychiatric symptoms in HD is independent of the length of the trinucleotide expansion (Weigell-Weber et al., 1996; Naarding et al., 2001; Vassos et al., 2007). Although research on familial factors has received little attention, the few studies that have been carried out suggest that familial factors may play a role in the psychiatric

presentation of HD i.e. some psychiatric symptoms/syndromes may occur with higher frequency within some HD families than can be accounted for by chance.

#### 2.9.6.1 Familiality of affective disorders in HD

HD and affective disorder (including bipolar disorder and major depressive disorder) have been demonstrated to cosegregate in certain families (Folstein et al., 1983). In this study, Folstein and colleagues found a significant difference in the prevalence of major affective disorder in HD families where the HD proband had affective disorder (20 of 23 HD affected relatives had affective disorder) compared to those HD families where the HD proband did not have affective disorder (only 5 of the 23 HD affected relatives had affective disorder). This is the only study to date investigating the familiality of affective disorder in HD but suggests that familial factors (whether genetic or shared environmental factors) are important in the aetiology of mood disorders in HD.

#### 2.9.6.2 Familiality of suicide in HD

A study has demonstrated a possible predisposition to suicide in some HD families, with 40 out of 143 (28%) families included in the study having 99 out of the 205 (48%) cases of suicide (Di Maio et al., 1993).

#### 2.9.6.3 Familiality of OCD in HD

A pedigree has also been described where three cases of OCD and two cases of pathological gambling were identified in the family members who carried the HD gene mutation only (De Marchi et al., 1998).

#### 2.9.6.4 Familiality of psychotic symptoms in HD

There have been reports of a possible association between HD and schizophrenia-like psychotic symptoms due to findings that a subset of HD families have a predisposition to developing psychosis (Heathfield, 1967; Lovestone et al., 1996; Tsuang et al., 1998; Tsuang et al., 2000; Corrêa et al., 2006). Heathfield (1967) described a family where a brother and sister with HD also both had a diagnosis of paranoid schizophrenia as did another brother, although he did not develop motor symptoms of HD. Another family has been described where four family members presented with a severe psychiatric disorder (three were diagnosed with a schizophrenia-like syndrome and the other family member with depression) before the onset of motor symptoms (Lovestone et al., 1996). Additionally, two other family members at 50% risk for HD, who were displaying no signs of chorea or dementia, had received psychiatric treatment for schizoaffective disorder and major depression respectively (Lovestone et al., 1996).

Tsuang et al., (1998) compared two juvenile-onset HD families, one where the proband had schizophrenia-like symptoms and one where the proband had no psychotic presentation. HD co-occurring with schizophrenia-like symptoms was only found in the family members (the father and paternal grandmother) of the proband who also exhibited psychotic symptoms. A further study by Tsuang and colleagues (2000) on a larger group of Huntington's disease patients produced similar results where the HD probands who had psychotic symptoms were significantly more likely to have a first degree relative with psychosis than the probands who did not have psychosis. Finally, a family pedigree has been described where a three-

generation-long family history of HD and schizophrenia-like psychosis occurred, with the psychosis preceding motor onset by at least 5 years (Corrêa et al., 2006).

## *2.10 Summary and Aims of Study*

*Prevalence of psychiatric symptoms/syndromes in HD:*

Psychiatric syndromes and symptoms are undoubtedly common in HD as summarised in Table 2.1. It is apparent, however, that the use of a variety of instruments and differing definitions to measure prevalence rates, over different time courses and different disease stages has resulted in a wide range of prevalence rates being reported. In addition, the great deal of overlap between symptoms of various psychiatric disorders (major depression, bipolar disorder, OCD, psychotic disorders) and symptoms of HD itself, make the process of reaching a psychiatric diagnosis in the setting of HD very difficult. The fact that an exclusion clause of DSM criteria is that the psychiatric episodes are not attributable to an organic mental disorder adds to the difficulty of accurately assessing and diagnosing psychiatric syndromes in HD. However, it has been argued that the DSM criteria should be used as the gold standard measure for psychiatric diagnoses and that additional standardised instruments should be used to assess the presence/absence of other neuropsychiatric symptoms such as irritability, perseverative thinking and apathy in HD (van Duijn et al., 2007).

*Aetiology of psychiatric syndromes/symptoms in HD*

The basis of psychiatric disorders and symptoms in HD is complex, with genetic factors (including the HD gene) and non-genetic factors (including psychosocial factors)

hypothesised to play a role. Family studies provide a useful means to investigate the relative roles the shared genetic and/or shared environmental factors play in the aetiology of psychiatric disorders/symptoms.

However, the majority of these studies in HD families (Heathfield, 1967; Lovestone et al., 1996; De Marchi et al., 1998; Tsuang et al., 1998; Corrêa et al., 2006) have described one or two family pedigrees only, which are not generalisable to the HD population. Additionally, face-to-face interviews have not always been administered, instead relying on retrospective case notes and/or family informants to draw conclusions about psychiatric diagnoses and HD symptomatology. Two of the studies (Heathfield, 1967; Folstein et al., 1983) were conducted before the HD gene was identified, rendering the diagnostic criteria for HD less reliable than post-1993 studies. These family studies have also mainly focused on the association between HD and psychosis, rather than the more frequently observed psychiatric syndromes/symptoms in HD.

Therefore, there is a great need to build on this previous research by using gold-standard methodology to investigate a wide range of psychopathology in a large sample of HD families to better understand the role shared genetic and/or environmental factors may play in the aetiology of psychiatric syndromes/symptoms in HD . This research has implications not only for improving the clinical management of HD patients but also for enabling the development of more effective treatments and maybe even for preventing the onset of psychiatric symptoms. Research of this type in HD may also provide important insight regarding the aetiology of psychiatric disorders in the general population.

*Aims of Study:*

The main aims of this thesis are to:

1. Determine whether a broad range of psychiatric syndromes and symptoms aggregate in families affected with HD by conducting a systematic, standardised psychiatric assessment on a large sample of sibling pairs with HD.
2. Further improve current understanding of the relative role the HD gene, other genetic factors and psychosocial factors may play in explaining the increased prevalence of psychiatric symptoms in HD. This will be achieved by administering the psychiatric assessment to unaffected siblings who have had a negative HD genetic test.

Secondary aims include:

1. To assess and determine the lifetime prevalence rates of a broad range of psychiatric symptoms and syndromes defined using DSM-IV criteria in a large sample of unrelated individuals with HD.
2. To compare the depression phenotype in this HD sample with that in a large sample of individuals with unipolar depression without HD.
3. To validate the use of self-report depression rating scales in HD so that depression can be more accurately assessed in this population.

The following chapter (Chapter 3) describes the recruitment, assessment and clinical description of 50 unrelated individuals with HD and 40 of their siblings.

# CHAPTER 3: METHODS AND CLINICAL DESCRIPTION OF THE HD FAMILY SAMPLE

This chapter will outline the methods and clinical description of the sample relevant to Chapters 4 and 5. It will describe the recruitment, clinical and neuropsychiatric assessments of 50 unrelated individuals with HD, 40 of their siblings with HD and five gene negative siblings. The demographic characteristics and HD clinical features of the index and sibling samples will then be discussed.

## *3.1 Ethical Approval*

Multi-centre NHS ethical approval was granted by Cornwall and Plymouth Research Ethics Committee, reference: 08/H0203/157. Local Trust Research and Development (R&D) approval was then sought for the sites throughout the U.K. that had agreed to act as participant identification centres. These initially were: Birmingham and Solihull Mental Health Foundation Trust; University Hospital Wales, Cardiff; NHS Fife; Leicestershire Partnership NHS Trust; Central Manchester and Manchester Children's University Hospitals NHS Trust.

Local R&D approval was obtained from the following four extra sites half way through the study to increase potential recruitment: North Bristol NHS Trust; Newcastle Upon Tyne Hospitals NHS Foundation Trust; Oxford Radcliffe Hospitals NHS Trust, and; Sheffield Children's NHS Foundation Trust. Recruitment began from the sites once the relevant R&D approvals had been awarded.

## *3.2 Recruitment of Participants*

The recruitment of participants took place between February 2009 and March 2011. Families where at least two siblings were known to have the HD gene were recruited to the study.

### 3.2.1 Sibling sample ascertainment

#### 3.2.1.1 Consultant approach

The main recruitment of families to the study was achieved with the help of the Consultants, HD specialists and HD researchers at the HD centres where local R&D approval had been obtained: Dr Hugh Rickards, Consultant Neuropsychiatrist, Birmingham; Dr David Craufurd, Consultant Neuropsychiatrist, Manchester; Professor Anne Rosser, Consultant Neurologist, Cardiff; Carole Clayton, HD Nurse Specialist, Leicester; Jillian Foster, HD Team Leader, Fife; Dr Oliver Quarrell, Consultant in Clinical Genetics, Sheffield; Dr Baldev Singh, Consultant Neuropsychiatrist, Newcastle; Dr Andrea Nemeth, Consultant in Clinical Genetics, Oxford and; Dr Kasia Sierazdan, Consultant Neurologist, Bristol. Whether an HD patient is seen by a Neuropsychiatrist, Neurologist or Clinical Geneticist is dependent on the location of HD services within each local Trust only rather than whether the patient has any psychiatric symptoms. The Consultants at all of the sites were responsible for systematically screening their caseloads and making the initial contact with suitable participants. The recruitment process via the Consultants is outlined in Figure 3.1.

Potential participants were identified by their local Consultant during their routine HD clinic appointments. Participants were approached about the study on the basis that they were thought to meet the inclusion/exclusion criteria outlined in Table 3.1.

**Table 3.1 Inclusion and exclusion criteria for the HD gene positive sibling pairs.**

| Inclusion criteria | Exclusion criteria |
|---|---|
| A genetic diagnosis of HD | Any individual who was adopted away from their biological sibling |
| Over 18 years of age | Any individual who was a monozygotic twin of their sibling |
| Cognitively able to give informed consent | |
| Fluent in English | |
| Have at least one full, biological sibling that met the above criteria | |

The Consultant outlined the purpose of the study and what taking part involved. After this initial contact, if a patient was interested in taking part then the Consultant gave the patient a copy of the patient information sheet (Appendix Ai pg. 217) together with a reply slip (Appendix Ai pg. 222) and stamped addressed envelope to take home. If after reading the information sheet individuals were still interested in taking part, then they were asked to complete the reply slip with their contact details and return in the stamped addressed envelope to JDS.

Once the reply slip had been returned, the patient was contacted within two weeks to discuss the study further and clarify any questions he/she had and if still interested to arrange a suitable time to conduct the interview. Patients were interviewed at a location of their choice for example, at their home, at a sibling's home or at hospital.

Gene positive siblings were approached via one of two possible methods. Firstly, if the sibling was registered with the same participating HD service as their sibling, then the

relevant Consultants contacted the sibling(s) directly about the study. Contact was made either in clinic (if the sibling was due to attend the clinic in the next couple of months) or by a phone call. If the sibling was interested in receiving further information then they were either given or sent in the post the information sheet, reply slip and stamped addressed envelope and were asked to complete and return their contact details to JDS. Secondly, for those siblings not in the same participating HD service, the sibling already recruited to the study was asked to forward the patient information sheet onto their sibling(s) together with the reply slip and stamped addressed envelope for them to return to JDS with their contact details. Once the reply slip had been received by JDS, then the same recruitment procedure as described in the paragraph above was followed. As a result of this recruitment process, 47 families were recruited to the study.

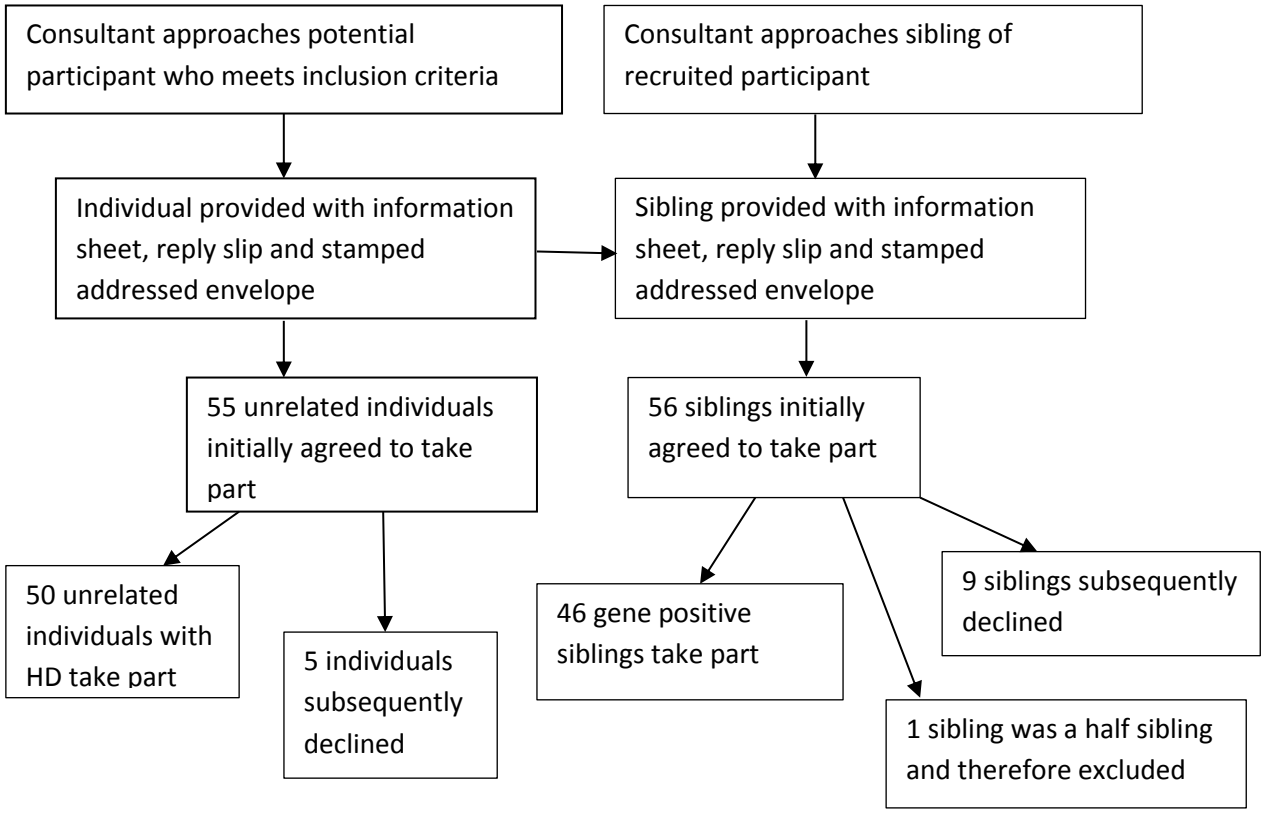



**Figure 3.1 Recruitment process of HD gene positive siblings via Consultants**

#### 3.2.1.2 Huntington's Disease Association

To facilitate recruitment to the study, other means of promoting the study were employed. The study was advertised on the charity Huntington's Disease Association (HDA) website where many patients and carers regularly log on for details about the latest HDA meetings, news and research. The advertisement (Appendix Ai, pg. 223) briefly outlined the purpose of the study, who would be suitable to participate and what taking part involved. Anyone interested was asked to contact JDS directly and it was then possible to answer any questions and if they were suitable and still interested then they were sent the patient information sheets. One sibling pair was recruited via this method.

JDS also attended support group meetings run by the HDA in Bristol, Stoke-on-Trent and Northampton to present the study to patients and carers. Two families returned their reply slips to JDS following these meetings and were subsequently recruited to the study.

**Table 3.2 Frequencies of families recruited to the study from the different sites and HDA.**

| **Centre** | **Number of families** |
|---|---|
| Birmingham | 16 |
| Bristol | 3 |
| Cardiff | 6 |
| Leicester | 3 |
| Manchester | 6 |
| Newcastle | 4 |
| Oxford | 2 |
| Sheffield | 4 |
| Fife | 3 |
| HDA meeting | 2 |
| HDA website | 1 |
| **Total** | **50** |

A summary of the number of families recruited to the study and the site or means of how they were recruited is displayed in Table 3.2. Of the 50 families that took part in the study, the siblings that were the first family member to be recruited to the study were all interviewed. For 40 of these 50 families, at least one HD gene positive sibling was also interviewed. However for 9 families, although the sibling had initially agreed to take part, they subsequently decided not to participate, the reasons for which are outlined in Table 3.3. Two individuals were having a difficult family time (one was going through a divorce and the other had not told her family about having the HD gene) and decided that it was not a good time for them to take part in research. Similarly, two individuals were in the process of moving to a nursing home so decided they no longer wanted to take part. Two individuals were unable to be contacted despite numerous attempts. One individual cancelled appointments continuously and then subsequently stated that he did not want to take part in the study after all. One individual decided not to sign the consent form and a further individual was hospitalised in the time between my initial contact and then arranging an interview date and so it was not possible for them to take part in the study. In addition, one sibling was discounted from the study after it became apparent during the interview that they were only half-siblings.

**Table 3.3 Frequencies of families that took part in the research and reasons for siblings not participating.**

| | **Frequency** |
|---|---|
| Families that were recruited to the study | 50 |
| Families where at least 2 gene positive siblings were interviewed | 40 |
| Families where sibling was having a difficult family time | 2 |
| Families where sibling was moving to a nursing home | 2 |
| Families where sibling was unable to be contacted | 2 |
| Families where sibling decided not to participate | 2 |
| Families where sibling was hospitalised | 1 |
| Families where siblings were half-siblings | 1 |

### 3.2.2 Gene negative sibling sample ascertainment

For those families where in addition to the HD gene positive sibling pair there was a sibling who had received a negative predictive test result, a sibling already recruited to the study was again asked to contact the gene negative sibling about taking part in the study. The inclusion and exclusion criteria for the gene negative sibling are shown in Table 3.4.

**Table 3.4 Inclusion and exclusion criteria for the HD gene positive sibling pairs.**

| Inclusion criteria | Exclusion criteria |
|---|---|
| A negative genetic test for HD | Any individual who was adopted away from their biological sibling |
| Over 18 years of age | |
| Cognitively able to give informed consent | |
| Fluent in English | |
| Have two gene positive full siblings who meet all of the inclusion criteria for the HD gene positive sample | |

The gene positive sibling was given a participant information sheet (Appendix Ai, pg. 220), reply slip and stamped addressed envelope to forward to the gene negative sibling. If the gene negative sibling was interested in taking part then they were asked to return their contact details to JDS. They were then contacted by telephone to confirm that they had indeed received a gene negative test result, to answer any questions they had about the study and to arrange a suitable time to visit them if they were still interested in taking part. This was a particularly difficult means of recruiting individuals as it relied on HD patients (who typically have difficulties with their memory, apathy and executive functions and are generally difficult to get hold of anyway) contacting their siblings. Any siblings who were unsure of their genetic status but were currently symptom free were not included in the study. Five gene negative siblings from 5 different families were recruited to the study.

A summary of the families and number of siblings that took part for each site/recruitment method is displayed in Table 3.5. Thirty one families had two gene positive siblings take part, four families had two gene positive and one gene negative sibling take part, three families had three gene positive siblings take part, one family had three gene positive and one gene negative sibling take part, one family had four gene positive siblings take part and there were ten families where only the initial gene positive sibling recruited to the study took part. Therefore, in total, 96 patients with HD and 5 unaffected siblings were recruited to the study.

**Table 3.5 Frequencies of families recruited to the study and the number of siblings for each family that took part from each site.**

| **Centre** | **Number of families** | | | | | | |
|---|---|---|---|---|---|---|---|
| | Total | 1 gene positive sibling | 2 gene positive siblings | 2 gene positive siblings + 1 gene negative | 3 gene positive siblings | 3 gene positive siblings + 1 gene negative | 4 gene positive siblings |
| Birmingham | 16 | 6 | 7 | 2 | 0 | 1 | 0 |
| Bristol | 3 | 1 | 2 | 0 | 0 | 0 | 0 |
| Cardiff | 6 | 1 | 3 | 1 | 1 | 0 | 0 |
| Leicester | 3 | 0 | 2 | 0 | 1 | 0 | 0 |
| Manchester | 6 | 1 | 4 | 0 | 0 | 0 | 1 |
| Newcastle | 4 | 0 | 3 | 1 | 0 | 0 | 0 |
| Oxford | 2 | 1 | 1 | 0 | 0 | 0 | 0 |
| Sheffield | 4 | 0 | 4 | 0 | 0 | 0 | 0 |
| Fife | 3 | 0 | 2 | 0 | 1 | 0 | 0 |
| HDA meeting | 2 | 0 | 2 | 0 | 0 | 0 | 0 |
| HDA website | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Total** | **50** | **10** | **31** | **4** | **3** | **1** | **1** |

## *3.3 Informed Consent*

All participants had received prior to the interview the patient information sheet detailing the background to the study, what taking part involved as well as relevant contact numbers. In addition, they were all telephoned so that any concerns or questions they had

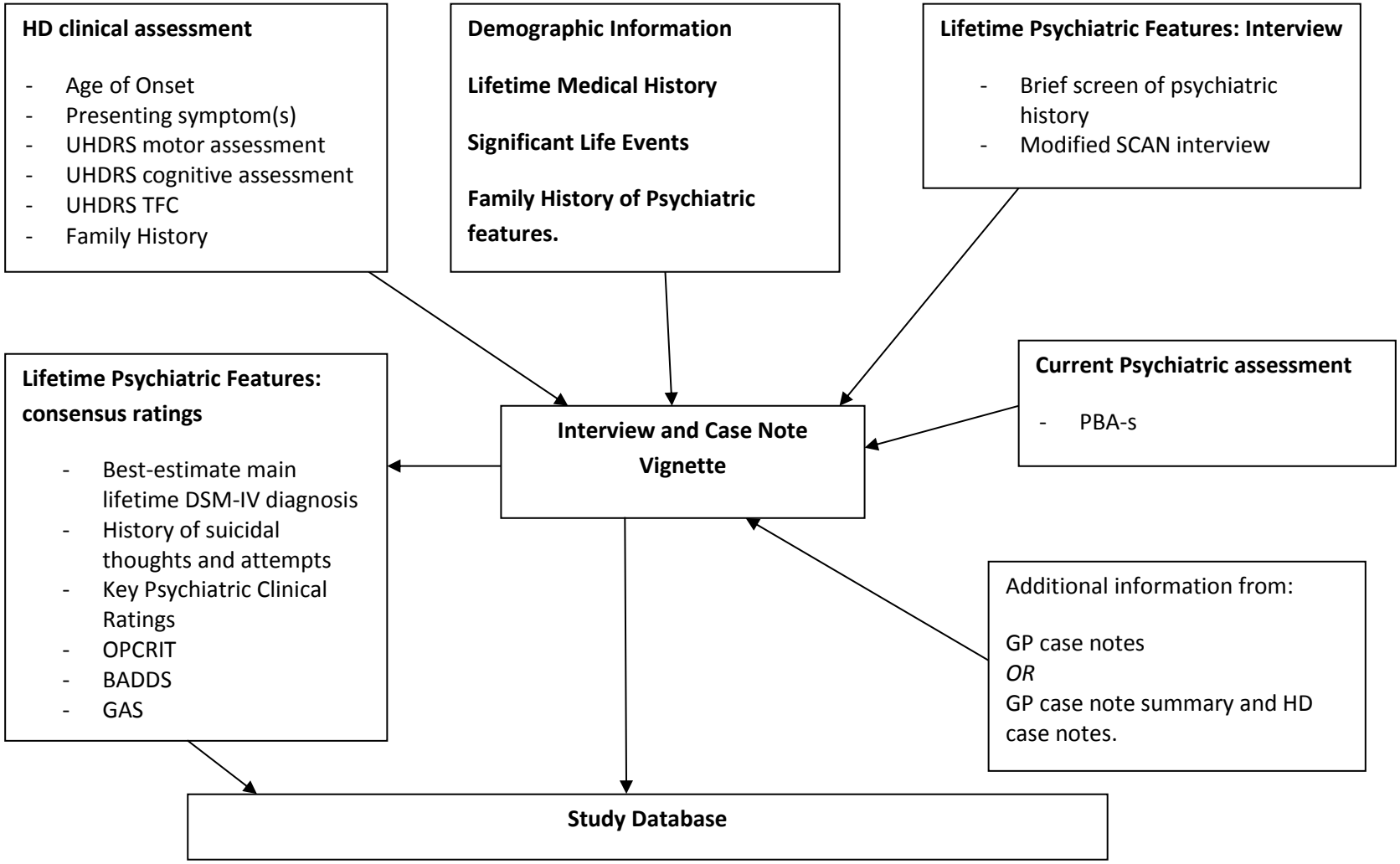
surrounding the study could be clarified before a suitable date and time to conduct the interview was arranged.

Informed consent was taken by JDS at the start of each patient interview. The consent sheet (gene positive participant - Appendix Ai, pg. 224, gene negative participant – Appendix Ai, pg. 225) was read through with the participant and any points were explained if necessary. Subsequently, if the patient was still happy to take part then the form was signed and dated by both the participant and JDS. All participants were then sent a copy of their consent form for them to keep and additional copies were sent to their GP (Appendix Ai, pg. 226) and kept by JDS in a locked filing cabinet.

### *3.4 Clinical and Neuropsychiatric Assessment of Participants*

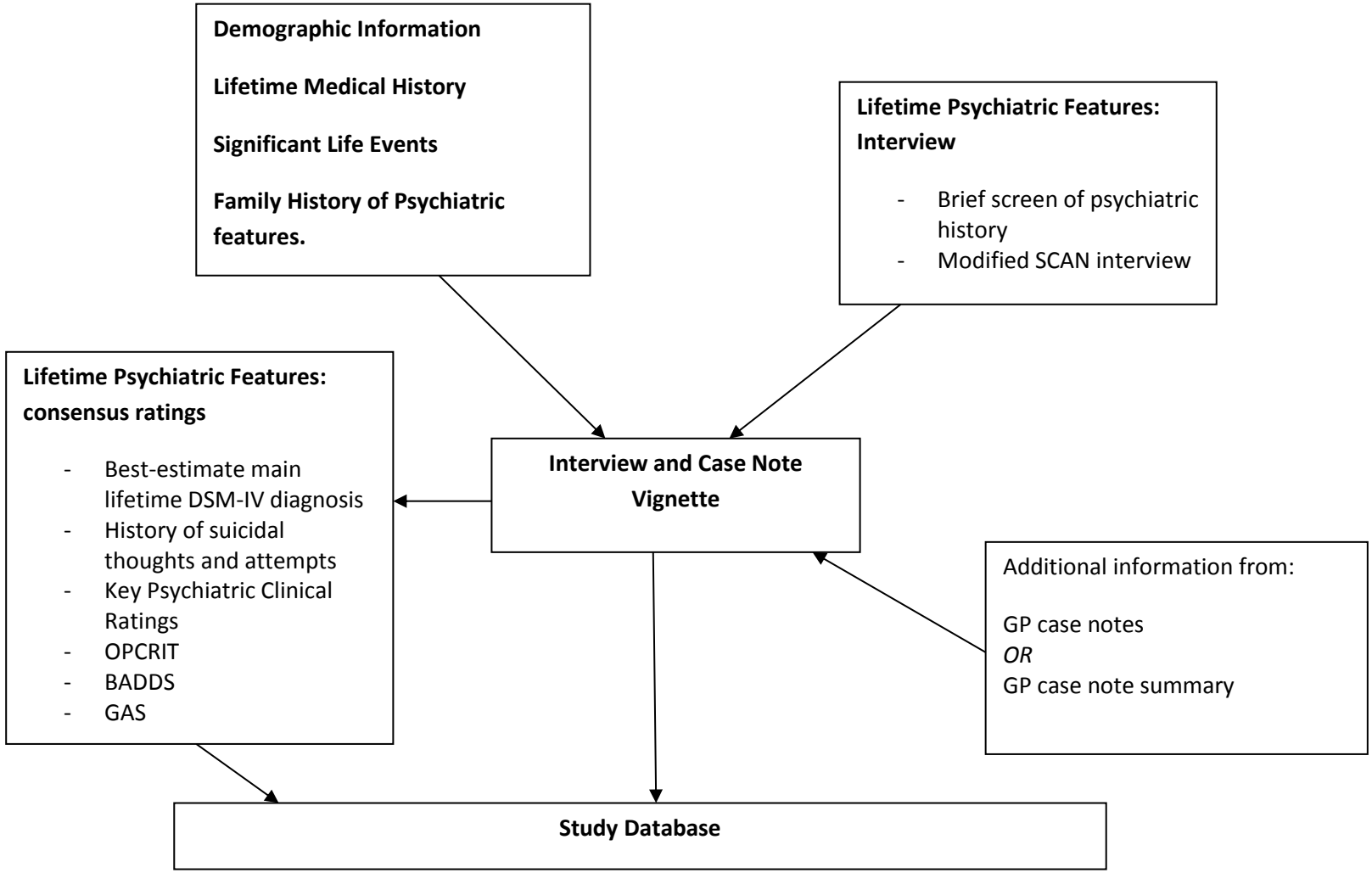
The following section describes the clinical and neuropsychiatric assessment of the 96 HD gene positive and five gene negative individuals. The only differences in the assessment of the gene positive and gene negative individuals were that the gene negative individuals were not administered assessments of the clinical features of HD (section 3.4.4) or the Problem Behaviours Assessment (section 3.4.7.1), as this is a scale designed for use in the HD population. All participants (apart from one who was interviewed in a hospital and one individual for whom a telephone interview was only feasible) were assessed at their homes in one session lasting approximately 2-3 hours. After obtaining written informed consent, a single, clinical neuropsychiatric assessment was administered and is summarised in Figure 3.2 and Figure 3.3. The data were entered into a relational Microsoft Windows Access Database designed by JDS.

**Figure 3.2 Clinical and Neuropsychiatric Assessment of 96 HD gene positive individuals**




**UHDRS**; Unified Huntington's Disease Rating Scale, **TFC**; Total Functional Capacity, **DSM-IV**; Diagnostic and Statistical Manual of Mental Disorders-fourth edition, **OPCRIT**; Operational Criteria diagnostic system, **BADDS**; Bipolar Affective Disorder Dimensional Scale, **GAS**; Global Assessment Scale, **SCAN**; Schedules for Clinical Assessment in Neuropsychiatry, **PBA-s**; Problem Behaviours Assessment for Huntington's disease – short version.

**Figure 3.3 Clinical and Neuropsychiatric Assessment of 5 HD gene negative individuals**




**DSM-IV**; Diagnostic and Statistical Manual of Mental Disorders-fourth edition, **OPCRIT**; Operational Criteria diagnostic system, **BADDS**; Bipolar Affective Disorder Dimensional Scale, **GAS**; Global Assessment Scale, **SCAN**; Schedules for Clinical Assessment in Neuropsychiatry.

### 3.4.1 Demographic Information

Information was obtained on a variety of demographic variables (see Appendix Aii, pg. 227) including: date of birth, place of birth, sex, ethnicity, education, occupation, co-morbid conditions, current medication(s), height, weight and name of GP and GP's address.

### 3.4.2 Lifetime Physical Medical History

A lifetime history of physical illnesses including age at onset of symptoms and duration of symptoms was recorded using self-report as well as the participants' medical notes. Other important lifetime events such as age at the time of receiving a predictive test result, having to give up work due to HD symptoms or age of getting divorced were also recorded here using the same sources of information.

### 3.4.3 Family History

A family pedigree was drawn using as much information as possible from the information provided by all the siblings. The family history of HD as well as lifetime psychiatric diagnoses experienced by family members was also noted.

### 3.4.4 Assessment of Clinical Features of HD

#### 3.4.4.1 HD History

All participants were asked their age at the time of their genetic test. If applicable, participants were subsequently asked the age at onset of symptoms and what their initial presenting symptom(s) was (were).

### 3.4.4.2 HD severity assessments

As a measure of HD severity, participants who were positive for the HD gene were also administered the Unified Huntington's Disease Rating Scale (UHDRS, Huntington Study Group, 1996) motor, cognitive and total functional capacity (TFC) sections. The UHDRS is a research tool which has been developed by the Huntington Study Group to provide a uniform measure of clinical performance and course of HD. The UHDRS has undergone extensive reliability and validity testing and has been used in many HD research studies as a primary outcome measure (UHDRS, Huntington Study Group, 1996).

#### *3.4.4.2.1 UHDRS Motor assessment:*

The UHDRS motor section comprises standardised ratings of oculomotor function, dysarthria, chorea, dystonia, gait and postural stability (Appendix Aiii, pg. 229). Higher scores (range 0-124) indicate greater impairment. Training and certification in administering the UHDRS motor assessment has been undertaken annually by JDS by means of an online video assessment.

#### *3.4.4.2.2 UHDRS Cognitive assessment:*

The UHDRS cognitive assessment consists of a phonetic letter fluency test, the symbol digit modalities test and the stroop test, which tap into the neuropsychological deficits typically observed in HD. These tests have been found to differentiate pre-motor manifest HD individuals from controls with medium to large effect sizes (Paulsen et al., 2011).

1) The letter fluency test (Appendix Aiii, pg. 233): this test measures the speed and flexibility of verbal thought processes. Participants were asked to generate in one

minute as many words as possible beginning with the letters F, A and S. The score was the total sum of correct responses across the three trials. Proper nouns and derivatives of the same word stem were not admissible.

2) The symbol digit modalities test, SDMT (Appendix Aiii, pg. 235): the SDMT involves a simple substitution task and assesses attention, psychomotor speed and working memory. Using a reference key, the participants had to pair specific numbers with given geometric figures. An initial practice test consisting of 10 responses was performed to allow the participants to understand the task. The number of correct written responses in 90 seconds was recorded.
3) The Stroop test: this test examines attention, mental speed and mental control and consists of the following procedure, which includes 3 conditions:

i) Naming blocks of colour (Appendix Aiii, pg. 236)
ii) Reading colour words printed in black ink (Appendix Aiii, pg. 237)
iii) Naming ink colour of incongruous colour words : the 'interference' condition (Appendix Aiii, pg. 238)

The score for this test consisted of the number of correct answers given in a 45 second period for each condition.

*3.4.4.2.3 Functional assessment:*

The Total Functional Capacity (TFC, range 0-13) is a measure of a person's ability to work, look after their finances, perform the household chores and activities of daily living as well as whether they can be looked after at home or in a nursing home (Appendix Aiii, pg. 239). The lower the score, the greater the functional impairment. For clinical and research purposes,

the progression of HD is often divided into five stages according to scores obtained on the TFC, summarised in Table 3.6 (Shoulson and Fahn, 1979).

**Table 3.6 The TFC stages (Shoulson and Fahn, 1979)**

| TFC Stage | Score range | Brief Description |
|---|---|---|
| Stage 1: Early Stage | 11-13 | The person is diagnosed as having HD and can function fully both at home and work. |
| Stage 2: Early Intermediate Stage | 7-10 | The person remains employable but at a lower capacity. They are still able to manage their daily affairs despite some difficulties. |
| Stage 3: Late Intermediate Stage | 3-6 | The person can no longer work and/or manage household responsibilities. They need considerable help or supervision to handle daily financial affairs. Other daily activities may be slightly difficult but usually only require minor help. |
| Stage 4: Early Advanced Stage | 1-2 | The person is no longer independent in daily activities but is still able to live at home supported by their family or professional carers. |
| Stage 5: Advanced Stage | 0 | The person with HD requires complete support in daily activities and professional nursing care is usually needed. |

### 3.4.5 Assessment of Lifetime Psychiatric Features – Interview

#### 3.4.5.1 Brief screen of psychiatric history

In order to determine at the beginning of the interview whether the participant had a history of any particular psychiatric symptoms, a brief screen based on the Schedules for Clinical Assessment in Neuropsychiatry (SCAN, see section 3.4.5.2) was administered (Appendix Aiv, pg. 240). This consisted of questions referring to panic and anxiety disorders, depressive disorders, manic symptoms, psychotic symptoms, obsessive and compulsive disorders, eating disorders and other problems such as alcohol abuse/dependence. In order to get an idea of the severity of the symptoms, if participants answered affirmatively to any of the screen questions, they were then asked whether they had sought help from their GP, been prescribed medication, received counselling, been referred to and seen a psychiatrist, and/or been admitted to hospital. A positive brief screen resulted in the relevant sections of

the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) Interview (Wing et al., 1990) being administered to assess the presence of these features in further detail.

#### 3.4.5.2 Schedules for Clinical Assessment in Neuropsychiatry (SCAN) Interview

The SCAN is a widely used semi-structured interview aimed at assessing, measuring and classifying the psychopathology associated with major psychiatric disorders. The SCAN consists of prompted questions that assess the presence or absence of a symptom as well as the severity of that symptom in the time frame being measured, which was lifetime ever occurrence for the purpose of this study. If a participant responds positively to probe questions about core psychiatric symptoms, then the presence of associated symptoms are investigated further.

For this study, a modified version of the SCAN was administered to reduce the length of the interview. Items were selected that assess for the presence of clinical symptoms that are required to make a lifetime diagnosis of a psychiatric disorder according to standardised diagnostic criteria. Consequently, the following sections of the SCAN were administered where relevant: 4 – panic/anxiety and phobias; 5 – obsessional symptoms; 6 – depressed mood and ideation; 7 – thinking, concentration, energy, interests; 8 – bodily functions; 9 – eating disorders; 10 – expansive mood and ideation; 11 – use of alcohol; 12 – substance use; 17 – hallucinations; 18 – experiences of thought disorder and replacement of will, and; 19 – delusions.

Careful questioning was required in administering the SCAN to individuals with HD, owing to the fact that many core symptoms of HD overlap with core symptoms of psychiatric disorders (e.g. perseverative thinking due to cognitive impairment or obsessive thinking as seen in OCD, poor concentration due to cognitive changes in HD or as part of an episode of depression). Psychiatric symptoms were only rated as present if it was clear that the symptom was associated with psychiatric illness rather than the gradual changes typical of HD. Training in administering the SCAN was undertaken at the WHO approved centre of Nottingham University. The course consisted of 5 days training including seminars, small group tutorials and clinical interviews. Further familiarisation with the SCAN, ICD-10 and DSM-IV was carried out following the training and some practice interviews were carried out in attendance with a research psychologist with 9 years experience in using the SCAN. In addition, the same psychologist attended the first two interviews conducted for the study to ensure that the SCAN was being administered thoroughly and correctly.

In order to supplement (and verify) the information obtained from the interview, GP case notes were requested. If a patient case note summary was provided rather than a copy of their full notes, additional medical notes were obtained by JDS visiting the HD services and viewing the patient medical records stored there.

### 3.4.6 Assessment of Lifetime Psychiatric Features – Consensus Ratings

Information obtained from the psychiatric interview together with available medical notes were reviewed and structured vignettes then written for each patient summarising all the psychiatric data. The vignettes were then used to make numerous psychiatric lifetime ratings

as outlined in the following sections. All ratings were made independently by JDS and KGS (a research psychologist with 9 years experience of making psychiatric diagnoses and using the rating tools) and after meeting regularly to discuss the psychiatric lifetime ratings, consensus was reached (with the input of a third independent rater, LAJ, research supervisor, when necessary). The consensus ratings were used in all data analyses and a copy of the consensus rating sheet is provided in Appendix v, pg. 241.

#### 3.4.6.1 Best-Estimate Main Lifetime Psychiatric Diagnoses

Best-estimate main lifetime psychiatric diagnoses were made according to the standardised operational diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000) and the International Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research, 10$^{th}$ Edition (ICD-10, World Health Organisation, 1993). The diagnoses reported in the subsequent chapters are those according to DSM-IV to allow comparisons with previous literature. In the instances where an individual had more than one lifetime psychiatric disorder, the degree of impairment caused by the disorder was used to determine which diagnosis was considered the main, second or third lifetime psychiatric diagnosis, with most impairment indicating a main diagnosis.

#### 3.4.6.2 History of suicidal thoughts and suicide attempts

Ratings of lifetime history of suicidal thoughts and attempts were made according to the rating scale displayed in Table 3.7. Scores ranged from 0 (the absence of any suicidal thoughts or attempts) through to 5 (multiple suicide attempts likely to result in death).

**Table 3.7 Rating of Lifetime History of Suicidal Thoughts and Attempts**

| | Rating |
|---|---|
| Absent | **0** |
| Tedium vitae | **1** |
| Suicidal ideation | **2** |
| Suicide attempt unlikely to result in death | **3** |
| Suicide attempt likely to result in death | **4** |
| Multiple suicide attempts likely to result in death | **5** |

### 3.4.6.3 Key psychiatric clinical variables

Ratings of other key psychiatric clinical variables were also made where relevant, including: age of onset of any psychiatric illness, age of onset of specific psychiatric illnesses, which caused clinically significant impairment and number of admissions to hospital as a result of psychiatric illness. In addition, the number of episodes and longest duration of affective illness were recorded.

### 3.4.6.4 The OPerational CRITeria checklist (OPCRIT)

The OPCRIT checklist (McGuffin et al., 1991) consists of a 90 item symptom checklist that can be used to generate diagnoses for the main affective and psychotic disorders according to a number of operationalized diagnostic systems. For this study, a modified 63-item version of the checklist was used that incorporated items referring to depressive, manic, psychotic and psychotic affective symptoms. This modified version of OPCRIT has been shown to be valid for use in studies of mood disorders (Craddock et al., 1996) and has been used extensively by the Mood Disorders Research group. Using interview data and information obtained from case notes, it was possible to record the lifetime ever presence and absence of affective and psychotic symptoms. Symptoms were coded as absent 0, present 1 and unsure 9. A copy of the OPCRIT rating sheet is provided in Appendix vi, pg. 243.

#### 3.4.6.5 The Bipolar Affective Disorder Dimension Scale (BADDS)

The BADDS (Craddock et al., 2004) is a dimensional rating scale that can be used alongside best estimate lifetime diagnostic procedures to provide useful information, particularly about subclinical cases of psychopathology. The four domains measured by the scale include: mania (M); depression (D); psychosis (P), and; incongruence (I). Each dimension is measured on a 0-100 scale, which represents the severity and frequency of clinical features. Ratings were made for each individual based on information obtained from the SCAN and case note review. A copy of the BADDS ratings guidelines is provided in Appendix vii, pg. 245.

#### 3.4.6.6 The Global Assessment Scale (GAS)

The GAS (Endicott et al., 1976) rates the function of a person according to their psychological well-being and functional capacity during a specified time frame. A score of 100 indicates functioning at the highest level with no psychological problems and a score of 0 represents the need for constant supervision for several days to prevent self-harm. For this study, GAS ratings were made for the lowest level of functioning in the worst depressive episode. A copy of the GAS ratings guidelines is provided in Appendix viii, pg. 251.

### 3.4.7 Assessment of other psychiatric symptoms

#### 3.4.7.1 Problem Behaviours Assessment Scale for Huntington's disease (PBA-HD)

For the neuropsychiatric symptoms of irritability, aggression, apathy and perseverative thinking/behaviours, which are commonly observed in HD patients but not well-covered by the SCAN, the relevant items of the PBA-HD (Craufurd et al., 2001) were administered (see Appendix ix, pg. 253). The PBA-HD is a semi-structured interview specifically designed to

provide a reliable assessment of behavioural problems in HD. It measures the frequency and severity of symptoms (score range 0-4) over the past month and the values obtained are multiplied to give a total score for each item (score range 0-16). For this study, lifetime ever ratings of the neuropsychiatric symptoms were made, which measured their frequency and severity during the worst episode and the age of onset was also recorded where relevant for these neuropsychiatric symptoms. Informants were also interviewed whenever possible and any additional information provided by the GP case notes were taken into account when ratings were made.

### *3.5 Analysis of the Demographics and HD Clinical Features of 50 unrelated individuals with HD and 40 of their siblings with HD*

This study was designed to address questions about the familiality of psychiatric syndromes/symptoms in HD and therefore, sibling pairs were recruited to the study. In order to ensure that only independent observations were reported, the total sample of 96 gene positive individuals was divided into an index and sibling sample for analysis. The advantage of this is that data are presented for two separate (although, not independent) samples.

The index sample consisted of one individual per family so that no members of this sample were related. The sibling sample consisted of one sibling for each family where two or more siblings positive for the HD gene took part in the study. For the ten families where only one individual took part in the study, this individual automatically became part of the index sample. For the other 40 families, the random number generator in Microsoft Windows Excel was used to select which member of the sibling pair was randomised to the index or

sibling samples. This was done in order to reduce any possible bias from automatically allocating the sibling first recruited to the study into the index sample.

### *3.6 Demographic characteristics*

Table 3.8 summarises the demographic characteristics of the sample. The mean age of the index sample was 49.0 years and the majority of participants were female (66.0%). All the sample was comprised of UK/Eire Caucasian individuals and 90.0% were (or had been) married or lived as though married. Most (62.0%) were living in their own home with a spouse and/or children. The majority (58.0%) were unemployed and receiving benefits but 16.0% were employed full-time and 16.0% were retired. The main lifetime occupation categories that were most frequently reported were 'legislator/senior officials, managers and professionals' (24.0%) as well as 'service, shop and market workers' (20.0%).

The demographic profile of the sibling sample was very similar to the index sample. The mean age was 48.5 years and most of the participants were female (60.0%). UK/Eire Caucasian individuals comprised the entire sample and 82.5% of individuals were (or had been) married or lived as though married. Most individuals (60.0%) were living in their own home with a spouse and/or children. The majority (60.0%) were unemployed and receiving benefits, although 12.5% were employed full-time and a further 16.0% were retired. The main lifetime occupation category that was most frequently reported was 'legislator/senior officials, managers and professionals' (22.5%) followed by 'service, shop and market workers' (20.0%).

## Table 3.8 Demographic Characteristics of the index and sibling samples

| Demographics | Descriptives and Percentages | |
|---|---|---|
| | Index Sample (N=50) | Sibling Sample (N=40) |
| **Age (years)** | | |
| Mean (95% CI) | 49.0 (46.5-51.5) | 48.5 (45.5-51.5) |
| Standard Deviation | 9.0 | 11.1 |
| Range | 28-76 | 24-73 |
| | | |
| | **N (%)** | **N (%)** |
| **Female** | 33 (66.0) | 24 (60.0) |
| | | |
| **Ethnic Origin** | | |
| UK/Eire Caucasian | 50 (100.0) | 40 (100.0) |
| | | |
| **Marital status** | | |
| Has married/lived as married | 45 (90.0) | 33 (82.5) |
| Has never married/lived as married | 5 (10.0) | 7 (17.5) |
| | | |
| **Current Social Circumstances** | | |
| Lives in own home with spouse and/or children | 31 (62.0) | 24 (60.0) |
| Lives alone | 10 (20.0) | 6 (15.0) |
| Lives in home of parents or children | 4 (8.0) | 4 (10.0) |
| Lives with partner of at least one year but not married | 3 (6.0) | 2 (5.0) |
| Residential facility | 0 (0.0) | 3 (7.5) |
| Other | 2 (4.0) | 1 (2.5) |
| | | |
| **Current Employment Status** | | |
| Employed full time | 8 (16.0) | 5 (12.5) |
| Employed part time | 3 (6.0) | 4 (10.0) |
| Not working – receiving benefits | 29 (58.0) | 24 (60.0) |
| Not working – not receiving benefits | 0 (0.0) | 1 (2.5) |
| Homemaker | 2 (4.0) | 0 (0.0) |
| Retired | 8 (16.0) | 6 (15.0) |
| | | |
| **Main Lifetime Occupation** | | |
| Legislator/senior officials, managers and professionals | 12 (24.0) | 9 (22.5) |
| Technicians and associate professionals | 2 (4.0) | 1 (2.5) |
| Clerks | 2 (4.0) | 4 (10.0) |
| Service workers & shop & market workers | 10 (20.0) | 8 (20.0) |
| Craft & related trade workers | 2 (4.0) | 5 (12.5) |
| Plant & machinery operators and assemblers | 8 (16.0) | 6 (15.0) |
| Homemaker | 2 (4.0) | 1 (2.5) |
| Never worked | 0 (0.0) | 1 (2.5) |
| Other | 12 (24.0) | 5 (12.5) |

The frequencies and percentages of the highest level of education qualifications achieved by the 50 individuals in the index sample and the 40 individuals in the sibling sample are summarised by age group in Tables 3.9 and 3.10 respectively. For the index sample, the majority of participants had obtained O-levels/CSEs or GCSEs (44.0%). Just over a quarter had achieved A-levels (28.0%) and nearly another quarter had no qualifications (22.0%). Four per cent of the index sample had a degree and 1 individual reported passing the 11+ as their highest educational qualification. Four out of the 5 index participants aged between 61 and 80 had either no qualifications or the 11+ as their highest qualification whereas in all the other age group categories (21-30, 31-40, 41-50 and 51-60), the majority of individuals had obtained O-levels/CSEs or GCSEs (100%, 60.0%, 45.8%, 46.7%).

**Table 3.9 Highest Level of Educational Qualifications by Age Groups for the Index Sample, N = 50**

| | **Age at Interview** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 21-30 N=1 | | 31-40 N = 5 | | 41-50 N = 24 | | 51-60 N = 15 | | 61-70 N = 4 | | 71-80 N = 1 | | **All N = 50** | |
| | N | % | N | % | N | **%** | N | % | N | % | N | % | **N** | **%** |
| **No qualifications** | 0 | 0.0 | 0 | 0.0 | 5 | 20.8 | 3 | 20.0 | 3 | 75.0 | 0 | 0.0 | **11** | **22.0** |
| **11+** | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 25.0 | 0 | 0.0 | **1** | **2.0** |
| **O-levels/CSEs/ GCSEs** | 1 | 100.0 | 3 | 60.0 | 11 | 45.8 | 7 | 46.7 | 0 | 0.0 | 0 | 0.0 | **22** | **44.0** |
| **A level/ HND/ BTEC** | 0 | 0.0 | 2 | 40.0 | 7 | 29.2 | 4 | 26.7 | 0 | 0.0 | 1 | 100.0 | **14** | **28.0** |
| **Degree** | 0 | 0.0 | 0 | 0.0 | 1 | 4.2 | 1 | 6.6 | 0 | 0.0 | 0 | 0.0 | **2** | **4.0** |

Similarly to the index sample, the majority of participants in the sibling sample had obtained O-levels/CSEs or GCSEs (42.5%) as their highest level of educational qualification. Nearly a

third (30.0%) had no qualifications and 17.5% had achieved A-levels. A degree had been obtained by 5% of the sibling sample and 2 individuals reported passing the 11+ as their highest educational qualification. Six out of 7 of the sibling sample participants aged between 61 and 80 had either no qualifications or the 11+ as their highest qualification. However, in all the other age group categories, the highest level of educational qualification that was most frequently reported was O-levels/CSEs or GCSEs.

**Table 3.10 Highest Level of Educational Qualifications by Age Groups for the Sibling Sample, N = 40**

| | **Age at Interview** | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 21-30 N=1 | | 31-40 N = 8 | | 41-50 N = 17 | | 51-60 N = 7 | | 61-70 N = 5 | | 71-80 N = 2 | | **All N = 40** | |
| | N | % | N | % | N | **%** | N | % | N | % | N | % | **N** | **%** |
| **No qualifications** | 0 | 0.0 | 3 | 37.5 | 3 | 17.6 | 2 | 28.6 | 3 | 60.0 | 1 | 50.0 | **12** | **30.0** |
| **11+** | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 20.0 | 1 | 50.0 | **2** | **5.0** |
| **O-levels/CSEs/ GCSEs** | 1 | 100.0 | 3 | 37.5 | 9 | 52.9 | 3 | 42.9 | 1 | 20.0 | 0 | 0.0 | **17** | **42.5** |
| **A level/ HND/ BTEC** | 0 | 0.0 | 2 | 25.0 | 4 | 23.5 | 1 | 14.3 | 0 | 0.0 | 0 | 0.0 | **7** | **17.5** |
| **Degree** | 0 | 0.0 | 0 | 0.0 | 1 | 5.9 | 1 | 14.3 | 0 | 0.0 | 0 | 0.0 | **2** | **5.0** |

## *3.7 HD Clinical Characteristics*

All participants from the index and sibling samples had a genetic diagnosis of HD. Forty-two of the 50 individuals in the index sample had also received a clinical diagnosis. Of the 8 participants without a clinical diagnosis, 7 were considered pre-motor symptomatic from self-report at the time of the interview, their scores obtained on the UHDRS motor assessment (≤5) and review of their medical notes. A score of ≤5 on the UHDRS motor assessment (range 0-124) is the cut-off typically employed in HD research to differentiate

pre-motor manifest from HD manifest individuals (Tabrizi et al.,2011). One participant was considered to be symptomatic, although he had not received an official clinical diagnosis. The individual reported that he had not experienced any symptoms of HD, however, his partner said that she had noticed obvious "twitching" for the last year and chorea was apparent during the interview and UHDRS motor assessment (a score of 7), which indicated that he was symptomatic. Therefore, 43 participants in the index sample were considered to have manifest HD and 7 individuals were classified as pre-motor manifest.

Thirty-two of the 40 individuals in the sibling sample had received both a genetic and clinical diagnosis of HD. Seven participants without a clinical diagnosis were classified as pre-motor manifest using the same criteria as described in the previous paragraph for the index sample. One participant who had not yet received an official clinical diagnosis was considered to have manifest HD. The individual reported that she believed she was still pre-motor symptomatic, however, observable chorea throughout the interview and a motor score of six suggested otherwise. Therefore, in the sibling sample, 33 individuals were classified as having manifest HD and 7 individuals were considered to be pre-motor manifest.

### 3.7.1 Age at Onset of HD and duration of HD

For those participants in both samples who were symptomatic, the age of motor onset of HD was obtained from self-report and then verified using their medical notes. The descriptives and distributions for both the index and sibling samples are summarised in Table 3.11 and Figure 3.4. The median age of onset in the index sample was 44 years. The youngest age of

onset was a male who was 25 when he first showed any symptoms and the oldest was a female who was symptom free until she was 75. The most common age of onset was between the ages of 41 and 50 (47% of individuals) and only 1 participant had an age of onset over 61 years. The median duration of having HD in the index sample was 5 years although the range of duration was from 1 year through to 16 years (a female in the advanced stages of the illness).

**Table 3.11 Age at Onset and Duration of HD (years) in the index and sibling samples.**

| | N | Median | Range | Inter quartile range |
|---|---|---|---|---|
| **Index Sample** | | | | |
| Age of Onset of HD | 43 | 44 | 25-75 | 9.5 |
| Duration of HD | 43 | 5 | 1-16 | 6.0 |
| | | | | |
| **Sibling Sample** | | | | |
| Age of Onset of HD | 33 | 41 | 23-63 | 11.0 |
| Duration of HD | 33 | 5 | <1-24 | 11.0 |

For the sibling sample, the median age of onset was 41 and the most common age of onset was between the ages 31 and 40 (39%). The youngest age of onset in the sample was a male who was 23. The oldest age of onset was a male who remained symptom free until he was 63 and he was also the only individual in the sibling sample with an age of onset greater than 61 years. The median duration of having HD in the sibling sample was 5 years with a range of less than 1 year (someone who had become symptomatic in recent months) through to 24 years (a female in the latter stages of the illness).

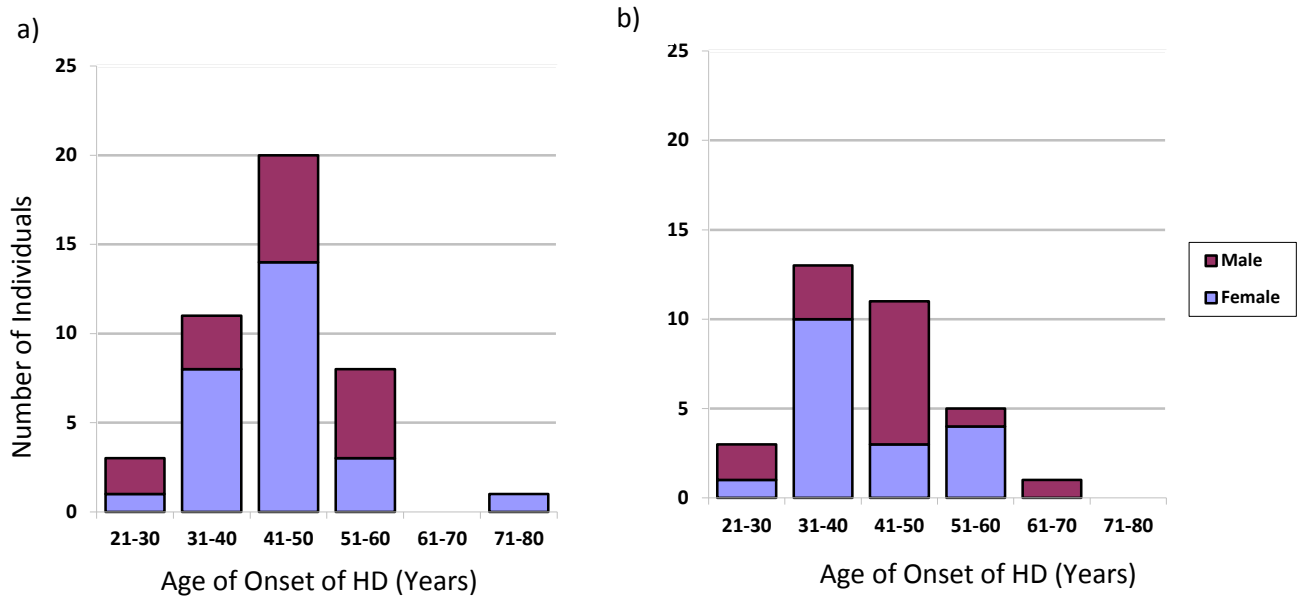



**Figure 3.4 Age at onset of HD – distributions for a) the index sample, N = 43 and b) the sibling sample, N = 33**

### 3.7.2 Current severity of HD

The current HD severity of the participants, determined using the Shoulson Fahn cut-offs on the Total Functional Capacity scale (as described earlier in the chapter in Table 3.6), is displayed in Table 3.12. The majority of individuals in the index sample (16, 37.2%) were classified as being in stage 1, i.e. the early stage of the illness. Fifteen individuals (34.9%) were in the early intermediate stage of HD (stage 2), 10 individuals (23.3%) were classified as being in the late intermediate stage (stage 3) and two individuals (4.7%) were classified as early advanced (stage 4).

For the sibling sample, the majority of individuals (13, 39.4%) were classified as being in Stage 2, i.e. the early intermediate stage of the illness. Six individuals (18.2%) were in the early stage of HD (stage 1), eight (24.2%) were in the late intermediate stage of HD (stage 3), five (15.2%) were classified as early advanced (stage 4) and one (3.0%), a 73 year old female, was in the advanced stages of HD (stage 5).

**Table 3.12 Current severity of HD in the index and sibling samples, by sex.**

| | Index Sample, N = 43 | | | | Sibling Sample, N = 33 | | | |
|---|---|---|---|---|---|---|---|---|
| | Male N = 16 | | Female N = 27 | | Male N = 15 | | Female N = 18 | |
| | N | % | N | % | N | % | N | % |
| Stage 1 – early HD | 7 | 41.2 | 9 | 27.3 | 3 | 18.8 | 3 | 12.5 |
| Stage 2 – early intermediate | 6 | 35.3 | 9 | 27.3 | 5 | 31.3 | 8 | 33.3 |
| Stage 3 – late intermediate | 3 | 17.6 | 7 | 21.2 | 4 | 25.0 | 4 | 16.7 |
| Stage 4 – early advanced | 0 | 0.0 | 2 | 6.0 | 3 | 18.8 | 2 | 8.3 |
| Stage 5 - advanced | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 4.2 |

### 3.7.3 Duration of HD and current severity of HD

The mean number of years of HD symptoms experienced by individuals in different stages of illness is displayed in Figure 3.5 a) for the index sample and b) for the sibling sample. For those individuals in Stage 1 of the illness (early HD), the mean duration of HD was 2.3 years and 1.8 years for the index and sibling samples respectively. The number of years of manifest HD increased with each successive stage up to 22 years for the individual in Stage 5 of the illness in the sibling sample.

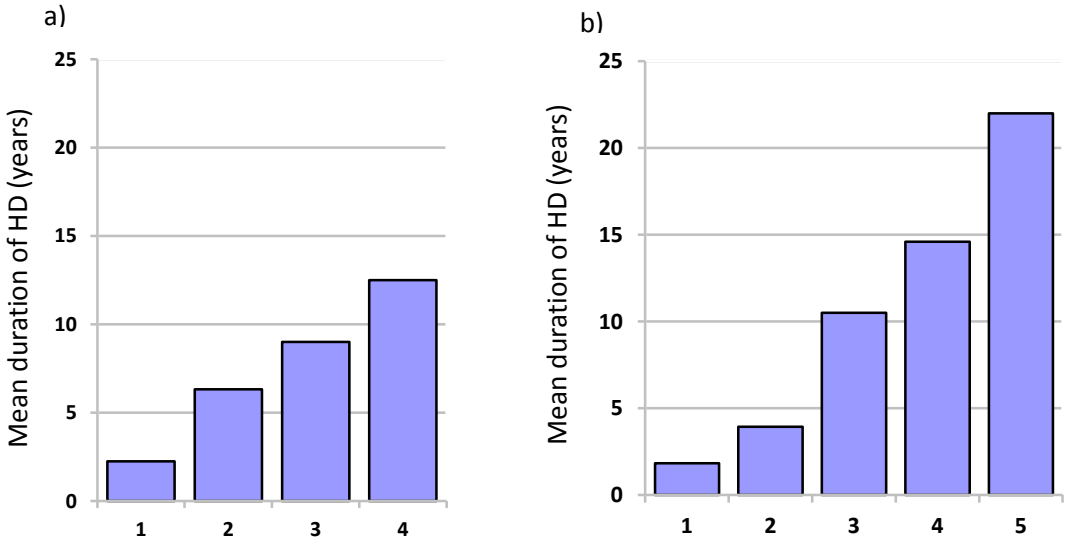



**Figure 3.5 Mean duration of HD in years according to current severity of illness for a) the index sample, N = 43 and, b) the sibling sample, N = 33**

### 3.7.4 Motor ratings

UHDRS motor scores were obtained for 43 of the 50 individuals in the index sample and 36 of the 40 individuals in the sibling sample. Table 3.13 summarises the motor data for both samples and Figure 3.6 displays the frequency distribution of the motor scores for the individuals.

**Table 3.13 UHDRS motor scores in the index and sibling samples, by sex.**

| UHDRS Motor Score | Index Sample: N = 43 | | | Sibling Sample: N = 36 | | |
|---|---|---|---|---|---|---|
| | Total | Male: N = 15 | Female: N =28 | Total | Male: N =15 | Female: N=21 |
| Median | 25 | 25 | 23.5 | 26.5 | 28 | 25.0 |
| Range | 0-85 | 2-63 | 0-85 | 0-75 | 5-75 | 0-74 |
| Inter Quartile Range | 29 | 13 | 34 | 46.5 | 38.0 | 45 |

The median motor score for the index sample was 25. UHDRS motor scores were obtained for six of the seven pre-motor symptomatic participants in the index sample, which were all in the 0-5 range. The distribution of motor scores in this sample was positively skewed with 65.1% of the sample having motor scores of 30 or less and the remaining 34.9% of the sample having scores ranging from 31 to 85. The participant with the highest motor score of 85 was a female in Stage 4 of the illness. The median UHDRS motor scores were similar in males (25) and females (23.5).

A similar positively skewed distribution was observed for the sibling sample with the majority of individuals (58.3%) having UHDRS motor scores of 30 or less. The median UHDRS motor score was 26.5 and the 6 pre-motor symptomatic individuals with UHDRS motor scores comprised the 0-5 score range. The median UHDRS motor score was slightly higher for males (27) than females (24.5) in the sibling sample.

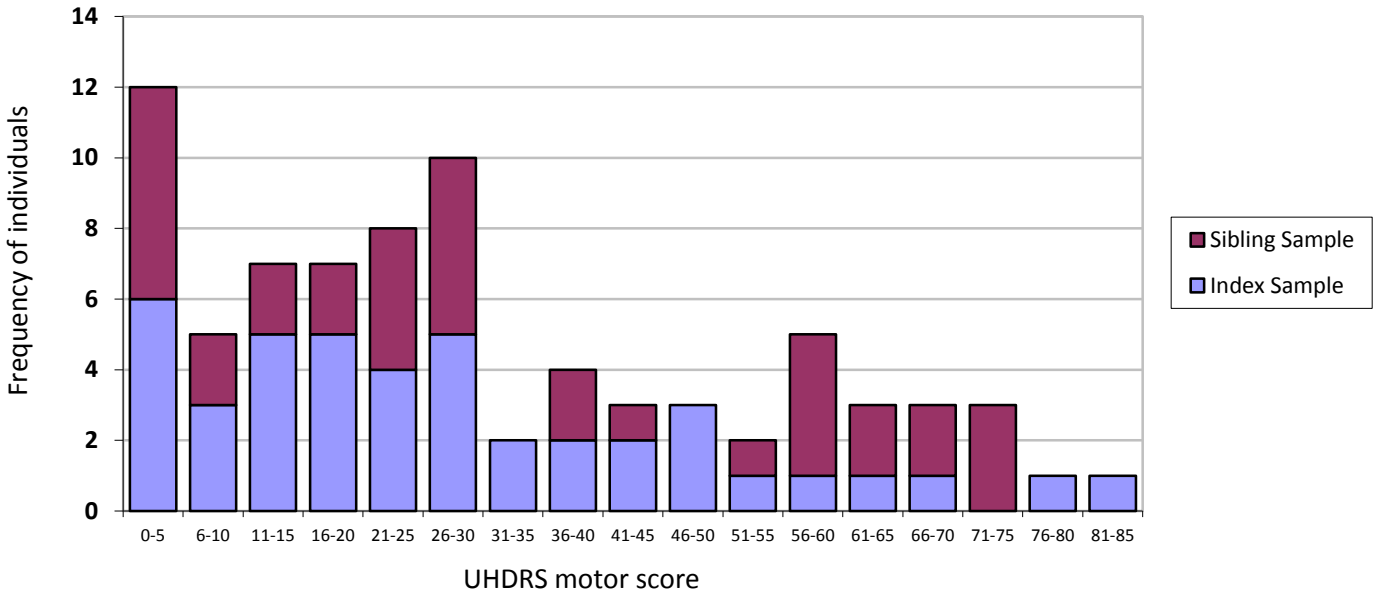



**Figure 3.6 Frequency distribution of the UHDRS motor scores for the index sample, N = 43 and sibling sample, N = 36.**

### 3.7.5 Cognitive scores

Complete UHDRS cognitive scores were obtained for 38 individuals in the index sample and 32 individuals in the sibling sample and are summarised in Table 3.14. In the index sample, one participant completed the Verbal Fluency test and Symbol Digit Modalities test but not the Stroop test and an additional participant completed the Verbal Fluency test and Stroop test but not the Symbol Digit Modalities test. Therefore, 40 participants completed the Verbal Fluency, 39 completed the Symbol Digit Modalities test and 39 individuals completed all 3 parts of the Stroop test. In the sibling sample, one participant completed the Verbal Fluency test and Symbol Digit Modalities test but not the Stroop test and an additional 2 participants completed the Verbal Fluency test and Stroop test but not the Symbol Digit Modalities test. Therefore, 35 participants completed the Verbal Fluency, 33 completed the Symbol Digit Modalities test and 34 individuals completed all 3 parts of the Stroop test.

For the index sample, the mean total score on the cognitive tests was 181.1. The lowest total score obtained was 78, which was by a 51 year old female in Stage 1 of the illness and the highest score of 348 was obtained by a newly symptomatic 39 year old male. The mean scores on the Verbal Fluency, Symbol Digit Modalities test and the Stroop colour naming, Stoop word reading and Stroop interference were 22.3, 27.9, 45.0, 57.7 and 24.8 respectively and are displayed in Figure 3.7. The total mean scores obtained on the cognitive tests were similar in males (186.7) and females (178.1).

The mean total score obtained on the cognitive tests by the sibling sample was 177.1. The lowest total score was 71, which was by a 61 year old male in Stage 3 of the illness and the highest score of 307 was obtained by a 43 year old pre-motor manifest female. The mean scores on the Verbal Fluency, Symbol Digit Modalities Test and the Stroop colour naming, Stroop word reading and Stroop interference were 17.1, 27.1, 44.0, 57.2 and 24.6 respectively and are displayed in Figure 3.7. The total mean scores obtained on the cognitive tests were slightly higher for females (179.7) than males (164.7).

**Table 3.14 UHDRS cognitive scores**

| **UHDRS Total Cognitive Scores** | **Descriptives** | | |
|---|---|---|---|
| **Index Sample** | **Total: N=38** | **Male: N = 13** | **Female: N = 25** |
| Mean (95% C.I.) | 181.1 (156.4-205.7) | 186.7 (141.1-232.3) | 178.1 (148.5-207.1) |
| Standard deviation | 77.5 | 83.9 | 75.54 |
| Range | 78-348 | 81-348 | 78-325 |
| | | | |
| **Sibling Sample** | **Total: N=32** | **Male: N = 11** | **Female: N = 21** |
| Mean (95% C.I.) | 174.6 (150.6-198.7) | 164.7 (123.5-205.9) | 179.7 (149.6-209.8) |
| Standard deviation | 69.4 | 69.7 | 70.4 |
| Range | 71-307 | 71-271 | 74-307 |

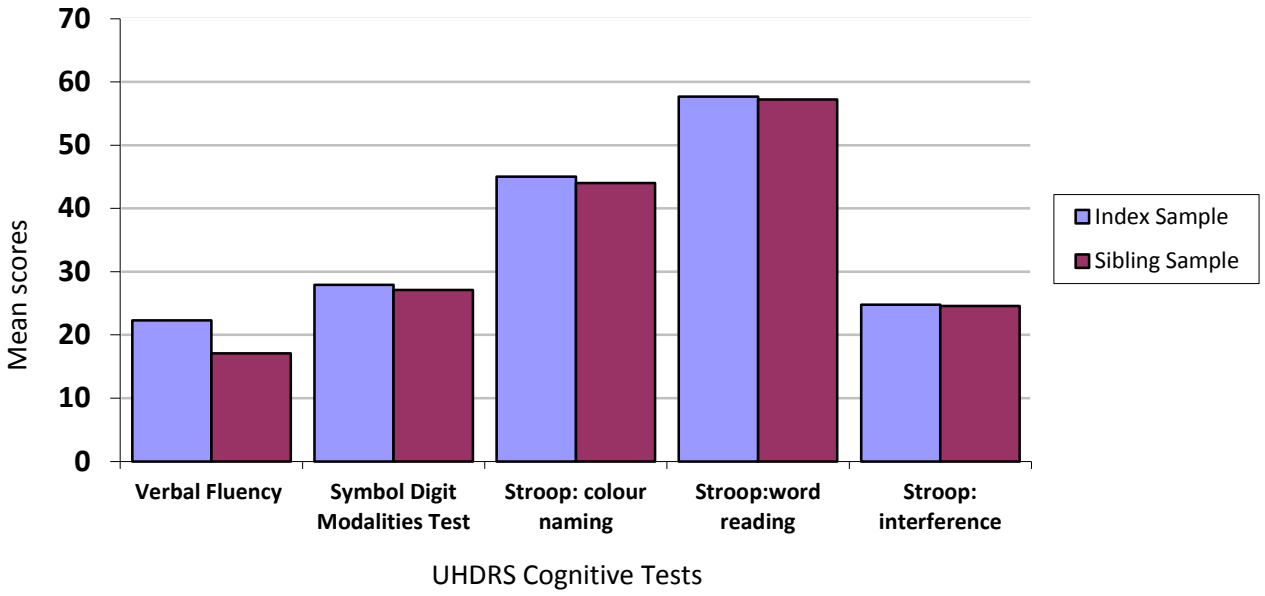



**Figure 3.7 Mean scores obtained on the individual cognitive tests for the index and sibling samples.**

Figure 3.8 displays the frequency distribution of the UHDRS cognitive scores for the 38 individuals in the index sample and 32 individuals in the sibling sample with complete data. In the index sample, the largest proportion of individuals (31.6%) achieved a total score of between 101 and 150. Four of the five individuals that obtained a total score in the highest range of 301-350 were either not yet symptomatic or had only recently been diagnosed where as in the lowest range (51-100) of scores, the majority of the individuals (80%) were in Stage 2 or 3 of the illness.

For the sibling sample, nine of the 32 individuals (28.1%) obtained a total cognitive score of between 151 and 200 and a further nine individuals (who were in Stages 2, 3 or 4 of the illness) only achieved a score of between 51 and 100. A pre-symptomatic female achieved a score in the highest range of 301-350.

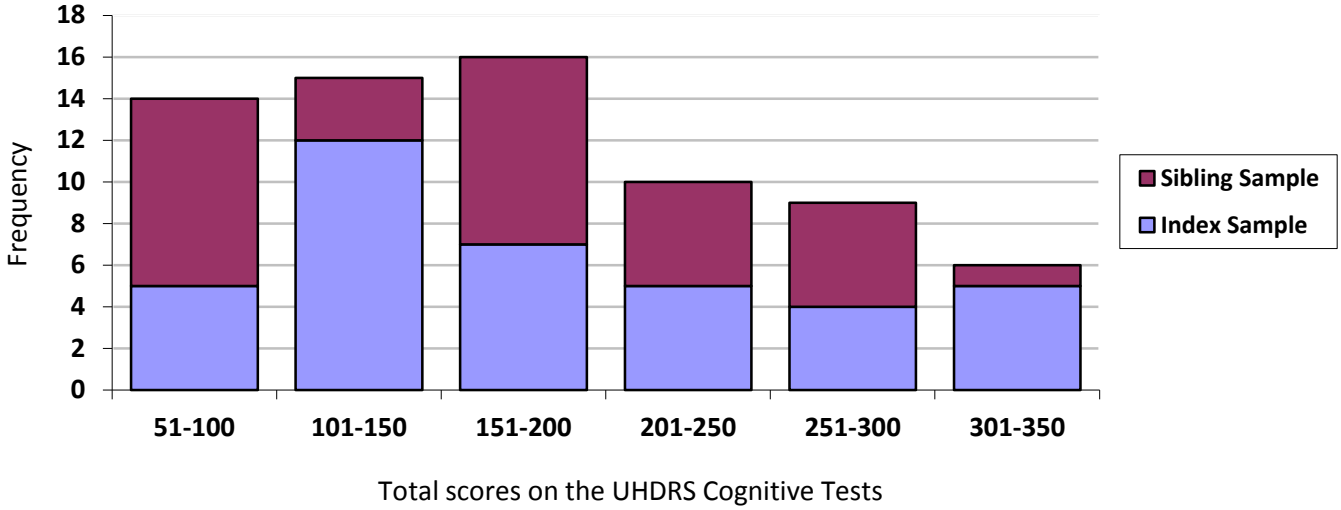



**Figure 3.8 Frequency distribution of the UHDRS cognitive scores for the 38 individuals in the index sample and 32 individuals in the sibling sample with complete data.**

### 3.7.6 Comorbid Physical Medical Conditions

Current comorbid physical medical conditions were reported for 26 of the 50 individuals in the index sample and 23 of the 46 individuals in the sibling sample and are summarised in Table 3.15. Individuals who had a current diagnosis of more than one illness in addition to HD, for example had a diagnosis of eczema and an underactive thyroid, are included in more than one comorbid medical condition category. For the index sample, there were 14 individuals with one comorbid medical condition, six individuals with two comorbid medical conditions, five individuals with three comorbid medical conditions and 1 person had four comorbid medical conditions. Nine individuals had a current diagnosis of hypertension, which was the most frequently reported comorbid condition. The other conditions which were reported by more than 3 individuals include: asthma (5 individuals), arthritis (4 individuals) and bladder problems (4 individuals).

**Table 3.15 Frequency of comorbid medical conditions**

| Comorbid Medical Conditions | Index Sample N=50 | | Sibling Sample N=40 | |
|---|---|---|---|---|
| | N | % | N | % |
| Hypertension | 9 | 18.0 | 2 | 5.0 |
| Asthma | 5 | 10.0 | 4 | 10.0 |
| Arthritis | 4 | 8.0 | 3 | 7.5 |
| Bladder problems | 4 | 8.0 | 1 | 2.5 |
| High cholesterol | 2 | 4.0 | 1 | 2.5 |
| Fibromyalgia | 1 | 2.0 | 2 | 5.0 |
| Learning Disability | 1 | 2.0 | 2 | 5.0 |
| Underactive thyroid | 2 | 4.0 | 1 | 2.5 |
| Cardiac problems | 2 | 4.0 | 1 | 2.5 |
| Hypotension | 0 | 0.0 | 2 | 5.0 |
| Eczema | 1 | 2.0 | 1 | 2.5 |
| Type II diabetes | 2 | 4.0 | 0 | 0.0 |
| Circulatory Problems | 1 | 2.0 | 1 | 2.5 |
| Myalgic Encephalitis | 0 | 0.0 | 2 | 5.0 |
| Stroke | 1 | 2.0 | 1 | 2.5 |
| Hearing Problems | 1 | 2.0 | 1 | 2.5 |
| Psoriasis | 1 | 2.0 | 1 | 2.5 |
| Spondylosis | 2 | 4.0 | 0 | 0.0 |
| Migraines | 0 | 0.0 | 1 | 2.5 |
| Prolapsed disc | 1 | 2.0 | 0 | 0.0 |
| Childhood Epilepsy | 0 | 0.0 | 1 | 2.5 |
| Poor Liver Function | 1 | 2.0 | 0 | 0.0 |
| Crohn's Disease | 1 | 2.0 | 0 | 0.0 |
| Polycystic Ovary Syndrome | 1 | 2.0 | 0 | 0.0 |
| Anaemia | 0 | 0.0 | 1 | 2.5 |
| Sciatica | 0 | 0.0 | 1 | 2.5 |
| Brain tumour | 1 | 2.0 | 0 | 0.0 |
| Scoliosis | 1 | 2.0 | 0 | 0.0 |
| Non-Epileptic Attack Disorder | 1 | 2.0 | 0 | 0.0 |

Note: Individuals are included in the table more than once in the instance when they have more than one comorbid medical condition.

For the sibling sample, there were 15 individuals with one comorbid medical condition, seven individuals with two comorbid medical conditions and one individual with three comorbid medical conditions. Four individuals had a current diagnosis of asthma, which was the most frequently reported comorbid condition. The other conditions which were reported by 2 or more individuals include: arthritis (3 individuals), hypertension (2

individuals), fibromyalgia (2 individuals), myalgic encephalitis (2 individuals); learning disability (2 individuals) and hypotension (2 individuals).

### 3.7.7 Medication

The majority of participants were taking medication for their HD symptoms (61% of the index sample and 60% of the sibling sample). Participants were also taking medication for their comorbid physical medical conditions, however, this is not reported here.

**Table 3.16 Symptomatic HD medication use in the index and sibling samples**

| **Medication class:** Medication name | Index sample N=50 N (%) | Sibling sample N=40 N (%) | Typical indications |
|---|---|---|---|
| **Anti-dyskinetic:** | | | |
| Sulpiride | 0 (0.0) | 7 (17.5) | Chorea/dyskinesia/irritability |
| Risperidone | 3 (6.0) | 3 (7.5) | Chorea/dyskinesia/aggression/psychosis |
| Olanzapine | 3 (6.0) | 1 (2.5) | Chorea/dyskinesia/aggression/psychosis |
| Amantadine hydrochloride | 0 (0.0) | 2 (5.0) | Chorea/dyskinesia |
| Tetrabenazine | 1 (2.0) | 1 (2.5) | Chorea/dyskinesia |
| **Anti-depressant:** | | | |
| Citalopram | 10 (20.0) | 7 (17.5) | Depression/irritability |
| Fluoxetine | 3 (6.0) | 1 (2.5) | Depression/irritability |
| Paroxetine | 1 (2.0) | 0 (0.0) | Depression/irritability |
| Mirtazepine | 2 (4.0) | 1 (2.5) | Depression/insomnia |
| Venlafaxine | 1 (2.0) | 3 (7.5) | Depression/anxiety |
| Carbamazepine | 1 (2.0) | 2 (5.0) | Depression/irritability |
| Amitriptyline | 1 (2.0) | 0 (0.0) | Depression/insomnia |
| Sodium valproate | 2 (4.0) | 3 (7.5) | Depression/irritability |
| **Anxiolytics:** | | | |
| Diazepam | 0 (0.0) | 1 (2.5) | Anxiety |
| Clonazepam | 0 (0.0) | 1 (2.5) | Anxiety |
| Hydroxyzine | 0 (0.0) | 1 (2.5) | Anxiety/insomnia |
| **Hypnotics/Sedatives:** | | | |
| Zopiclone | 1 (2.0) | 3 (7.5) | Insomnia |
| Temazepam | 2 (4.0) | 1 (2.5) | Insomnia |
| **Nutritional supplements:** | | | |
| Vitamins/Folic acid/Omega 3 triglycerides/Fortisip | 6 (12.0) | 3 (7.5) | |

Table 3.16 lists for both samples, the most frequently prescribed symptomatic HD medications by their respective medication class according to the Anatomical Therapeutic

Chemical (ATC) Classification System (WHO, 1976). The most commonly prescribed medication class in the index sample was anti-depressants (42.0%) followed by anti-dyskinetics (14.0%), nutritional supplements (12.0%) and hypnotics/sedatives (6.0%). In the sibling sample, anti-depressants were also the medication class most frequently prescribed (42.5%) followed by anti-dyskinetics (35.0%), hypnotics/sedatives (10.0%), anxiolytics (7.5%) and nutritional supplements (7.5%).

The following chapter (Chapter 4) describes the psychiatric phenotype in the index and sibling samples and will compare the depression phenotype in HD and individuals with unipolar depression without HD.

# CHAPTER 4: DESCRIPTION OF THE PSYCHIATRIC PHENOTYPE IN HD WITH A FOCUS ON THE DEPRESSION PHENOTYPE.

This chapter is concerned with describing the psychiatric phenotype in HD. It will detail the methodology and statistical analysis specific to this chapter before describing the psychiatric presentation of the index and sibling samples including: lifetime DSM-IV diagnoses, lifetime suicidal behaviour and ratings of other key psychiatric clinical variables. The chapter will then focus on depression in HD and will compare the depression phenotype in the HD index sample with a unipolar depression sample without HD. A discussion of the results will then follow.

## *4.1 Introduction*

It is well established that people with HD frequently report significant behavioural and psychiatric symptoms as discussed in detail in Chapter 2. The most frequently reported neuropsychiatric symptoms in HD are depression, irritability, apathy and anxiety, each with prevalence rates between 33% and 76% (van Duijn et al., 2007). Reported prevalence rates vary greatly as a result of the use of different assessment methods with varying definitions. The main aim of this chapter is to describe the lifetime ever presence of operational psychiatric disorders according to DSM-IV (American Psychiatric Association, 2000) in the 50 individuals with HD that comprise the index sample and the 40 individuals with HD of the sibling sample. In addition, although it has been known since George Huntington's original description of HD that depression is a particularly common problem in HD, very little is known about the presentation of depression in HD and whether the phenotype exhibited is similar/dissimilar to that of individuals in the general population who have depression.

Therefore, in order to address this issue, the illness course data obtained for those HD patients with depression will be compared with data obtained from a large sample of individuals without HD recruited to a mood disorders research study.

## *4.2 Methods*

The methods and clinical features of the index and sibling samples were described in Chapter 3. In addition to these samples of HD patients, a further sample was required consisting of individuals without HD but with a DSM-IV diagnosis of unipolar depression. This was to enable comparisons to be made between the presentation of depression in HD patients and depression in individuals without HD. This sample is described in section 4.5.1.

## *4.3 Statistical analysis*

All statistical tests were performed using the statistical package SPSS version 19.0 (IBM Corp., 2010) and all statistical tests were considered significant at the $p<0.05$ level (two tailed). Normality of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests and the significance of these results were used to inform whether parametric or non-parametric tests were subsequently performed.

*Means and medians:*

Means were calculated for the variables that were normally distributed and where the data were not normally distributed, medians were used.

*Proportions:*

For all proportions calculated, 95% confidence intervals are also reported.

*Categorical data:*

Relationships between categorical variables were calculated using Pearson's chi square tests. In the instances where the expected cell count was less than 5, p-values were calculated using Fisher's exact test.

*Continuous data:*

Parametric data: the independent samples *t*-test was used to compare differences between two groups.

Non-parametric data: comparisons between two groups were made using the Mann-Whitney U test.

## *4.4 Results*

### 4.4.1 Lifetime Psychiatric Features in the HD Index and Sibling Samples

#### 4.4.1.1 Main Best-Estimate Lifetime DSM-IV Diagnoses

Table 4.1 summarises the presence/absence of any lifetime DSM-IV diagnosis for the index and sibling samples. In the index sample, 33 individuals (66%) had a lifetime DSM-IV diagnosis. For one individual (classified as uncertain), it was suggested from the interview and the medical notes that there was a history of psychiatric illness, however, there was not enough information to determine a definite lifetime DSM-IV diagnosis. There was no significant difference between the proportion of females (69.7%) and males (58.8%) that had a lifetime DSM-IV diagnosis ($\chi^2$= 0.591, df = 1, p=0.44).

Twenty-six individuals (65%) in the sibling sample had a lifetime DSM-IV diagnosis and a further three individuals were classified as uncertain, owing to a lack of information to

enable a definite lifetime DSM-IV diagnosis. A significantly higher proportion of females (79.2%) than males (43.8%, 95%) had a lifetime DSM-IV diagnosis ($\chi^2$= 5.293, df = 1, p=0.021).

**Table 4.1 Summary of the presence/absence of any lifetime DSM-IV Diagnoses**

| | **Total** | **Male** | **Female** |
|---|---|---|---|
| | **N (%)**<br>95% CI | **N (%)**<br>95% CI | N (**%**)<br>95% CI |
| **Index sample** | **N = 50** | **N = 17** | **N = 33** |
| Any DSM-IV Disorder | **33 (66.0)**<br>52.9-79.1 | **10 (58.8)**<br>35.4-82.2 | **23 (69.7)**<br>54.0–85.4 |
| Uncertain | **1 (2.0)**<br>0.0-5.9 | **0 (0.0)**<br>- | **1 (3.0)**<br>0.0-8.8 |
| No DSM-IV Disorder | **16 (32.0)**<br>19.1-44.9 | **7 (41.2)**<br>17.8-64.6 | **9 (27.3)**<br>12.1-42.5 |
| **Sibling sample** | **N = 40** | **N = 16** | **N = 24** |
| Any DSM-IV Disorder | **26 (65.0)**<br>50.2-79.8 | **7 (43.8)**<br>19.4-68.1 | **19 (79.2)**<br>63.0-95.4 |
| Uncertain | **3 (7.5)**<br>0.0-15.7 | **1 (6.3)**<br>0.0-18.1 | **2 (8.3)**<br>0.0-19.3 |
| No DSM-IV Disorder | **11 (27.5)**<br>13.7-41.3 | **8 (50.0)**<br>25.5-74.5 | **3 (12.5)**<br>0.0-25.7 |

CI; Confidence Interval

The frequencies of the specific main best-estimate lifetime DSM-IV diagnoses for the index and sibling samples are summarised in Table 4.2. For both the index and sibling samples, depressive disorders were the most frequent main lifetime DSM-IV diagnoses (48% of the index sample and 57.5% of the sibling sample), followed by anxiety disorders (14% of the index sample and 7.5% of the sibling sample). There were no significant differences between the proportion of males and females with a specific main best-estimate lifetime DSM-IV diagnosis for both samples.

**Table 4.2 Main Best-Estimate Lifetime DSM-IV Diagnoses**

| | **Index sample** | | | **Sibling sample** | | |
|---|---|---|---|---|---|---|
| | **Total N = 50** | **Male N=17** | **Female N=33** | **Total N = 40** | **Male N = 16** | **Female N =24** |
| **DSM-IV Diagnosis** | **N (%)** 95% CI | **N (%)** 95% CI | **N (%)** 95% CI | **N (%)** 95% CI | **N (%)** 95% CI | **N (%)** 95% CI |
| Major Depressive Disorder | **19 (38.0)** 24.6-61.5 | **5 (29.4)** 7.7-51.1 | **14 (42.4)** 25.5-59.3 | **16 (40.0)** 24.8-55.2 | **5 (31.3)** 8.6-54.0 | **11 (45.8)** 25.9-65.7 |
| *Recurrent Episodes* | ***12 (24.0)*** 12.2-35.8 | ***4 (23.5)*** 3.3-43.7 | ***8 (24.2)*** 9.6-38.8 | ***9 (22.5)*** 9.6-35.4 | ***2 (12.5)*** 0.0-28.7 | ***7 (29.2)*** 11.0-47.4 |
| *Single Episode* | ***7 (14.0)*** 4.4-23.6 | ***1 (5.9)*** 0.0-17.1 | ***6 (18.2)*** 5.0-31.4 | ***7 (17.5)*** 5.7-29.3 | ***3 (18.8)*** 0.0-37.9 | ***4 (16.7)*** 1.8-31.6 |
| Depression NOS | **5 (10.0)** 1.7-18.3 | **2 (11.8)** 0.0-27.1 | **3 (9.1)** 0.0-18.9 | **7 (17.5)** 5.7-29.3 | **2 (12.5)** 0.0-28.7 | **5 (20.8)** 4.6-37.0 |
| Panic Disorder | **2 (4.0)** 0.0-9.4 | **0 (0.0)** - | **2 (6.1)** 0.0-14.3 | **1 (2.5)** 0.0-7.3 | **0 (0.0)** - | **1 (4.2)** 0.0-12.2 |
| *With Agoraphobia* | ***0 (0.0)*** - | ***0 (0.0)*** - | ***0 (0.0)*** - | ***1 (2.5)*** 0.0-7.3 | ***0 (0.0)*** - | ***1 (4.2)*** 0.0-12.2 |
| *Without Agoraphobia* | ***2 (4.0)*** 0.0-9.4 | ***0 (0.0)*** - | ***2 (6.1)*** 0.0-14.3 | ***0 (0.0)*** - | ***0 (0.0)*** - | ***0 (0.0)*** - |
| Anxiety Disorder NOS | **5 (10.0)** 1.7-18.3 | **2 (11.8)** 0.0-27.1 | **3 (9.1)** 0.0-18.9 | **2 (5.0)** 0.0-11.8 | **0 (0.0)** - | **2 (8.3)** 0.0-19.3 |
| Alcohol Abuse | **1 (2.0)** 0.0-9.4 | **1 (5.9)** 0.0-17.1 | **0 (0.0)** 0.0-18.9 | **0 (0.0)** - | **0 (0.0)** - | **0 (0.0)** - |
| Psychotic Disorder NOS | **1 (2.0)** 0.0-9.4 | **0 (0.0)** - | **1 (3.0)** 0.0-8.8 | **0 (0.0)** - | **0 (0.0)** - | **0 (0.0)** - |
| Unknown | **1 (2.0)** 0.0-9.4 | **0 (0.0)** - | **1 (3.0)** 0.0-8.8 | **3 (7.5)** 0.0-15.7 | **1 (6.3)** 0.0-18.2 | **2 (8.3)** 0.0-19.3 |
| Unaffected | **16 (32.0)** 19.1-44.9 | **7 (41.2)** 17.8-64.6 | **9 (27.3)** 12.1-42.5 | **11 (27.5)** 13.7-41.3 | **8 (50.0)** 25.5-74.5 | **3 (12.5)** 0.0-25.7 |

NOS; Not Otherwise Specified, CI; Confidence Interval

#### 4.4.1.2 Co-morbid DSM-IV Diagnoses

Sixteen of the 33 individuals (48.5%) in the index sample who had a psychiatric diagnosis and eleven of the 26 individuals (42.3%) in the sibling sample, had more than one lifetime DSM-IV diagnosis. Table 4.3 summarises the co-morbid diagnoses for these participants. In the index sample, all 16 individuals had a comorbid depressive and anxiety disorder with two of these individuals also having a third lifetime DSM-IV diagnosis of alcohol abuse. In the sibling sample, of the eleven individuals with a co-morbid diagnosis, nine individuals had a DSM-IV

diagnosis of a depressive and anxiety disorder (one of whom also had a third lifetime DSM-IV diagnosis of alcohol abuse) and two individuals had a history of a depressive disorder and alcohol abuse.

**Table 4.3 Co-morbid DSM-IV Diagnoses**

| Main DSM-IV Diagnosis | Second DSM-IV Diagnosis | Third DSM-IV Diagnosis | Number of Cases |
|---|---|---|---|
| **Index sample** | | | |
| Major Depressive Disorder (R) | Panic Disorder with agoraphobia | N/A | 3 |
| Major Depressive Disorder (R) | Panic Disorder with agoraphobia | Alcohol Abuse | 1 |
| Major Depressive Disorder (R) | Panic Disorder without agoraphobia | N/A | 2 |
| Major Depressive Disorder (R) | Anxiety Disorder NOS | N/A | 2 |
| Major Depressive Disorder (R) | Anxiety Disorder NOS | Alcohol Abuse | 1 |
| Major Depressive Disorder (S) | Panic Disorder with agoraphobia | N/A | 1 |
| Major Depressive Disorder (S) | Panic Disorder without agoraphobia | N/A | 1 |
| Depression NOS | Panic Disorder with agoraphobia | N/A | 1 |
| Panic Disorder without agoraphobia | Major Depressive Disorder (S) | N/A | 2 |
| Anxiety Disorder NOS | Depression NOS | N/A | 2 |
| | | | |
| **Sibling sample** | | | |
| Major Depressive Disorder (R) | Panic Disorder with agoraphobia | N/A | 1 |
| Major Depressive Disorder (R) | Panic Disorder without agoraphobia | N/A | 2 |
| Major Depressive Disorder (R) | Panic Disorder without agoraphobia | Social Phobia | 1 |
| Major Depressive Disorder (R) | Alcohol Abuse | N/A | 2 |
| Major Depressive Disorder (S) | Agoraphobia without panic disorder | Alcohol Abuse | 1 |
| Major Depressive Disorder (S) | Anxiety Disorder NOS | N/A | 1 |
| Panic Disorder with agoraphobia | Major Depressive Disorder (S) | N/A | 1 |
| Anxiety Disorder NOS | Depression NOS | N/A | 2 |

R; recurrent episodes, S; single episode, NOS; not otherwise specified

Table 4.4 includes the co-morbid diagnoses to give an overall frequency of the number of individuals with a specific lifetime DSM-IV diagnosis for both the index and sibling samples. Table 4.5 provides a summary of this data and this is also represented graphically in Figure 4.1. In the index sample, 28 of the 50 (56%) participants had a lifetime diagnosis of a depressive disorder, 19 (38%) individuals were diagnosed as having a history of an anxiety disorder, 3 (6%) individuals had a diagnosis of alcohol abuse and a further individual (2%) had a diagnosis of psychotic disorder NOS. There were no significant differences between

the proportion of males and females with a particular DSM-IV lifetime diagnosis and although there were five times as many women with a history of panic disorder as men, this did not reach statistical significance (Fisher's, p=0.073). There were also no significant differences between the proportion of females and males with any mood or anxiety disorder.

**Table 4.4 All Best-Estimate Lifetime DSM-IV Diagnoses**

| | **Index Sample** | | | **Sibling Sample** | | |
|---|---|---|---|---|---|---|
| | **Total N = 50** | **Male N = 17** | **Female N = 33** | **Total N = 40** | **Male N = 16** | **Female N = 24** |
| **DSM-IV Diagnosis** | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** |
| Major Depressive Disorder | **21 (42.0)** 28.3-55.7 | **5 (29.4)** 7.7-51.1 | **16 (48.5)** 31.5-65.6 | **17 (42.5)** 27.2-57.8 | **5 (31.3)** 8.6-54.0 | **12 (50.0)** 30.0-70.0 |
| *Recurrent Episodes* | ***12 (24.0)*** 12.2-35.8 | ***4 (23.5)*** 3.3-43.7 | ***8 (24.2)*** 9.6-38.8 | ***9 (22.5)*** 9.6-35.4 | ***2 (12.5)*** 0.0-28.7 | ***7 (29.2)*** 11.0-47.4 |
| *Single Episode* | ***9 (18.0)*** 7.4-28.7 | ***1 (5.9)*** 0.0-17.1 | ***8 (24.2)*** 9.6-38.8 | ***8 (20.0)*** 7.6-32.4 | ***3 (18.8)*** 0.0-37.9 | ***5 (20.8)*** *4.6-37.0* |
| Depression NOS | **7 (14.0)** 4.4-23.6 | **3 (17.6)** 0.0-35.7 | **4 (12.1)** 1.0-23.2 | **9 (22.5)** 9.6-35.4 | **2 (12.5)** 0.0-28.7 | **7 (29.2)** 11.0-47.4 |
| Panic Disorder | **11 (22.0)** 10.5-33.5 | **1 (5.9)** 0.0-17.1 | **10 (30.3)** 14.6-46.0 | **5 (12.5)** 2.3-22.8 | **1 (6.3)** 0.0-18.2 | **4 (16.7)** 1.8-31.6 |
| *With Agoraphobia* | ***6 (12.0)*** 3.0-21.0 | ***1 (5.9)*** 0.0-17.1 | ***5 (15.2)*** 3.0-27.5 | ***2 (5.0)*** 0.0-11.8 | ***0 (0.0)*** - | ***2 (8.3)*** 0.0-19.3 |
| *Without Agoraphobia* | ***5 (10.0)*** 1.7-18.3 | ***0 (0.0)*** - | ***5 (15.2)*** 3.0-27.5 | ***3 (7.5)*** 0.0-15.7 | ***1 (6.3)*** 0.0-18.2 | ***2 (8.3)*** 0.0-19.3 |
| Agoraphobia without panic disorder | **0 (0.0)** - | **0 (0.0)** - | **0 (0.0)** - | **1 (2.5)** 0.0-7.3 | **0 (0.0)** - | **1 (4.2)** 0.0-12.2 |
| Social Phobia | **0 (0.0)** - | **0 (0.0)** - | **0 (0.0)** - | **1 (2.5)** 0.0-7.3 | **1 (6.3)** 0.0-18.2 | **0 (0.0)** - |
| Anxiety Disorder NOS | **8 (16.0)** 5.8-26.2 | **4 (23.5)** 3.3-43.7 | **4 (12.1)** 1.0-23.2 | **3 (7.5)** 0.0-15.7 | **0 (0.0)** - | **3 (12.5)** 0.0-25.7 |
| Alcohol Abuse | **3 (6.0)** 0-12.6 | **2 (11.8)** 0.0-27.1 | **1 (3.0)** 0.0-8.8 | **3 (7.5)** 0.0-15.7 | **0 (0.0)** - | **3 (12.5)** 0.0-25.7 |
| Psychotic Disorder NOS | **1 (2.0)** 0.0-5.9 | **0 (0.0)** - | **1 (3.0)** 0.0-8.8 | **0 (0.0)** - | **0 (0.0)** - | **0 (0.0)** - |
| Unknown | **1 (2.0)** 0.0-5.9 | **0 (0.0)** - | **1 (3.0)** 0.0-8.8 | **3 (7.5)** 0.0-15.7 | **1 (6.3)** 0.0-18.2 | **2 (8.3)** 0.0-19.3 |
| Unaffected | **16 (32.0)** 19.1-44.9 | **7 (41.2)** 17.8-64.6 | **9 (27.3)** 12.1-42.5 | **11 (27.5)** 13.7-41.3 | **8 (50.0)** 25.5-74.5 | **3 (12.5)** 0.0-25.7 |

CI; Confidence Interval

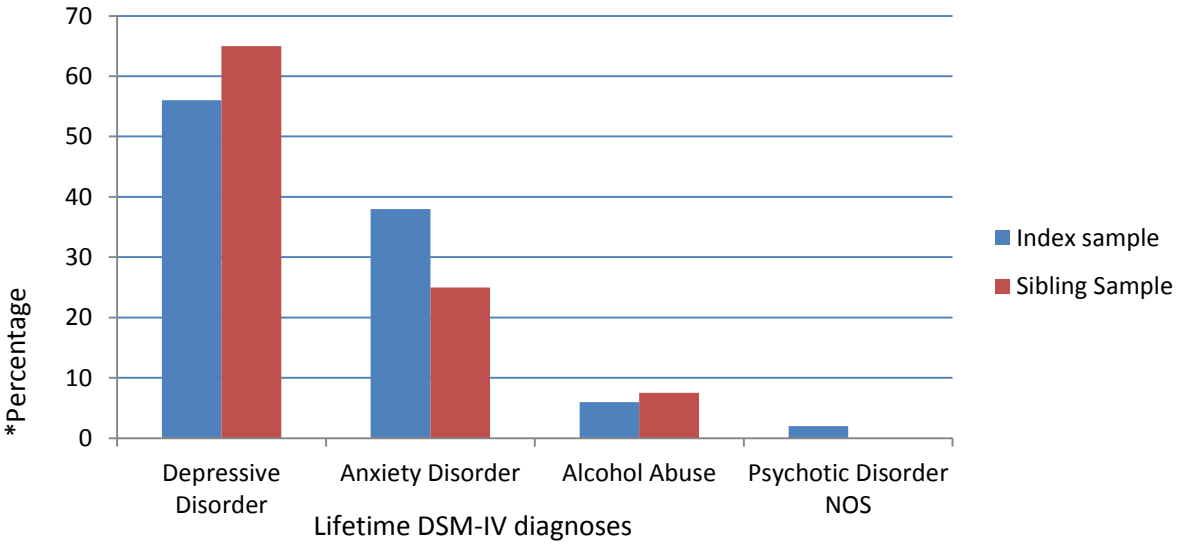
Where individuals have more than one lifetime DSM-IV diagnosis, they are included in more than one category

In the sibling sample, 26 of the 40 (65%) individuals had a lifetime diagnosis of a depressive disorder, 9 (22.5%) individuals had a diagnosis of an anxiety disorder and 3 (7.5%) individuals were diagnosed as having a history of alcohol abuse. There were no significant differences between the proportion of males and females with a specific DSM-IV lifetime diagnosis, however, women (79.2%) were significantly more likely than men (43.8%) to have a lifetime DSM-IV diagnosis of any mood disorder ($\chi^2$= 5.293, df = 1, p=0.021).

**Table 4.5 Summary of all Lifetime DSM-IV Diagnoses**

| | **Index sample** | | | **Sibling sample** | | |
|---|---|---|---|---|---|---|
| | **Total N = 50** | **Male N = 17** | **Female N = 33** | **Total N = 40** | **Male N = 16** | **Female N = 24** |
| | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** |
| Any DSM-IV Mood Disorder | **28 (56.0)** 42.2-69.8 | **8 (47.1)** 23.4-70.8 | **20 (60.6)** 43.9-77.3 | **26 (65.0)** 50.2-79.8 | **7 (43.8)** 19.5-68.1 | **19 (79.2)** 63.0-95.4 |
| Any DSM-IV Anxiety Disorder | **19 (38.0)** 25.6-51.4 | **5 (29.4)** 7.7-51.1 | **14 (42.4)** 25.5-59.3 | **10 (25.0)** 11.6-38.4 | **2 (12.5)** 0.0-28.7 | **8 (33.3)** 14.4-52.2 |
| Alcohol Abuse | **3 (6.0)** 0.0-12.6 | **2 (11.8)** 0.0-27.1 | **1 (3.0)** 0.0-8.8 | **3 (7.5)** 0.0-15.7 | **0 (0.0)** - | **3 (12.5)** 0.0-25.7 |
| Psychotic Disorder NOS | **1 (2.0)** 0.0-5.9 | **0 (0.0)** - | **1 (3.0)** 0.0-8.8 | **0 (0.0)** - | **0 (0.0)** - | **0 (0.0)** - |

NOS; not otherwise specified
Where individuals have more than one lifetime DSM-IV diagnosis, they are included in more than one category




*Where individuals have more than one lifetime DSM-IV diagnosis, they are included in more than one category

**Figure 4.1 The proportion of individuals in the index and sibling samples with a lifetime DSM-IV diagnosis**

#### 4.4.1.3 History of Suicidal Thoughts and Suicide Attempts

The frequencies of individuals with a history of suicidal thoughts and suicide attempts are summarised in Table 4.6 for both samples and the percentages are illustrated in Fig 4.2. 'Suicidal thoughts' includes those individuals with a history of tedium vitae, suicidal ideation or suicide attempt and 'suicide attempts' includes individuals who had made at least one suicide attempt.

In the index sample, 18 individuals (36%) had experienced suicidal thoughts and of these, eight individuals (16%) had made a suicide attempt at some point during their lives. For one individual, there was a suggestion of a history of suicidal thoughts but there was not enough information to be certain and therefore this individual was classsified as unsure. There was no significant difference between the percentage of males (11.8%) and females (18.2%) who had made at least one attempt at suicide (Fisher's, p =0.70) or who had a history of suicidal thoughts (males: 29.4%; females: 39.4%, $\chi^2$= 0.485, df = 1, p=0.49).

In the sibling sample, 16 individuals (40%) had experienced suicidal thoughts and of these, five individuals (12.5%) had made a suicide attempt at some point during their lives. Two individuals (5%) were classified as unsure due to a suggestion of a history of suicidal thoughts but not enough information to be certain. There was no significant difference between the percentage of males (6.3%) and females (16.7%) who had made at least one attempt at suicide (Fisher's, p =0.63) or who had a history of suicidal thoughts (males: 25%; females: 50%, $\chi^2$= 2.5, df = 1, p=0.11).

**Table 4.6 History of Suicidal Thoughts and Suicide Attempts**

| | Index Sample | | | Sibling Sample | | |
|---|---|---|---|---|---|---|
| | **Total N = 50** | **Male N = 17** | **Female N = 33** | **Total N = 40** | **Male N = 16** | **Female N = 24** |
| | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** | **N (%) 95% CI** |
| Suicide attempt(s) | **8 (16.0)** 5.8-26.2 | **2 (11.8)** 0.0-27.1 | **6 (18.2)** 5.0-31.4 | **5 (12.5)** 2.3-27.8 | **1 (6.3)** 0.0-18.2 | **4 (16.7)** 1.8-31.6 |
| Suicidal thoughts | **18 (36.0)** 22.7-49.3 | **5 (29.4)** 7.7-51.1 | **13 (39.4)** 22.7-56.1 | **16 (40.0)** 24.8-55.2 | **4 (25.0)** 3.8-46.2 | **12 (50.0)** 30.0-70.0 |
| Unknown | **1 (2.0)** 0.0-5.9 | **0 (0.0)** - | **1 (3.0)** 0.0-8.8 | **2 (5.0)** 0.0-11.8 | **1 (6.3)** 0.0-18.2 | **1 (4.2)** 0.0-12.2 |
| None | **31 (62.0)** 48.6-75.5 | **12 (70.6)** 48.9-92.3 | **19 (57.6)** 40.7-74.5 | **22 (55.0)** 39.6-70.4 | **11 (68.8)** 46.1-91.5 | **11 (45.8)** 25.9-65.7 |

CI; Confidence Interval

Individuals who had made an attempt at suicide are also included in the suicidal thoughts category

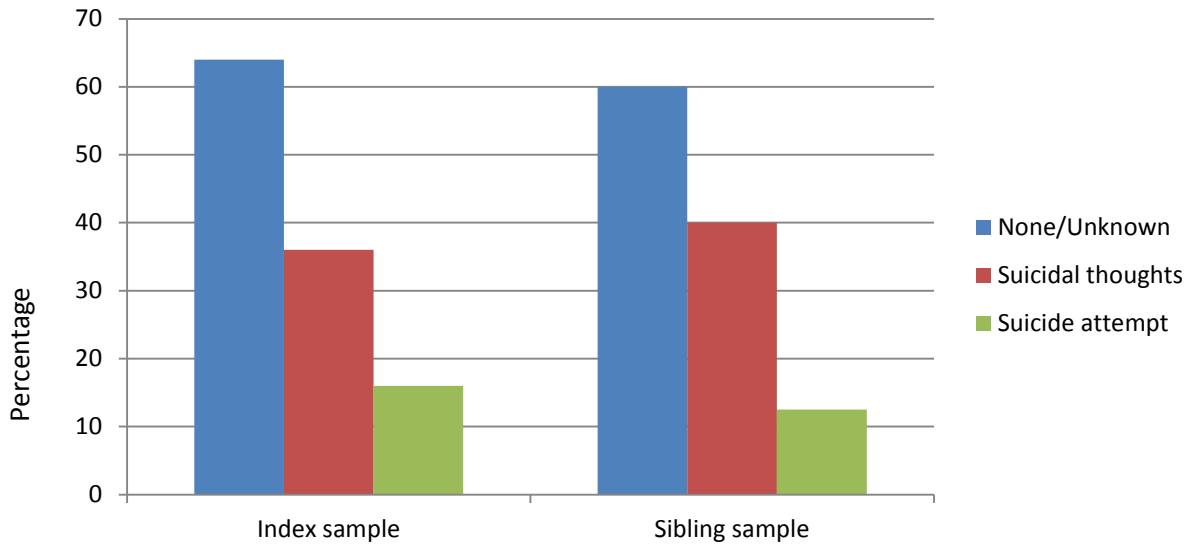



**Figure 4.2 Proportion of individuals in the index and sibling samples with a history of suicidal thoughts and suicide attempts.**

### 4.4.2 Age at Onset of Psychiatric Illness

Ratings for the age of onset of psychiatric illness were made for the 33 individuals in the index sample and the 26 individuals in the sibling sample who had a lifetime diagnosis of any DSM-IV psychiatric disorder. For one individual in the sibling sample, the age of onset was

not known as the individual could not recall at which age her psychiatric symptoms started and the medical notes simply stated in an entry when she was 41 years old that there was a long history of depression. Therefore, Figure 4.3 displays the median age at onset for all lifetime DSM-IV diagnoses for 33 individuals in the index sample and 25 individuals in the sibling sample. For those individuals with more than one lifetime DSM-IV diagnosis, their age of onset is included for their main DSM-IV diagnosis as well as subsequent diagnoses.

For the index sample, the median age at onset for any psychiatric symptom was 41 years and ranged from 13 to 55 years. The median ages at onset for individuals with a DSM-IV diagnosis of any depressive disorder, any anxiety disorder and for the one individual with psychotic disorder NOS were similar at 42 years, 41 years and 39 years respectively. The median age at onset for the three individuals with a DSM-IV diagnosis of alcohol abuse was lower at 29 years.

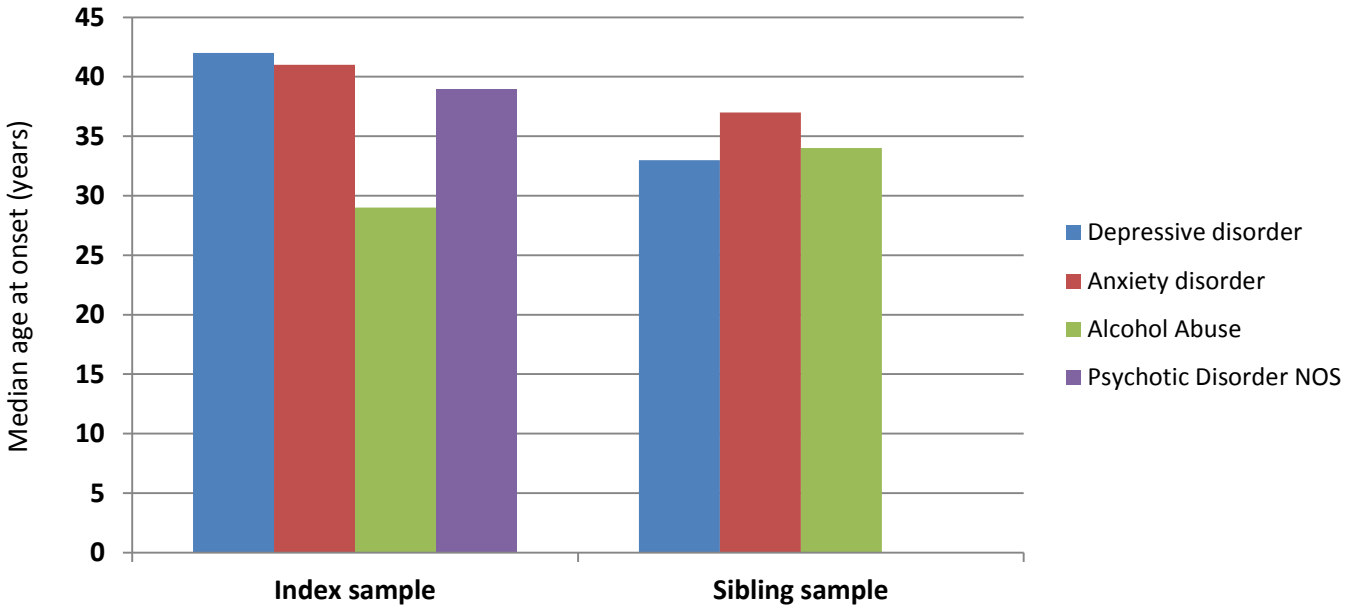



**Figure 4.3 Median age at onset for DSM-IV lifetime diagnoses for 33 individuals in the index sample and 25 individuals in the sibling sample.**

For the sibling sample, the median age at onset for any psychiatric symptom was 34.5 years and ranged from 11 to 58 years. The median ages at onset were similar for all individuals with a lifetime DSM-IV diagnosis of any depressive disorder (33 years), any anxiety disorder (37 years) and alcohol abuse (34 years).

#### 4.4.2.1 Relationship between age of onset of psychiatric illness and age of onset of HD

Table 4.7 summarises the difference in years between the age of onset of psychiatric illness and the age of onset of HD (defined as motor onset) for the index sample. Only individuals with a clinical diagnosis of HD were included in the sample. The median age of onset for the 25 individuals with any depressive disorder was one year prior to the age of HD onset. For the 18 individuals with any anxiety disorder, the median age of onset was 6 months prior to HD onset and for the 2 individuals with a diagnosis of alcohol abuse who were HD symptomatic, the median age of psychiatric onset was 10 years prior to the age of HD onset. The pie charts in Figure 4.4 demonstrate that half or more of the individuals with a diagnosis of a depressive and/or anxiety disorder (56% and 50% respectively) experienced the onset of their psychiatric illness before their HD onset.

**Table 4.7 Difference in years between the age of onset of psychiatric illness and the age of onset of HD for the index sample**

| **DSM-IV Diagnosis** | N | Median | Range | Inter-Quartile Range |
|---|---|---|---|---|
| Depressive disorder | 25 | -1 | -25 - +10 | 9.0 |
| Anxiety disorder | 18 | -0.5 | -26 - +12 | 9.25 |
| Alcohol Abuse | 2 | -10 | -27 - -7 | 20.0 |
| Psychotic Disorder NOS | 1 | 0 | N/A | N/A |

Negative value means onset of psychiatric illness was prior to HD onset
Positive value means onset of psychiatric illness was post HD onset

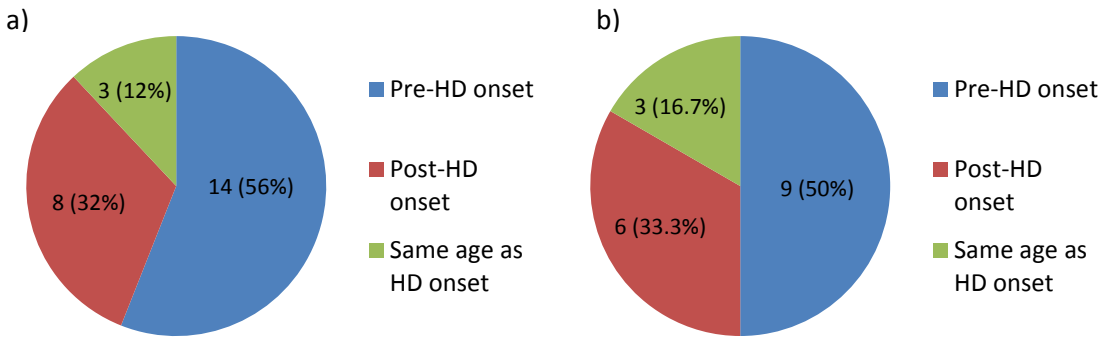



**Figure 4.4 Pie charts displaying the percentage of individuals whose onset of psychiatric illness was pre, post or at the same time as their HD onset for a) those with a DSM-IV lifetime diagnosis of a depressive disorder and, b) those with a DSM-IV lifetime diagnosis of an anxiety disorder for the index sample.**

Table 4.8 summarises the difference in years between the age of onset of psychiatric illness and the age of onset of HD for the sibling sample. Only individuals with a clinical diagnosis of HD were included in the sample. The median ages of onset of any depressive disorder and any anxiety disorder were 7 years and 4 years respectively prior to HD onset. For the three individuals with a DSM-IV diagnosis of alcohol abuse, the median age at psychiatric onset was at the same time as their HD onset. The pie charts in Figure 4.5 demonstrate that the majority of individuals with a diagnosis of a depressive and/or anxiety disorder (78.3% and 60% respectively) experienced the onset of their psychiatric illness before their HD onset.

**Table 4.8 Difference in years between the age of onset of psychiatric illness and the age of onset of HD for the sibling sample**

| **DSM-IV Diagnosis** | N | Median | Range | Inter-Quartile Range |
|---|---|---|---|---|
| Depressive disorder | 23 | -7 | -25 - +2 | 11.5 |
| Anxiety Disorder | 5 | -4 | -13 - +9 | 16.0 |
| Alcohol Abuse | 3 | 0 | -1 - +1 | 1.0 |

Negative value means onset of psychiatric illness was prior to HD onset
Positive value means onset of psychiatric illness was post HD onset

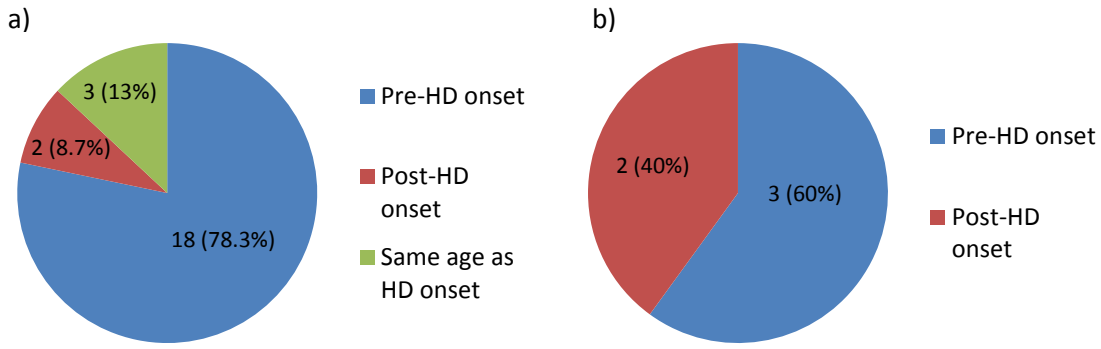



**Figure 4.5 Pie charts displaying the percentage of individuals whose onset of psychiatric illness was pre, post or at the same time as their HD onset for a) those with a DSM-IV lifetime diagnosis of a depressive disorder and, b) those with a DSM-IV lifetime diagnosis of an anxiety disorder for the sibling sample.**

### 4.4.3 Problem Behaviours Assessment

Lifetime prevalences of the neuropsychiatric symptoms irritability, aggression, apathy and perseverative thinking were obtained for 50 individuals in the index sample and 39 individuals in the sibling sample and are displayed in Figure 4.6. Data were missing for one individual in the sibling sample as their illness was too advanced to accurately self-report, there was no partner/carer available to provide any information and there was no information concerning these symptoms in the participant's case notes. Approximately fifty percent or more of individuals in both samples had a lifetime history of irritability, aggression, apathy and perseverative thinking. Irritability was the most common of the items experienced by individuals in the index sample, and apathy closely followed by irritability were the most frequently experienced items by individuals in the sibling sample.

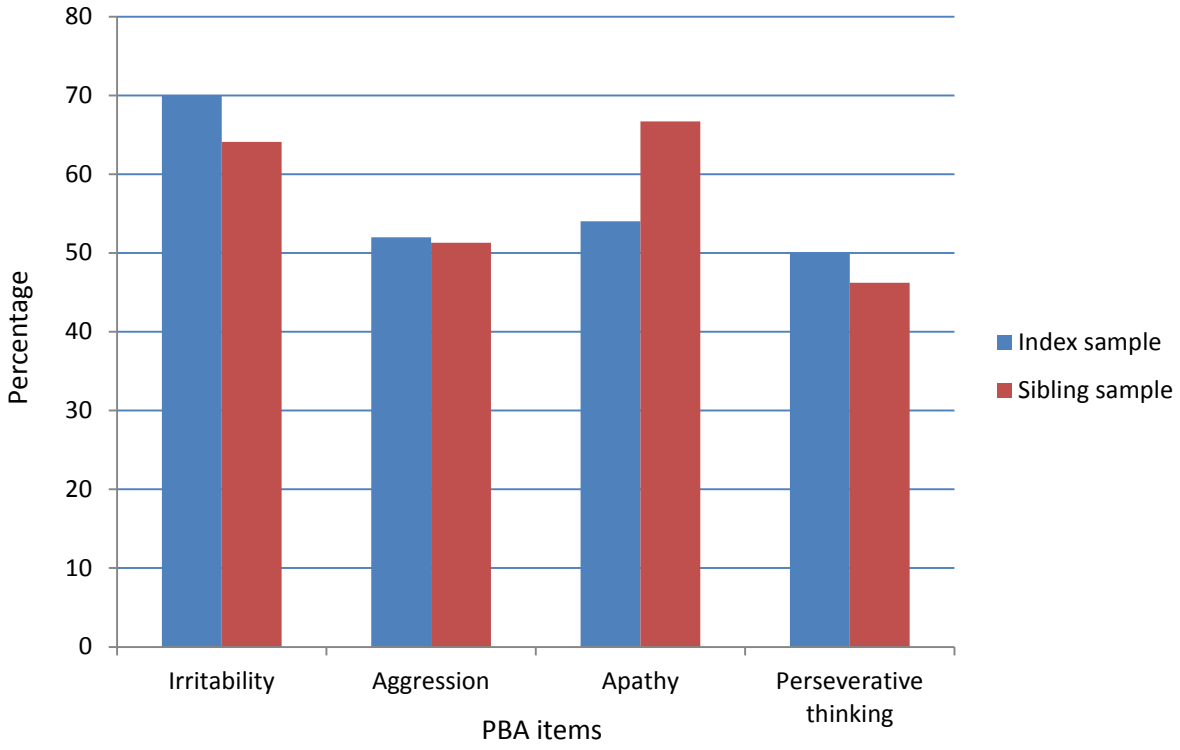



**Figure 4.6 Proportion of individuals in the index and sibling samples with a lifetime history of irritability, aggression, apathy and perseverative thinking.**

The median age of onset of these neuropsychiatric symptoms for the individuals in both samples who reported a positive lifetime history are recorded in Table 4.9. There was at least one individual in each category for whom the median age at onset was not known as they could not report an accurate age at onset and these symptoms are not routinely recorded in patients' medical notes. The median age at onset was found to be in the 40s for both samples and for all neuropsychiatric symptoms. In both samples, the median age at onset was lowest for the symptom irritability and highest for the symptom perseverative thinking.

**Table 4.9 The median age at onset of irritability, aggression, apathy and perseverative thinking for individuals in the index and sibling samples who reported a lifetime history of these symptoms.**

| PBA item | N | Unknown | Median | Range | Inter Quartile Range |
|---|---|---|---|---|---|
| **Index sample** | | | | | |
| Irritability | 35 | 1 | **43.5** | 27-65 | 10.75 |
| Aggression | 26 | 1 | **45.0** | 27-61 | 10.0 |
| Apathy | 27 | 3 | **45.0** | 32-61 | 12.0 |
| Perseverative thinking | 25 | 5 | **47.5** | 27-62 | 10.5 |
| | | | | | |
| **Sibling sample** | | | | | |
| Irritability | 25 | 1 | **41.5** | 24-65 | 12.5 |
| Aggression | 19 | 1 | **42.5** | 28-68 | 11.0 |
| Apathy | 26 | 4 | **46.0** | 24-71 | 17.5 |
| Perseverative thinking | 18 | 4 | **46.5** | 34-68 | 11.5 |

#### 4.4.3.1 Relationship between the age at onset of irritability, aggression, apathy and perseverative thinking and the age at onset of HD.

Table 4.10 summarises the difference in years between the age at onset of the PBA items irritability, aggression, apathy and perseverative thinking and the age at onset of HD (defined as motor onset) for the index sample. Only individuals with a clinical diagnosis of HD were included in the sample. The median age at onset for all four PBA items was after the onset of HD, with the median age of onset for the 32 individuals with a lifetime history of irritability and for the 24 individuals with a lifetime history of aggression being within a year of HD motor onset. For the 24 individuals with apathy, the median age at onset was four years after the age at HD onset and for the 20 individuals with a lifetime history of perseverative thinking, the median age at onset was 4.5 years after the onset of HD. The pie charts in Figure 4.7 demonstrate that half or more of the individuals in the index sample with a lifetime history of irritability, aggression, apathy and perseverative thinking experienced onset of their neuropsychiatric symptoms after the motor onset of their HD.

**Table 4.10 Difference in years between the age at onset of irritability, aggression, apathy and perseverative thinking and the age of onset of HD for the index sample.**

| **PBA item** | N | Median | Range | Inter-Quartile Range |
|---|---|---|---|---|
| Irritability | 32 | +0.5 | -7 - +12 | 4.25 |
| Aggression | 24 | +1.0 | -7 - +12 | 6.5 |
| Apathy | 24 | +4.0 | -7 - +13 | 5.5 |
| Perseverative thinking | 20 | +4.5 | -1 - +16 | 5.25 |

Negative value means onset of psychiatric illness was prior to HD onset
Positive value means onset of psychiatric illness was post HD onset

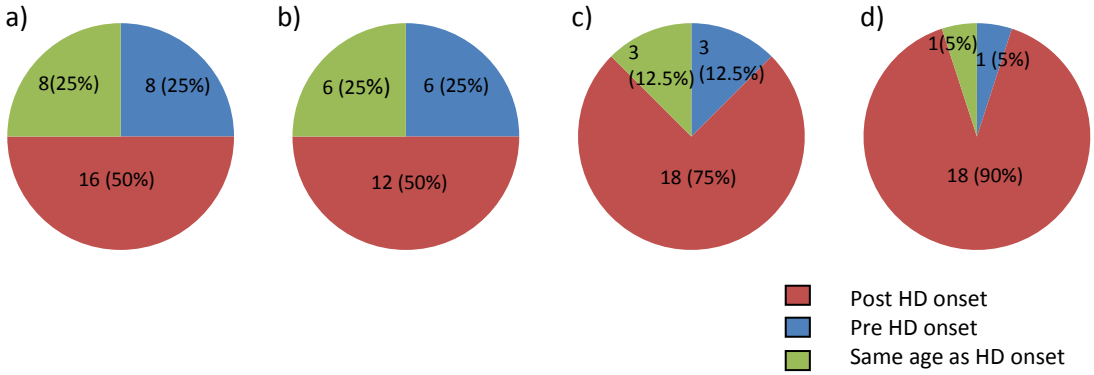



**Figure 4.7 Pie charts displaying the percentage of individuals whose onset of a) irritability, b) aggression, c) apathy and d) perseverative thinking was pre, post or at the same time as their HD onset for the index sample.**

Table 4.11 summarises the difference in years between the age at onset of the PBA items irritability, aggression, apathy and perseverative thinking and the age at onset of HD for the sibling sample. Only individuals with a clinical diagnosis of HD were included in the sample. For all four PBA items, the median age at onset of the neuropsychiatric symptoms was after the onset of HD. For the 22 individuals with a lifetime history of irritability, the median age at onset was 1.5years post HD onset, for the 16 individuals with a lifetime history of aggression and the 13 individuals with a lifetime history of perseverative thinking, the median age at onset was two years after the age at HD onset and for the PBA item apathy, the median age at onset was three years post HD onset. Figure 4.8 further demonstrates that the majority of individuals in the sibling sample with a lifetime history of irritability, aggression, apathy and

perseverative thinking experienced onset of their neuropsychiatric symptom(s) after the motor onset of their HD.

**Table 4.11 Difference in years between the age at onset of irritability, aggression, apathy and perseverative thinking and the age of onset of HD for the sibling sample.**

| PBA item | N | Median | Range | Inter-Quartile Range |
|---|---|---|---|---|
| Irritability | 22 | +1.5 | -9 - +20 | 8.25 |
| Aggression | 16 | +2.0 | -9 - +20 | 9.25 |
| Apathy | 21 | +3.0 | -1 - +17 | 10 |
| Perseverative thinking | 13 | +2.0 | 0 - +22 | 9 |

Negative value means onset of psychiatric illness was prior to HD onset
Positive value means onset of psychiatric illness was post HD onset

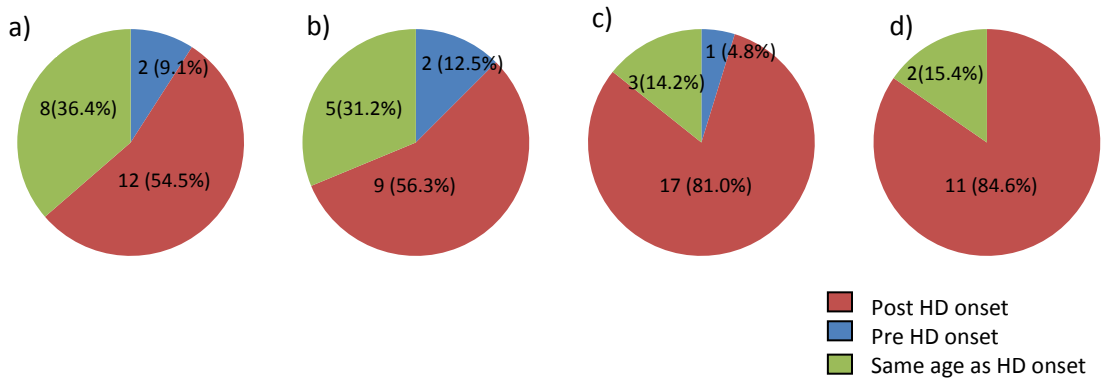



**Figure 4.8 Pie charts displaying the percentage of individuals whose onset of a) irritability, b) aggression, c) apathy and d) perseverative thinking was pre, post or at the same time as their HD onset for the sibling sample.**

## *4.5 Comparison between the depression phenotype in HD and individuals with unipolar depression and no HD*

### 4.5.1 Samples

#### 4.5.1.1 The HD sample

Given that the index and sibling HD samples are not independent, only the index sample (which will be referred to as the HD sample in the following sections) was used in the comparative analyses with the sample of individuals with unipolar depression and no HD.

#### 4.5.1.2 The Mood Disorders Research Group (MDRG) sample

##### 4.5.1.2.1 Recruitment of the MDRG sample

Participants were recruited (by individuals other than myself) to an ongoing molecular genetic and clinical study of affective disorders run by the Mood Disorders Research Group (MDRG) based jointly at Cardiff University and the University of Birmingham. A total of 784 unrelated individuals with a lifetime diagnosis of unipolar depression were recruited to the study via systematic and non-systematic methods. The main systematic recruitment method was via Community and Local Mental Health Team referrals, which accounted for 43.7% of the recruitment. The remaining 56.3% of the sample was recruited via non-systematic methods including adverts in local and national media (press, radio and TV) and via support organisations such as Depression Alliance.

##### 4.5.1.2.2 Inclusion and exclusion criteria

The following inclusion and exclusion criteria were applied when recruiting the participants to the MDRG study:

*Inclusion criteria:*

- Aged 18 years or over
- Of UK/Eire white ethnicity (due to the fact they were recruited for molecular genetic studies)
- A best-estimate lifetime diagnosis of major recurrent depressive disorder according to DSM-IV

*Exclusion criteria:*

- A lifetime diagnosis of intravenous drug dependency

- An experience of affective illness only as a result of alcohol or substance misuse
- An affective illness was experienced only secondary to medical illness or medication
- Onset of affective symptoms after the age of 65 years
- A first or second degree relative with a clear diagnosis of bipolar affective disorder or schizophrenia, schizotypal disorder, persistent delusional disorder, acute and transient psychotic disorders or schizoaffective disorder.
- An experience of mood incongruent psychosis or psychosis outside of mood episodes.

#### 4.5.1.2.3 Neuropsychiatric assessment of MDRG participants

The MDRG participants are an ideal, comparative sample as the same assessment tools were used as in the current study. Participants were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990), which provided detailed information about lifetime psychopathology. Psychiatric and general practice case-notes where available were also reviewed. Based on these data, best-estimate lifetime diagnoses were made according to DSM-IV criteria and key clinical variables, such as age at onset and number of mood episodes, were rated. In addition, ratings of lifetime suicidal behaviour were made and the OPerational CRITeria diagnostic system (OPCRIT) (McGuffin et al., 1991), Bipolar Affective Disorder Dimension Scale (BADDS) (Craddock et al., 2004) and Global Assessment Scale (GAS) (Endicott et al., 1976) were completed (see Chapter 3.4.6 for further details of these assessments).

Diagnostic and clinical ratings were made by at least two members of the research team blind to each other's rating and consensus was reached via discussion where necessary. Inter-rater reliability was formally assessed using 20 random cases. Mean kappa statistics were 0.85 for DSM–IV diagnoses and ranged between 0.81 and 0.99 for other key clinical categorical variables. Mean intra-class correlation coefficients were between 0.91 and 0.97 for key clinical continuous variables. Team members involved in the interview, rating and diagnostic procedures were all research psychologists or psychiatrists.

#### 4.5.1.2.4 MDRG sample data

Anonymised data for the 784 individuals with a DSM-IV diagnosis of unipolar depression were extracted from the MDRG database and included the following information:

1) Demographic characteristics: age, gender, ethnicity, marital status, highest level of education, highest lifetime occupation.
2) Lifetime psychiatric features: DSM-IV diagnosis, suicidal behaviour (lifetime ever), OPCRIT ratings in context of depressed mood (lifetime ever), BADDS – depression subscale score, GAS scores for lifetime worst functioning in a depressive episode, age at first impairment due to depression (lifetime ever), number of episodes of depression (lifetime ever), longest duration of a depressive episode (lifetime ever) and number of hospital admissions due to depression.

#### 4.5.1.2.5 Sample descriptives

The HD and MDRG samples comprised 12 and 784 individuals respectively with a lifetime diagnosis of a DSM-IV major depressive disorder – recurrent (MDDR). Given that a diagnosis

of MDDR, major depressive disorder – single episode (MDDS) and depression not otherwise specified (NOS) vary greatly in terms of severity, only individuals with a diagnosis of MDDR in the HD sample were used in the subsequent analyses, and the 16 individuals with MDDS (n=9) and depression NOS (n=7) were excluded.

Furthermore, given that all 12 of the HD sample with MDDR were recruited via systematic methods, analyses were performed to determine whether there were any differences between those individuals with MDDR in the MDRG sample that were recruited via systematic and non-systematic methods. Although, no significant differences were found for the demographic characteristics, there were significant differences for some key illness course features and therefore, only those individuals recruited via systematic methods were included in the comparative analysis. This resulted in final samples of 12 individuals with HD and MDDR and 345 individuals with no HD and MDDR who were systematically recruited.

### 4.5.2 Demographic characteristics of the HD and MDRG samples

The demographics of the HD and MDRG sample are summarised in Table 4.12 and the samples were found to have similar demographic characteristics. The only significant difference between the samples was for the highest level of education attained where individuals in the HD sample were significantly more likely than individuals in the MDRG sample to have a lower level of educational attainment ($\chi^2 = 16.79$, df = 1, $p$=0.002).

## Table 4.12 Demographic characteristics of the HD and MDRG samples

| Demographics | Descriptives and Percentages | | |
|---|---|---|---|
| | **HD MDDR sample (N=12)** | **MDRG sample (N = 345)** | ***p*-value[a,b,c]** |
| **Age (years)[a]** | | | |
| Mean (95% CI) | **47.6 (43.6-51.6)** | **47.5 (46.2-48.8)** | 0.95 |
| Standard Deviation | **7.0** | **12.0** | |
| Range | **39-63** | **19-75** | |
| | | | |
| **Female[b]** | **N (%) (95% CI)** | **N (%) (95% CI)** | |
| | **8 (66.7)** (40.0-93.4) | **228 (66.1)** (61.1-71.1) | 1.00 |
| | | | |
| **Ethnic Origin[c]** | | | |
| White Caucasian | **12 (100.0)** (-) | **345 (100.0)** (-) | 0.85 |
| | | | |
| **Marital status[c]** | | | |
| Has married/lived as married | **12 (100.0)** (-) | **289 (83.8)** (79.9-87.7) | 0.32 |
| Has never married/lived as married | **0 (0.0)** (-) | **48 (13.9)** (10.3-17.6) | |
| Unknown | **0 (0.0)** (-) | **8 (2.3)** (0.7-3.9) | |
| | | | |
| **Highest Level Education[c]** | | | |
| No qualifications/11+ | **1 (8.3)** (0.0-23.9) | **83 (24.1)** (19.6-28.6) | 0.002 |
| O-levels/CSEs/ GCSEs | **8 (66.7)** (40.0-93.4) | **67 (19.4)** (15.2-23.6) | |
| A level/ HND/ BTEC | **2 (16.7)** (0.0-37.8) | **54 (15.7)** (11.9-19.5) | |
| Degree/Post-graduate degree | **1 (8.3)** (0.0-23.9) | **81 (23.5)** (19.0-28.0) | |
| Unknown | **0 (0.0)** (-) | **60 (17.4)** (13.4-21.4) | |
| | | | |
| **Highest Lifetime Occupation[c]** | | | |
| Professionals | **2 (16.7)** (0.0-37.8) | **113 (32.8)** (27.9-37.8) | 0.17 |
| Associate professionals | **2 (16.7)** (0.0-37.8) | **73 (21.2)** (16.9-25.5) | |
| Service workers * | **6 (50.0)** (21.7-78.3) | **74 (21.4)** (17.1-25.7) | |
| Plant & machinery operators | **1 (8.3)** (0.0-23.9) | **10 (2.9)** (1.1-4.6) | |
| Other** | **1 (8.3)** (0.0-23.9) | **39 (11.3)** (8.0-14.6) | |
| Unknown | **0 (0.0)** (-) | **36 (10.4)** (7.2-13.6) | |

[a] Independent t-test was used; [b] Fisher's exact test for significance (2-sided) was used; [c]Chi square test was used.

*Service workers category includes: shop, market, craft and related trade workers, skilled agricultural and fishery workers,**Other category includes: elementary occupations, armed forces, full-time student, homemaker, never worked.

### 4.5.3 History of Suicidal Thoughts and Suicide Attempts in the HD and MDRG samples

Table 4.13 summarises the number of individuals in the HD and MDRG samples with a history of suicidal thoughts and suicide attempts (defined as outlined in section 4.4.1.3). As there were no significant differences found between males and females, only the total numbers of individuals are reported.

**Table 4.13 History of suicidal thoughts and attempts for the HD and MDRG samples**

| | **HD sample Total: N = 12** | **MDRG sample Total: N = 345** |
|---|---|---|
| | **N (%) 95% CI** | **N (%) 95% CI** |
| Suicide attempt | **6 (50.0)** 21.7-78.3 | **111 (32.2)** 27.3-37.1 |
| Suicidal Ideation | **12 (100.0)** - | **290 (84.1)** 80.2-88.0 |
| Unknown | **0 (0.0)** - | **5 (1.4)** 0.2-2.6 |
| None | **0 (0.0)** - | **50 (14.5)** 10.8-18.2 |

CI; Confidence Interval
Individuals who had made an attempt at suicide are also included in the suicidal ideation category

All of the HD sample had a history of suicidal ideation with half of these individuals (50%) having made an attempt at suicide at some point during their lifetime. The majority of the MDRG sample (84.1%) also had a history of suicidal ideation and nearly a third of the sample had made an attempt at suicide (32.2%).There were no significant differences found between the samples in the proportion of individuals with a history of suicidal ideation (Fisher's, p=0.23), suicide attempt(s)(Fisher's, p=0.21) or no suicidal behaviour (Fisher's, p=0.23).

### 4.5.4 Age at onset of depression in the HD and MDRG samples

The median age of onset of depression is reported in Table 4.14. The total numbers of individuals are reported only as there were no significant differences found between males and females. Individuals in the HD sample had a significantly older age of onset of depression than the MDRG sample (U=1063.5, *p*=0.005).

**Table 4.14 Median age of onset of depression (in years) for the HD and MDRG samples**

| | N | Median | Range | Inter-Quartile Range |
|---|---|---|---|---|
| HD sample | 12 | 41 | 18-47 | 7.25 |
| MDRG sample | 345 | 27 | 9-61 | 16 |

### 4.5.5 Frequency of depressive episodes per year of illness in the HD and MDRG samples

Figure 4.9 summarises the frequency of episodes of depression per year of illness experienced by individuals in the HD and MDRG samples. This was calculated for all 12 individuals in the HD sample and 336 of the individuals in the MDRG sample. Individuals in the HD sample were found to experience significantly more episodes of depression per year of illness than individuals in the MDRG sample (U=1082.0, *p*=0.006).

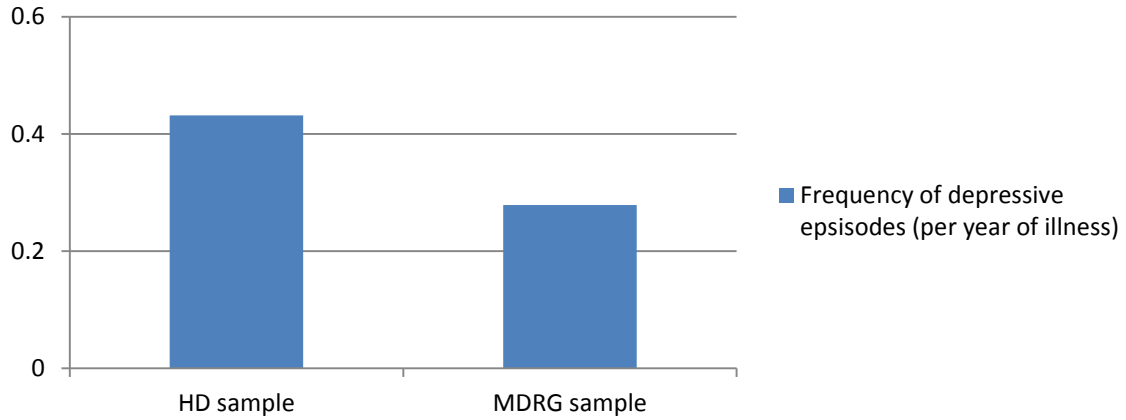



**Figure 4.9 Median frequency of depressive episodes per year of illness for individuals in the HD and MDRG sample.**

### 4.5.6 Longest duration of a depressive episode in the HD and MDRG samples

Figure 4.10 summarises the median length of the longest duration of a depressive episode (lifetime ever) in weeks for both samples. As there were no significant differences found between males and females, only the total numbers of individuals are reported. The longest duration of a depressive episode was known for eight of the 12 individuals in the HD sample and 340 of the 345 individuals in the MDRG sample. Although there was no significant difference found between the samples, the median length of the longest duration of a depressive episode was shorter for individuals in the HD sample than the MDRG sample and approached significance (U=833.0, *p*=0.06).

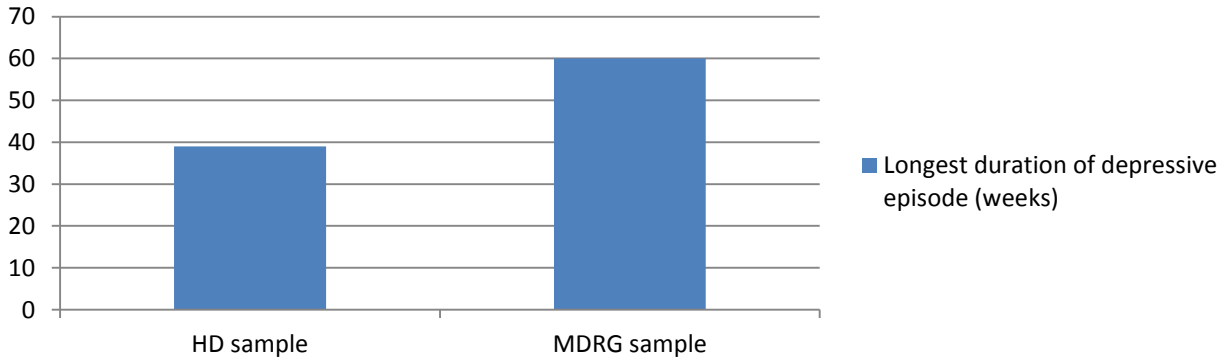



**Figure 4.10 Median length of the longest duration of a depressive episode (in weeks) for individuals in the HD and MDRG sample.**

### 4.5.7 Lifetime ever frequencies of OPCRIT depression items in the HD and MDRG samples

All individuals in both samples had complete ratings for the presence or absence of the OPCRIT depression items. The total numbers of individuals are reported only as there were no significant differences found between males and females. Those items that were rated as unsure were considered absent for the purpose of this analysis. Table 4.15 displays the frequencies of the OPCRIT items for both samples.

**Table 4.15 Lifetime frequencies of OPCRIT depression items for the HD and MDRG samples.**

| OPCRIT depression items | HD sample, N = 12<br>Symptom present<br>N (%)<br>95% CI | MDRG sample, N=345<br>Symptom present<br>N (%)<br>95% CI |
|---|---|---|
| Dysphoria | **12 (100)**<br>- | **342 (99.1)**<br>98.1-100.0 |
| Loss of Pleasure | **11 (91.7)**<br>76.1-100 | **333 (96.5)**<br>94.6-98.4 |
| Diurnal Variation** | **1 (8.3)**<br>0.0-23.9 | **158 (45.8)**<br>40.5-51.1 |
| Suicidal ideation | **12 (100)**<br>- | **299 (86.6)**<br>83.0-90.2 |
| Excessive self-reproach | **12 (100)**<br>- | **292 (84.6)**<br>80.8-88.4 |
| Poor concentration | **11 (91.7)**<br>76.1-100 | **336 (97.4)**<br>95.7-99.1 |
| Slowed activity | **5 (41.7)**<br>13.8-69.6 | **138 (40.0)**<br>34.8-45.2 |
| Loss of energy | **11 (91.7)**<br>76.1-100 | **335 (97.1)**<br>95.3-98.9 |
| Poor appetite | **7 (58.3)**<br>30.4-86.2 | **279 (80.9)**<br>76.8-85.1 |
| Weight loss | **7 (58.3)**<br>30.4-86.2 | **194 (56.2)**<br>51.0-61.4 |
| Increased appetite* | **0 (0.0)**<br>- | **94 (27.2)**<br>22.5-31.9 |
| Weight gain | **1 (8.3)**<br>0.0-23.9 | **84 (24.3)**<br>19.8-28.8 |
| Initial insomnia | **7 (58.3)**<br>30.4-86.2 | **256 (74.2)**<br>69.6-78.8 |
| Middle insomnia* | **4 (33.3)**<br>6.6-60.0 | **228 (66.1)**<br>61.1-71.1 |
| Early morning waking | **6 (50.0)**<br>21.7-78.3 | **194 (56.2)**<br>51.0-61.4 |
| Excessive sleep | **1 (8.3)**<br>0.0-23.9 | **65 (18.8)**<br>14.7-22.9 |
| Decreased libido | **2 (16.7)**<br>0.0-37.8 | **123 (35.7)**<br>30.6-40.8 |
| Agitation | **2 (16.7)**<br>0.0-37.8 | **101 (29.3)**<br>24.5-34.1 |

*p<0.05, **p=0.01

In general, the frequencies of the OPCRIT depression items were similar across the samples.

Three significant differences were found between the HD and MDRG samples: 1) diurnal

variation: individuals in the HD sample were significantly less likely to have experienced diurnal variation during an episode of depression ($\chi^2$ = 6.59, df = 1, p=0.01), 2) increased appetite: individuals in the HD sample were significantly less likely to have experienced an increase in their appetite during a depressive episode (Fisher's, p=0.041), and 3) middle insomnia: individuals in the HD sample were significantly less likely to have experienced middle insomnia during an episode of depression (Fisher's, p=0.029).

### 4.5.8 BADDS ratings – depression subscale in the HD and MDRG samples

Table 4.16 displays the mean BADDS depression subscale scores (a lifetime measure of the frequency and severity of depressive episodes) for the individuals in the HD and MDRG samples. As there were no significant differences found between males and females, only the total numbers of individuals are reported. No significant difference was found between the samples for the BADDS depression score (t=-1.07, df = 355, p=0.29).

**Table 4.16 BADDS – mean depression subscale scores for the HD and MDRG samples.**

| | N | Mean | Standard Deviation | Range |
|---|---|---|---|---|
| HD sample | 12 | 61.3 | 11.2 | 40-81 |
| MDRG sample | 345 | 64.3 | 9.7 | 35-93 |

### 4.5.9 GAS ratings in the HD and MDRG samples

GAS ratings were made for the level of functioning in the worst depressive episode and Table 4.17 displays the mean GAS scores for both samples. No significant differences were found between males and females and therefore, only the total numbers of individuals are reported. Individuals in the HD sample had a significantly higher level of functioning during their worst episode of depression than individuals in the MDRG sample (t=3.09, df = 355, *p*=0.002).

**Table 4.17 Mean GAS scores for the worst episode of depression for individuals in the HD and MDRG sample.**

| | N | Mean | Standard Deviation | Range |
|---|---|---|---|---|
| HD sample | 12 | 41.8 | 8.8 | 30-60 |
| MDRG sample | 345 | 35.4 | 7.0 | 9-54 |

## *4.6 Discussion*

In this chapter, data have been presented which describe the psychiatric phenotype in HD. The following section will discuss the results obtained. This will include a comparison of the lifetime prevalence rates of psychiatric disorders in the HD index and sibling samples with previously reported prevalence rates in the HD population as well as with the general population. Comparisons of other neuropsychiatric features such as suicidality and age at onset of psychiatric illness will be made between this study sample, other HD samples and the general population. The depression phenotype in HD and how this compares with the MDRG sample will also be discussed.

### 4.6.1 Lifetime prevalence of psychiatric disorders in HD

Two thirds of individuals in the index and sibling samples had a lifetime DSM-IV psychiatric diagnosis (66% and 65% respectively). This finding is consistent with previous research reporting a high prevalence of psychiatric symptoms in HD (van Duijn et al., 2007). The majority of studies reporting prevalence rates in the HD population have not used formal diagnostic criteria and have looked at current, rather than lifetime psychiatric prevalence rates. However, one study of 106 HD gene mutation carriers found that 42% of the sample had a lifetime DSM-IV diagnosis at baseline and after a two year follow-up, 5.5% of the sample had experienced new onset of a DSM-IV psychiatric disorder (Reedeker et al., 2012).

Given that 38.7% of the sample in the Reedeker study were pre-motor symptomatic (compared with 14% of the index sample and 4% of the sibling sample in the current study), it is likely that if these individuals were followed up for an even longer period of time, the new incident rate of psychiatric diagnoses would also increase, perhaps to nearer the prevalences found in the current study.

More females than males had a lifetime DSM-IV diagnosis in the index sample (69.7% versus 58.8%) and sibling sample (72.2% versus 43.8%) but the difference only reached significance in the sibling sample. Van Duijn et al (2008) in their HD sample found no significant difference between genders in the presence of DSM-IV psychiatric disorders in the past 12 months (although the raw data were not provided to show if there was a difference at all). However, the gender differences reported in this study are consistent with those reported in large epidemiological, general population studies (Alonso et al., 2004, Kessler et al., 2005). Women have a significantly higher risk than men of anxiety and mood disorders where as men are significantly more likely than women to experience substance use disorders (the only instance where these gender differences did not hold true in the current study was for alcohol abuse, where in the sibling sample, more women than men had a lifetime diagnosis of alcohol abuse) (Alonso et al., 2004, Kessler et al., 2005).

Prevalence rates of specific psychiatric disorders determined from the results of this study will be compared with previously reported prevalence rates in the HD population as well as in the general population. However, there are no published data reporting lifetime prevalence rates of psychiatric illness in the UK population using methodology directly

comparable to this study. In 2007, the Adult Psychiatric Morbidity Study (APMS) was carried out by the National Centre for Social Research in collaboration with the University of Leicester, which collected data on mental health among 7461 adults aged 16 and over living in private households in England (Adult Psychiatric Morbidity Study, 2007).This assessed the presence of clinically significant psychiatric symptoms in the past week only except for suicidal thoughts and attempts, which reported lifetime prevalences.

Alternative studies that are suitable for comparative purposes include the National Comorbidity Survey Replication (NCS-R) (Kessler et al., 2005) and the European Study of the Epidemiology of Mental Disorders (ESEMeD) (Alonso et al., 2004). The NCS-R is a survey of 9282 American individuals, aged 18 years and older and provides estimates of lifetime prevalence rates of DSM-IV disorders. Given the original article by Kessler and colleagues did not report gender differences, the 2007 update of the lifetime prevalence of DSM-IV disorders by sex will be that reported in the following sections (Kessler et al., 2007). The ESEMeD assessed 12-month and lifetime prevalence rates of mood, anxiety and alcohol disorders according to DSM-IV diagnostic criteria among 21,425 individuals aged 18 and over in six European countries (Belgium, France, Germany, Italy, the Netherlands and Spain).

#### 4.6.1.1 Mood disorders

##### 4.6.1.1.1 Depressive disorders

Depressive disorders were the most frequent psychiatric illnesses with 56% of the index and 65% of the sibling sample having experienced an episode of depression at some point during their lifetime. Depression NOS (a diagnosis for those individuals with some depressive

symptoms of lesser severity or temporality that do not meet the criteria for major depression yet still cause significant impairment and often require treatment) comprised a significant proportion of the DSM-IV depression diagnoses: one quarter of those individuals in the index sample with a diagnosis of depression and one third of those with depression in the sibling sample. A literature review on the prevalence of psychopathology in verified Huntington's disease carriers found the prevalence of depressed mood varied from 33% to 69% (van Duijn et al., 2007), which the results from this study support. However, of the six studies included in van Duijn et al's review, only one used formal DSM-IV criteria (Leroi et al., 2002). In the study by Leroi and colleagues (2002), of 21 individuals with HD, 42.8% of the sample were found to have a history of a depressive disorder: 28.6% with a lifetime DSM-IV diagnosis of major depression and 14.3% with non-major depression (this included diagnoses of brief recurrent depressive disorder, minor depressive disorder and dysthymia). In addition, a study of 89 pre-motor symptomatic HD mutation carriers found that 20% of the sample had a lifetime DSM-III diagnosis of major depression, 1% had a lifetime diagnosis of dysthymic disorder and a further 1% a lifetime diagnosis of cyclothymic disorder (Julien et al., 2007). Folstien et al (1983) using DSM-III criteria in a sample of 186 individuals with HD found that 33% of the sample had a diagnosis of major depressive disorder.

Compared to the general population, the prevalence rates of mood disorders found in the present study are over twice as high in the index sample (56%) and three times as high in the sibling sample (65%) as that reported in the NCS-R (21.4%) and ESEMeD (14%). For major depressive disorder only, the prevalence rates for the NCS-R and ESEMeD studies were 16.9% and 12.8% respectively. However, both these studies had a similar proportion of

males and females take part and given that like the present study, these large surveys also found females to have a higher prevalence of mood disorders, the lifetime prevalence rates of the current study will be inflated by the greater proportion of female participants (66% in the index sample and 58.7% in the sibling sample). Nevertheless, when comparing just female prevalence rates of mood disorders in all samples, the rates for the current study (60.6% in the index sample and 79.2% in the sibling sample) are as high relative to the two epidemiological studies (NCS-R: 24.9% and ESEMeD: 18.2%).

As previously described, females were more likely than males to have a lifetime DSM-IV diagnosis of a depressive disorder in both the index sample (60.6% versus 47.1%) and sibling sample (79.2% versus 43.8%), although the gender difference only reached significance in the sibling sample. Indeed, a greater proportion of females were found to have a lifetime diagnosis of all specific depressive disorder diagnoses: recurrent major depression, single episode major depression and depression NOS. Leroi and colleagues (2002) found no significant gender difference in the lifetime prevalence of DSM-IV depressive disorders in their study of 21 individuals with HD. However, a cross-sectional analysis of 1267 HD patients from the Registry project of the European Huntington's Disease Network found using the Unified Huntington's Disease Rating Scales that females were significantly more likely to have past depression (Females: 60.2%; Males: 46.5%, $p<0.001$) and current depression (Females: 36.2%; Males: 29.2%, $p=0.032$; Zielonka et al., 2013). Depressive symptoms as measured by the Beck Depression Inventory II (BDI-II: Beck et al., 1996) have been significantly associated with female gender in a large prodromal HD sample (Epping et al., 2013).

#### 4.6.1.1.2 Bipolar disorder

No individuals in the present study had a diagnosis of bipolar disorder. Previous literature on the presence of bipolar disorder in the HD population is difficult to interpret. Mood states such as irritability and disinhibition are commonly observed in the HD population (for example, approximately two thirds of the index sample and the sibling sample in the present study had a lifetime history of irritability) but are rarely accompanied by elevated mood and associated symptoms of mania (Craufurd and Snowden, 2014). Studies that have used assessment tools that measure psychiatric symptoms rather than using diagnostic systems such as DSM are perhaps describing the increased prevalence of irritability and disinhibition rather than true mania. Indeed, studies that have used formal diagnostic criteria report a prevalence rate no higher than in the general population. Julien et al (2007) reported in a sample of 89 HD gene mutation carriers that no individuals had a lifetime DSM-III diagnosis of bipolar disorder and only one individual had a history of cyclothymia. Leroi et al (2002) reported a lifetime DSM-IV prevalence of 4.8% for bipolar disorder (1 individual in a sample of 21 HD patients) and van Duijn and colleagues (2008) found that 2.1% of their sample of 140 HD mutation carriers had a 12-month DSM-IV prevalence of a “manic episode” that did not fulfil diagnostic criteria for bipolar disorder. These findings suggest the lifetime prevalence of bipolar disorder to be similar in individuals with HD and in the general population. The lifetime DSM-IV prevalence of bipolar disorder was found to be 4.4% in the NCS-R study (these data were not reported in the ESEMeD study) and in a review of studies reporting the epidemiology of bipolar disorder, a lifetime prevalence rate for males and females was found to be between 1-1.5% (Bebbington and Ramana, 1995).

#### 4.6.1.2 Anxiety disorders

Anxiety disorders were the next most frequently reported category of psychiatric illness with 38% of the index and 25% of the sibling sample having a lifetime DSM-IV diagnosis of an anxiety disorder. Anxiety disorder NOS again comprised a significant proportion of the anxiety disorder diagnoses (42% of those individuals in the index sample and 30% of the individuals in the sibling sample with a lifetime DSM-IV diagnosis of an anxiety disorder). Panic Disorder was the most frequently reported category of anxiety disorder with almost a 50:50 split between those who also experienced agoraphobia and those who did not in both the index and sibling samples. Lifetime prevalence rates for DSM-III anxiety disorders were found to be 17% in a sample of 89 pre-symptomatic HD patients (Julien et al., 2007) and van Duijn et al (2008) reported a 15.7% 12-month prevalence rate for all DSM-IV anxiety disorders in a sample of 140 HD mutation carriers. Four studies using either the UHDRS behaviour scale (Paulsen et al., 2001; Paulsen et al., 2005a and Murgod et al., 2001) or the Problem Behaviours Assessment (Craufurd et al., 2001) reported a range of between 37% and 61%, although all of these measures assess the presence of anxiety symptoms in the last month rather than a lifetime ever measure. The lifetime prevalence of anxiety disorders reported in the index sample is three times that reported in the general population ESEMeD study (total; 13.6%, females; 17.5%), although not much greater than that found in the general population NCS-R study (total; 31.2%, females; 36.4%). The lower prevalence of anxiety disorders in the sibling sample meant that this prevalence rate was nearly twice that reported in the ESEMeD study and lower than that found in the NCS-R epidemiological survey.

There were no significant differences found between the proportion of males and females that had a history of an anxiety disorder. However, five times as many women than men in the index sample had a lifetime DSM-IV diagnosis of panic disorder. There is no previous literature on gender differences in anxiety disorders in HD, although in the general population, women are more likely than males to experience anxiety disorders (any anxiety disorder: ESEMeD: males; 9.5%, females; 17.5% and NCS-R: males; 25.4%, females; 36.4%). This gender difference held true for both the NCS-R and ESEMed studies, not just for any anxiety disorder but for all specific DSM-IV diagnoses of anxiety disorders.

No individuals in the index or sibling sample were found to have a diagnosis of obsessive compulsive disorder (OCD) even though obsessive and compulsive symptoms are often reported as being prevalent in the HD population. Marder et al (2000) found in a sample of 960 patients with HD that 22.3% of these presented with obsessive and compulsive symptoms at their first clinic visit and Anderson et al (2001) using the Yale-Brown Obsessive Compulsive Scale reported that 14 of 27 HD patients endorsed at least one obsessive symptom (the most frequently reported being aggressive obsessions) and seven patients endorsed at least one current compulsive symptom (the most common being checking compulsions). However, only two of these patients fulfilled DSM-IV criteria for current OCD. Julien et al (2007) reported a lifetime DSM-III prevalence rate of 5% for OCD and van Duijn et al (2008) found a 12-month DSM-IV prevalence rate of 4.3% for OCD.

Obsessive compulsive symptoms are without doubt common to HD patients, however, this differs greatly from Obsessive Compulsive Disorder. Even though no individuals in both the

index and sibling samples were found to have a lifetime DSM-IV diagnosis of Obsessive Compulsive Disorder (OCD), on initial questioning, many of the individuals did respond to having symptoms of OCD. For example, they would report having to regularly check if the front door was locked, gas taps were switched off etc but on further probing, it turned out this was in general because they couldn't remember if they had locked the door or switched off the gas and there was no resistance to the checking, it did not cause any distress or significant functional impairment. Therefore, although on such questionnaires, many HD patients will report having obsessive compulsive symptoms, the prevalence of OCD is likely to be much lower. Indeed, even though there were no cases of OCD in this sample, approximately 50% of both the index and sibling samples reported a lifetime history of perseverative thinking or behaviour, which includes getting stuck on certain ideas or actions, getting obsessed about something, going on about it more than you should or doing something over and over again.

The NCS-R reported a lifetime OCD prevalence rate of 2.3% whereas the ESEMeD did not report the prevalence rate for OCD. A further study of seven international epidemiologic surveys found that the lifetime prevalence rate for OCD was consistent across the different countries with most of the rates falling within the range of 1.9% (Korea) to 2.5% (Puerto Rico) (Weissman et al., 1994).

#### 4.6.1.3 Alcohol abuse

Lifetime alcohol abuse was reported by 6% of the index sample (11.8% of males and 3% of females) and 7.5% of the sibling sample (0% of males and 12.5% of females).These figures

support findings in previous HD studies, which range between 3% and 30.9%. In a sample of 42 individuals with HD, King et al., (1985) used DSM-III criteria to determine a lifetime prevalence of alcohol abuse of 16.7% (24% for males and 5.9% for females). In this sample, six of the seven individuals with a history of alcohol abuse had begun to drink heavily before the onset of the first symptoms in HD. This was also true of the sample in the current study, where all three of the individuals in the index sample with a lifetime diagnosis of alcohol abuse had problems with alcohol before the onset of their HD and two of the three in the sibling sample also drank heavily pre-HD onset (the other individual started drinking heavily a year after her HD onset when she had to give up work). Julien et al (2007) found a lifetime DSM-III prevalence rate of 3% for alcohol dependence in HD and Pflanz et al., (1991) used the Present State Examination to determine a 16% prevalence of alcohol abuse in HD males and 9% prevalence in HD females. A recent study found a lifetime alcohol abuse prevalence of 30.9% (43% for males and 19% for females) in the HD population (Byars et al., 2012). The study also found that lifetime alcohol abuse was associated with an earlier age of HD onset in women but not in men. However, a diagnosis of alcohol abuse was determined by participant and family definition only.

Lifetime prevalence rates of 4.1% for alcohol abuse were found in the ESEMeD study and the NCS-R study reported a prevalence of 13.2% for alcohol abuse with/without dependence. In both studies, males were more likely than females to have a history of alcohol abuse (seven and a half times as likely in the ESEMeD study and over two and half times as likely in the NCS-R study).

#### 4.6.1.4 Psychotic symptoms

A DSM-IV lifetime diagnosis of a psychotic disorder was only found in one individual (a female) in the index sample to give a prevalence of 2% in the index sample and 0% in the sibling sample. However, two further individuals in the index sample (a male and a female) experienced psychotic symptoms as part of a severe depressive episode. Therefore, in a broader sense, 6% of the index sample and 0% of the sibling sample had experienced psychotic features. Julien et al (2007) found a lifetime DSM-III prevalence of 1% for schizophrenia in their sample of 89 pre-symptomatic HD patients. However, most studies that have investigated the prevalence of psychotic symptoms in HD have used instruments measuring current prevalence, which found a range of 3% (Craufurd et al., 2001) to 11% (Paulsen et al., 2001). Current prevalence of psychotic symptoms will be greatly influenced by the population from which the sample is selected e.g. an outpatient population versus an inpatient one. Caine and Shoulson (1983) found that three of 30 HD patients fulfilled DSM-III criteria for schizophrenic syndrome and a further two were diagnosed with atypical psychotic syndrome. However, this sample consisted of many individuals who had been referred due to "substantial behavioural disturbances". Van Duijn et al (2008) found a 12-month DSM-IV prevalence rate of 1.4% for nonaffective psychosis in their HD sample (the majority of the participants were recruited from Clinical Genetics or Neurology outpatient clinic). The NCS-R and the ESEMeD did not report the lifetime DSM-IV prevalence rates for psychosis. However, the UK general population survey APMS 2007, found a prevalence of 0.4% for psychotic disorders in the past year.

#### 4.6.1.5 Co-morbid diagnoses

The proportion of individuals with a lifetime DSM-IV diagnosis of more than one psychiatric disorder was high (32% of the index sample and 27.5% of the sibling sample). This represents almost half of those individuals with a lifetime DSM-IV diagnosis (66% of the index sample and 65% of the sibling sample). The majority of the comorbid diagnoses were a depressive and anxiety disorder (100% of the individuals with more than one psychiatric disorder in the index sample and 81.8% of the individuals in the sibling sample with comorbid diagnoses). Reedeker and colleagues (2012) reported in their study that some HD participants with a persistent psychiatric disorder at baseline had switched to another psychiatric disorder after two years. However, there is no previous literature indicating the prevalence of co-morbid psychiatric diagnoses in HD. The APMS 2007 UK general population study found that of the 23.0% of the sample that met the criteria for one of the psychiatric diagnostic conditions, a third of these (i.e. 7.2% of the sample) had more than one psychiatric condition. Strong tetrachoric correlations were found between depressive episodes and both generalised anxiety disorder (0.68) and panic disorder/phobias (0.68). Indeed, the presence of an anxiety disorder is the single, greatest clinical risk for the development of depression and patients who have depression and anxiety comorbidity have higher chronicity, higher severity of illness and have significantly greater impairment in functioning at work as well as on a psychosocial level than patients not suffering from comorbidity (Hirschfield, 2001).

#### 4.6.1.6 Suicidal thoughts and suicide attempts

In the index sample, 18 individuals (36%) had experienced suicidal thoughts (including tedium vitae and suicidal ideation) and of these, eight individuals (16%) had made a suicide

attempt. In the sibling sample, 16 individuals (40%) had a lifetime history of suicidal thinking and of these individuals, five (12.5%) had attempted suicide. This finding is consistent with George Huntington's original description of the disease and with subsequent reports of a high prevalence of suicidal behaviour in HD. Patients with HD have been found to commit suicide approximately four times more often than the general population (Schoenfield et al., 1984 and Farrer, 1986) and lifetime prevalence of suicide attempts for individuals with HD range from 5.3% (Brothers et al.,1964) to 17.7% (Farrer et al., 1986). The lifetime prevalence rate of suicidality (including suicidal thoughts and suicide attempts) was reported as 19.9% for a large, European cross-sectional study of 1280 motor symptomatic individuals (Orth et al., 2010). However, suicidality was assessed as present or absent as part of a general questionnaire on medical history and may under-report the true lifetime prevalence. Indeed, there may be a further underestimation of the true suicide rate due to recall bias or perhaps the fact that people may not want to admit to having had such thoughts in their lifetime. In the current study, there were two individuals who reported that they had no history of suicidal behaviour, yet their medical notes stated that they had attempted suicide previously. In the UK population study, the APMS, the lifetime prevalence rates of suicidal ideation and suicide attempts were higher for the self-completed questionnaire than for the face to face interview (Adult Psychiatric Morbidity Study, 2007). The lifetime prevalence rates of suicidal thoughts and attempts measured by face to face interview in the UK APMS study were 13.7% and 4.8% respectively. The findings in the present study were much greater than those observed in the UK general population. Previous research has suggested that the presence of depressed mood (and not necessarily a formal DSM-IV diagnosis of depression) is a significant predictor of suicidality in HD mutation carriers (Orth et al., 2010;

Wetzel et al.,2011; Hubers et al., 2012). Given the high proportion of individuals with HD relative to the general population that experience depressed mood, it is perhaps not surprising that the suicidal behaviour rate is also higher in the HD population.

#### 4.6.1.7 Summary of the lifetime prevalence of psychiatric disorders in HD

A summary of the lifetime DSM-IV prevalences of any mood disorder, major depression, bipolar I-II disorders, any anxiety disorder, panic disorder, OCD and alcohol abuse observed in the current study and reported in the NCS-R and ESEMeD general population studies are displayed in Table 4.18. Table 4.19 summarises the comparisons between the prevalence rates of suicidal thoughts and suicide attempts in the present study with the findings in the UK general population APMS study.

The findings of the current study are in general consistent with the prevalence of psychiatric disorders previously reported in the HD literature and indicate the existence of strong population associations between HD and any mood disorder, major depression and panic disorder as well as moderate population associations between HD and any anxiety disorders. The findings also suggest that the lifetime prevalence rate of alcohol abuse is similar to the general population and that bipolar disorders may be less common in the HD population than in the general population. Although the current study found the prevalence of OCD to be lower than that in the general population, some previous studies have suggested that HD mutation carriers are significantly more likely to experience OCD than the general population (Anderson et al., 2001; van Duijn et al., 2008). However, it is not clear whether these figures reflect true OCD or obsessive-compulsive symptoms.

**Table 4.18 Comparisons of the lifetime prevalence of mood disorders, anxiety disorders and alcohol abuse in the current study to the prevalence reported in two large general population studies.**

| | Lifetime prevalence (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | HD: Index sample | | HD: Sibling sample | | ESEMeD | | NCS-R | |
| **DSM-IV Diagnosis** | **Total** | **Female only** | **Total** | **Female only** | **Total** | **Female only** | **Total** | **Female only** |
| Any Mood Disorder | 56 | 60.6 | 65 | 79.2 | 14 | 18.2 | 21.4 | 24.9 |
| Major Depression | 42 | 48.5 | 42.5 | 50.0 | 12.8 | 16.5 | 16.9 | 20.2 |
| Bipolar I-II Disorder | 0 | 0.0 | 0 | 0.0 | - | - | 4.4 | 4.5 |
| Any Anxiety Disorder | 38 | 42.4 | 25 | 33.3 | 13.6 | 17.5 | 31.2 | 36.4 |
| Panic Disorder | 22 | 30.3 | 12.5 | 16.7 | 2.1 | 2.5 | 4.7 | 6.2 |
| OCD | 0 | 0.0 | 0 | 0.0 | - | - | 2.3 | 3.1 |
| Alcohol Abuse | 6 | 3.0 | 7.5 | 12.5 | 4.1 | 1.0 | 13.2 | 7.5***** |

OCD; Obsessive Compulsive Disorder, ESEMeD; European Study of the Epidemiology of Mental Disorders (Alonso *et al.,* 2004), NCS-R; National Comorbidity Survey-Replication (updated data as of July 19, 2007) (Kessler *et al.,* 2005).
*****This figure represents the lifetime prevalence of alcohol abuse with/without dependence.

**Table 4.19 Comparisons of the lifetime prevalence of suicidal thoughts and attempts in the HD index and sibling samples with the UK APMS Survey**

| | Lifetime prevalence (%) | | |
|---|---|---|---|
| | **HD: Index sample Total** | **HD: Sibling sample Total** | **APMS Survey* Total** |
| Suicide Attempts | 16 | 12.5 | 4.8 |
| Suicidal Thoughts** | 36 | 40 | 13.7 |

APMS; The Adult Psychiatric Morbidity Survey 2007
*****The APMS survey did not report the female and male differences in the prevalence rates for the face to face interview **Figures for the HD samples include individuals with a lifetime history of suicide attempts but it is not clear whether this is true for the APMS Survey

### 4.6.2 Age at Onset of Psychiatric Illness

The median age at onset for any psychiatric illness was 41 years for the index sample and 34.5 years for the sibling sample. Compared with the general population survey the NCS-R, the median age of onset of mood disorders, anxiety disorders and alcohol abuse was much later in the HD samples as summarised in Table 4.20. Anxiety disorders most notably had a much later age of onset in the HD samples than the general population sample. However, unlike the mood disorders and substance abuse disorders, the age of onset distributions for specific anxiety disorders in the general population sample were more diverse. Separation anxiety disorder and specific phobias had a median age of onset of 7 years, social phobia had a median age of onset of 13 years where as other anxiety disorders had later median ages of onset of between 19 and 31 years. This could partly account for the differences in age of onset observed given that the individuals with a history of an anxiety disorder in the current study predominantly had a diagnosis of the 'other anxiety disorders' with a later median age of onset. However, the median ages of onset for the HD samples are still considerably later than those found in the general population.

**Table 4.20 Comparison of the median age of onset of psychiatric disorder in the HD samples and the NCS-R sample.**

| | Age at onset (years) | | |
|---|---|---|---|
| | **HD: Index sample Median (IQR)** | **HD: Sibling sample Median (IQR)** | **NCS-R sample Median (IQR)** |
| Any mood disorder | 42 (31.25-46.25) | 33 (25-45) | 30 (18-43) |
| Any anxiety disorder | 41 (28.25-46.25) | 37 (29.5-40) | 11 (6-21) |
| Alcohol abuse* | 29 (24-39.5) | 34 (33-39.5) | 20 (18-27) |

IQR; Inter Quartile Range

*For the NCS-R sample, alcohol abuse was reported under the general category of substance use disorders

#### 4.6.2.1 Relationship between age at onset of psychiatric illness and age at onset of HD

The majority of individuals in the HD index and sibling samples with a lifetime diagnosis of a depressive and/or anxiety disorder had an onset of their psychiatric disorder before the onset of their HD (defined by motor onset). In the index sample, there was at least one individual for all DSM-IV diagnoses other than anxiety disorder NOS with an age of psychiatric onset that preceded HD onset by at least 20 years. For the sibling sample, there was only an individual with a DSM-IV diagnosis of recurrent major depression and one with depression NOS who had a psychiatric onset at least 20 years prior to their HD onset. However, four of the other six DSM-IV diagnostic categories were only comprised of one or two individuals. This is consistent with previous findings in HD suggesting the onset of psychiatric symptoms may occur up to 20 years before the onset of motor symptoms (Folstein et al 1983). Folstein and colleagues found in their study of individuals with HD in Maryland, USA that 23 out of 34 patients for whom accurate onset data was available experienced depressive symptoms before the onset of chorea by an average of 5.1 years (Folstein et al., 1983). Studies that have used a pre-motor symptomatic HD population also find a high proportion of individuals with psychiatric symptoms (Julien et al., 2007, Kingma et al., 2008). Previous studies have reported a clustering of affective symptoms around the time of motor onset (Watt and Seller, 1993; Julien et al., 2007) and for symptomatic patients in Stage 2 of the illness (Paulsen et al., 2005). However, no such clustering was found in this study and instead the findings are consistent with the research that suggests symptoms of depression (including depressed mood, depressive cognitions, anxiety and suicidal ideation) occur with roughly equal frequency at all stages of the illness (Craufurd et al., 2001, Kingma et al., 2008).

#### 4.6.2.2 Possible explanations for the older age at onset of psychiatric illness in HD and onset often prior to an HD clinical diagnosis.

The results suggest that the age at onset of psychiatric disorders in HD is significantly later than in the general population and is often before the age of motor onset of HD. This suggests that the presence of psychiatric symptoms in HD cannot be fully explained as a psychological reaction to receiving a clinical diagnosis of HD and the motor and cognitive symptoms that ensue. Both biological and psychological explanations can account for these findings, which are not necessarily mutually exclusive.

If neurobiological changes secondary to the HD gene mutation play a causal role in the development of psychiatric problems, then given that the typical age at onset of HD is in middle adult life (approximately age 30-50 years), the later age of onset of psychiatric disorders in the HD population could be partly explained by this. Many examples of particular structural brain changes and dysfunctional biological pathways common to both individuals with HD as well as individuals with psychiatric diagnoses and no HD have been described (see section 2.9.3 and 2.9.4), including: decreased caudate nucleus volume (Krishnan et al., 1992); decreased ventral striatal activation (Cummings, 1995; Epstein et al., 2006); abnormal metabolic activity in the orbitofrontal cortex and the anterior cingulate/caudal medial prefrontal cortex (Saxena et al., 2001); dysfunction of the frontal-subcortical circuits (Bonelli and Cummings, 2007); dysregulation of the serotonin (5-HT) signalling system (Du et al., 2013); hyperactivity of the hypothalamic pituitary adrenal (HPA) axis (Du et al., 2013) and alterations in the dopamine system (Chen et al., 2013). Some HD associated neuropathological changes including significant changes in whole brain volume and regional grey and white matter differences are known to occur in HD gene carriers many

years before motor symptoms are apparent (Aylward et al., 2004; Paulsen et al., 2006b; Tabrizi et al., 2009; Tabrizi et al., 2011), which could account for psychiatric onset prior to an HD motor diagnosis.

Psychological causes could also contribute to the finding that onset of psychiatric illness is older in individuals with HD and often prior to motor onset in HD. Psychosocial problems associated with having HD are indeed apparent many years before the symptoms of HD actually begin. Even from a young age, HD can considerably impact family life, especially for those young people at risk of HD. A study of young people's experiences of growing up in a family affected by Huntington's disease revealed that young people may often act as carers for an affected parent with HD, they may worry so much about their own risk for HD that it has a detrimental impact on their life physically and emotionally, and some young people may suffer directly from physical and/or sexual abuse by an affected family member (Forrest et al., 2007). Worrying about being at risk for HD and for some individuals choosing to undergo predictive testing brings with it further emotional and psychological problems before the onset of HD. An eleven year study of predictive testing for HD in Germany, found an average age at testing of 35 years (Bernhardt et al., 2009). Although surveys of attitudes toward predictive testing indicated that suicide would be contemplated by 11-15% of at-risk individuals if they received an increased-risk result (Kessler et al., 1987; Mastomauro et al., 1987), research has suggested that catastrophic events (including suicide, attempted suicide and psychiatric hospitalisation) are seemingly rare following an HD predictive test result (a worldwide survey found that 0.97% in a cohort of 4,527 test participants had experienced a catastrophic event) (Almqvist et al.,1999). However, some studies have reported that

depressed mood and feelings of hopeleness are common following a positive predictive test result with one study reporting that 58% of carriers were experiencing current depressed mood even after a mean of 3.7 years following the test result (Gargiulo et al., 2009). A further study found that the one year prevalence post-testing of major depression was 6.0% in those who received a positive result (versus 3.0% in those with a negative result) and 20.0% of the sample had clinically significant depressive symptoms (versus 12.6% in those with a negative test result) (Codori et al., 2004). Other studies have reported results to the contrary suggesting that although individuals who receive a positive predictive test result may suffer from general psychological distress short-term, longer-term their psychological adjustment is no different to their baseline measures (Wiggins et al., 1992; Codori et al., 1997).

HD continues to impact individuals psychologically throughout the preclinical phase prior to onset of motor symptoms. A positive correlation has been found between levels of stress (measured using the Perceived Stress Scale) and depression (measured using the Beck Depression Inventory-II) in prodromal Huntington's disease (Downing et al., 2012). Ho et al., (2011) found in their study of the impact of HD across the entire disease spectrum that in the pre-clinical phase, the concerns expressed by individuals gene positive for HD included anxiety regarding the impact of HD on their family and worry about themselves showing symptoms. Clearly there are numerous psychological issues that have the potential to result in clinically significant psychiatric problems even prior to an HD diagnosis. It is therefore of great importance that effective interventions are provided to the most vulnerable individuals throughout their lifespan.

### 4.6.3 Comparison between the depression phenotype in HD and unipolar depression

Of all the behavioural problems observed in HD, depression constitutes a significant component of the overall psychiatric morbidity (Guttman et al., 2003). This was true for the current study with over half the participants in both the index and sibling sample having a lifetime DSM-IV diagnosis of a depressive disorder. The following sections will discuss the findings relating to the depression phenotype for the HD MDDR sample in the present study and will compare them with the findings in a sample of non-HD individuals with a lifetime history of MDDR: the MDRG sample. This is the first study to compare the clinical presentation of depression in individuals with and without HD.

#### 4.6.3.1 Suicidality and depression

The majority of both depression samples were found to have a history of suicidal thoughts (100% index sample and 84.1% MDRG sample) and although the HD sample had a relatively higher proportion of individuals than the MDRG sample who had made at least one suicide attempt (50% versus 32.2%), this difference did not reach significance. This study further confirms the importance of prioritising assessment for suicidality in those HD individuals with a depressed mood whether they are pre-motor or motor symptomatic.

#### 4.6.3.2 Age at onset of depression

The median age at depression onset was significantly older for individuals in the HD sample than the MDRG sample (41 years versus 27 years respectively) (U=1063.5, $p$=0.005). Both biological and psychological explanations can account for this finding as described in section 4.6.2.2, which are unlikely to be mutually exclusive.

#### 4.6.3.3 Frequency of episodes of affective illness per year

Individuals in the HD sample were found to experience significantly more frequent episodes of depression (median = 0.432 episodes per illness year) than individuals in the MDRG sample (median = 0.28 episodes per illness year) (U=1082.0, *p*=0.006). This finding could be due to the fact that individuals with HD are also more likely to experience a depressive episode for a shorter duration (see 4.6.3.4) and therefore there is the opportunity for more episodes of depression per year.

#### 4.6.3.4 Longest duration of affective illness

The median length of the longest duration of a depressive episode was less for individuals in the HD sample (39 weeks) than in the MDRG sample (65 weeks) and approached significance (*p*=0.06). Possible explanations for why episodes of depression in HD may be of shorter duration than in the general population include the fact that HD patients typically receive regular out-patient appointments and therefore may receive earlier treatment and care, HD patients may respond better and quicker to anti-depressants and/or this finding could represent a less severe depression observed in the HD population relative to individuals without HD.

#### 4.6.3.5 OPCRIT

Individuals in both the HD and MDRG samples were most likely to experience the symptoms of depression most typically associated with sadness and low mood: dysphoria, loss of pleasure, excessive self-reproach, suicidal ideation and loss of energy. The lifetime frequencies of the “biological” items diurnal variation, increased appetite and middle insomnia were significantly lower for individuals in the HD sample than in the MDRG sample.

Additionally, although significance was not reached, individuals in the HD sample were less likely to experience poor appetite, weight gain and decreased libido as part of their depression than the MDRG sample.

These findings suggest that people with HD experience fewer core biological symptoms of depression than individuals with depression and no HD. Major depression within the general population is a heterogeneous entity with individuals not necessarily experiencing the same symptoms, severity of symptoms or duration (Goldberg, 2011). If depression in HD has a different aetiology to those with depression but no HD, it is quite possible that the phenotype could also be different.

A possible contribution to this finding is measurement difficulties when assessing depression in individuals with HD. An inclusive method where all symptoms regardless of their cause (HD or depression) are considered part of the psychiatric presentation likely results in an overdiagnosis of people with depression and HD. Conversely, an exclusive method where depressive symptoms are attributed more to having HD likely results in an underdiagnosis of depression in HD. In this study, the semi-structured interview allowed for psychiatric symptoms to be fully explored and rated only if they were clearly associated with the temporal course of psychiatric disorder rather than HD. At times, this was difficult to determine and therefore the symptom was classified as unknown. This may have led to an underreporting of those symptoms which are common to both HD and depression (including change in sleep and appetite) and may contribute to the finding that these symptoms were less common in the HD sample compared to the MDRG sample.

#### 4.6.3.6 The BADDS and GAS

The BADDS and the GAS were useful dimensional scales that provided extra information on an individual's lifetime experience of psychopathology relevant to depression. These scales were able to capture information that the more strict diagnostic categorical tools were not able to. For example, the BADDS and GAS provide ratings for the severity of depression and sub-clinical cases of depression, which available diagnostic categories are relatively unhelpful in doing.

The scores obtained on the BADDS and GAS further support the possibility that depression in HD is less severe than that observed in the general population. Individuals in the HD sample had non-significant lower scores on the BADDS, indicating a less severe depressive illness course. For the GAS ratings, individuals in the HD sample had significantly less impairment of functioning during their worst episode of depression than individuals in the MDRG sample.

The experience of less severe depression in individuals with HD could also be due to the explanations outlined in the previous section (section 4.6.3.5): depression in HD may have a different cause and therefore a different phenotype to the general population; and/or measurement difficulties. The contribution of genetic and environmental factors to the aetiology of psychiatric illness in HD will be further explored in the following chapter: the familiality of psychiatric symptoms in HD.

### *4.7 Summary and limitations*

This chapter has presented the findings of a systematic investigation of the psychiatric phenotype in HD using a battery of standardised categorical and dimensional measures. The main findings of the chapter are summarised below:

*Lifetime Prevalence of Psychiatric Features*

- 56% of the index sample and 65% of the sibling sample had a lifetime DSM-IV diagnosis of a depressive disorder.
- 38% of the index sample and 25% of the sibling sample had a lifetime DSM-IV diagnosis of an anxiety disorder.
- 6% of the index sample and 7.5% of the sibling sample had a lifetime DSM-IV diagnosis of alcohol abuse.
- No individuals in either HD sample were found to have a lifetime DSM-IV diagnosis of OCD or bipolar disorder, contrary to previous literature.
- 36% of the index sample and 40% of the sibling sample had a history of suicidal behaviour. 16% of the index sample and 12.5% of the sibling sample had made at least one previous attempt at suicide.

*Age of Onset of Psychiatric Illness*

- For the index sample and sibling samples, the median age of onset for any psychiatric illness was 41 and 34.5 years respectively.
- The median age of onset for any depressive disorder was 42 years for the index and 33 years for the sibling sample.
- The median age of onset for any anxiety disorder was 41 years and 37 years for the index and sibling samples respectively.

- The median age of onset for alcohol abuse was 29 years for the index sample and 34 years for the sibling sample.
- At least half of the HD symptomatic individuals in both the index and sibling samples with a lifetime DSM-IV diagnosis of a depressive and/or an anxiety disorder, experienced onset of their psychiatric disorder prior to the motor onset of their HD.

*Comparison of the depression phenotype in HD with the non-HD MDRG sample*

Given that depression is consistently the most frequently reported psychiatric disorder observed in individuals with HD, the depression phenotype was a specific focus of this chapter with a sample of individuals from a large mood disorders study with MDDR being used as a comparative non-HD sample. The MDRG sample was an ideal comparative sample, owing to the fact that the same gold standard assessment tools were used in the neuropsychiatric assessment of both samples.

- A lifetime history of suicidal behaviour was common to both the HD and MDRG samples but individuals with HD were more likely to have made a previous attempt at suicide.
- The median age of onset for depression was significantly older in the HD index sample than the MDRG sample.
- The HD individuals were significantly more likely to experience more frequent episodes of depression of a shorter duration than the MDRG individuals.
- Individuals with HD experienced core biological symptoms of depression less frequently than individuals in the MDRG sample. This finding was significant for the items diurnal variation, increased appetite and middle insomnia.

- Individuals with HD may experience less severe depression than those with MDDR in the general population as evidenced by scores obtained on the GAS and BADDS.

An important limitation of the study is the modest sample size of the index and sibling samples, which does mean that there is limited power to detect significant relationships. HD individuals were recruited to the current study solely on the basis that they had a sibling with a genetic diagnosis of HD, however, it is possible that individuals with psychiatric symptoms were more likely to be involved and well known to their HD service and consequently more likely to be recruited to the study, resulting in a recruitment-bias. Conversely, individuals with more severe psychiatric symptoms were likely to be under-represented in the sample as they would perhaps be less likely to respond to an invitation to take part in the study.

Other limitations include the retrospective reporting of an individual's psychiatric history, which could have led to some inaccuracies within the data. However, to try and minimise this, data was collected from as many different sources as possible including caregivers and case notes. Difficulties with measuring symptoms of depression in HD patients (see section 4.6.3.5) could have contributed to the finding that the depression phenotype in HD may be different to that in the non-HD population. Additionally, although the HD index sample and MDRG sample were well matched for age, gender and ethnic origin, individuals in the HD sample had a significantly lower level of educational attainment than individuals in the MDRG sample. Future studies should also match for education level to avoid potential confounding.

The findings observed in the current study require replication in a larger sample and for future research into the psychiatric phenotype of HD, a large sample of unrelated HD individuals should be much easier to recruit than the HD gene positive sibling sample required for this study. Nevertheless, the findings observed do highlight the prominent role psychiatric features play across the lifespan of an individual with HD and the importance of input from services to assess psychiatric well-being in HD families, especially those individuals at risk of suicide.

The following chapter attempts to further elucidate the cause of psychiatric disorders in HD by focusing on the familial relationship between HD and psychiatric disorders/symptoms in a sample of HD-affected sibling pair families.

# CHAPTER 5: THE FAMILIALITY OF PSYCHIATRIC SYMPTOMS IN HD

This chapter will focus on the aetiology of the high prevalence of psychiatric symptoms in HD by investigating whether such psychiatric symptoms/disorders cluster in families with HD. The chapter will therefore outline the methodology and statistical analysis specific to this chapter before detailing the results of the analyses, which will include: the familililality of lifetime psychiatric diagnoses, the familiality of psychiatric ratings for depression and age at onset of any lifetime DSM-IV psychiatric illness as well as a description of the HD gene negative sample. This will be followed by a discussion of the results and limitations.

## *5.1 Introduction*

It is consistently reported in the HD literature that the prevalence of psychiatric symptoms is greater in HD patients than in the general population (Paulsen et al., 2001) and the results obtained in the present study as described in the previous chapter support this finding. However, the reasons for this association are not yet known. Evidence to date suggests that, except for the neuropsychiatric symptom of apathy, the wide array of other behavioural changes observed in HD are not related to disease progression (Craufurd et al., 2001; Thompson et al., 2002) and the prevalence of psychiatric symptoms is independent of the length of the trinucleotide expansion (Naarding et al., 2001; Vassos et al., 2007). Other genetic and/or environmental factors that may influence the presence and severity of psychiatric phenotypes in HD have received little attention.

### 5.1.1 Aims

Therefore, the main aims of this chapter are to:

i) Determine whether a broad range of psychiatric syndromes and symptoms aggregate in families affected with HD by conducting a systematic, standardised psychiatric assessment on a large sample of sibling pairs with HD.

ii) Further improve current understanding of the relative role the HD gene, other genetic factors and psychosocial factors may play in explaining the increased prevalence of psychiatric symptoms in HD. This will be achieved by administering the psychiatric assessment to unaffected siblings who have had a negative HD genetic test.

### 5.1.2 Family studies

Family studies are an important step towards understanding the contribution of familial and non familial factors to a particular phenotype. Familiality indicates that the phenotype under investigation clusters within families and although hints at a genetic basis, it can be caused by any of the following factors: shared genetic predisposition between family members, shared environmental factors within families or an interaction between shared genes and the shared environment. The few studies that have explored the familiality of psychiatric syndromes/symptoms in HD are discussed below.

Tsuang et al (2000) investigated the familiality of psychotic symptoms in forty-four patients with HD, 22 with and 22 without psychosis. Of the 22 probands with psychosis, eight had psychosis only, eight had mixed affective and psychotic symptoms and six had psychotic

symptoms secondary to dementia. The HD patients with psychosis were found to be significantly more likely to have a first-degree relative with psychosis than the HD patients without psychosis. Furthermore, for eight of the nine HD probands with psychosis who had first-degree relatives with psychosis, the relatives' psychosis co-occurred with HD. Consequently, it was estimated that the risk of first-degree relatives with HD developing psychosis was 36% for those relatives of probands with psychosis compared with an 8% risk for the relatives of probands without psychosis. The authors suggested that other genetic factors may predispose individuals in certain HD families to develop psychosis, for example, modifying genes may increase this susceptibility by interacting with the HD gene.

Tsuang et al (1998) conducted a small case-control study investigating the aggregation of schizophrenia-like symptoms in two families, one where the juvenile onset HD proband had schizophrenia-like symptoms and one with a non-psychotic juvenile onset HD proband for comparison. The results demonstrated that in the family where the juvenile onset HD proband had schizophrenia-like symptoms, the proband's father and possibly the paternal grandmother (a diagnosis was based on medical records) all exhibited schizophrenia-like symptoms, which co-occurred with HD. Conversely, none of the HD affected family members of the juvenile HD onset proband without schizophrenia-like symptoms presented with such symptoms. Like other studies (Berrios et al., 2001; Naarding et al., 2001; Vassos et al., 2008), the predisposition to develop schizophrenia-like symptoms appeared to be independent of the CAG expansion size and again implicates a role for shared familial factors in the disease presentation.

Lovestone et al (1996) described a family where four members with HD initially presented with a severe psychiatric disorder between three and nine years before any choreic symptoms were apparent. Three of the four family members were diagnosed with a schizophrenia-like syndrome and the other received a diagnosis of depression. Additionally, of two further family members who had no signs of motor symptoms at presentation, one was diagnosed with major depressive disorder and the other with schizoaffective disorder. Similarly, Heathfield (1967) described a family where a brother and sister with HD were diagnosed with identical paranoid schizophrenic psychoses, while another brother who did not develop choreiform movements, also suffered from this psychotic disorder. Correa et al. (2006) described an HD family where all known family members who carried the HD gene also developed psychotic symptoms at least five years prior to the onset of any significant motor or cognitive symptoms. The authors proposed that in these HD families, the HD gene may behave as a large effect schizophrenia gene in the presence of a low load of small effect schizophrenia genes (Correa et al., 2006).

Folstein et al (1983), in order to investigate possible causes of depression in HD, interviewed first-and second-degree relatives of five consecutive HD probands with major affective disorder and five HD probands with no affective disorder, all ascertained from their Maryland case series. It was found that the HD affected relatives of the probands with HD and depression were significantly more likely themselves to have affective disorder (20 out of 23 relatives with HD) than the HD relatives of the probands without affective disorder (only 5 of 23 relatives had concurrent HD and affective disorder). The authors proposed that

the familial association of affective disorder with HD could be due to either genetic heterogeneity or genetic linkage between loci for HD and affective disorder.

An association between obsessive-compulsive disorder (OCD) and pathological gambling with HD has been described in an Italian pedigree (De Marchi et al., 1998). Of the seven children of an affected parent with OCD and HD, two individuals were found to have a diagnosis of OCD and a further two a diagnosis of pathological gambling. In addition, all four children were found to carry the HD gene after mutation analysis. However, of the additional three children without an OCD or pathological gambling diagnosis, one was also found to be HD gene positive. The authors hypothesised that their findings might be accounted for by the HD gene contributing to the overall clinical picture of OCD or genetic linkage between the gene(s) for OCD and the HD gene.

These studies demonstrate that familial factors may influence the psychiatric phenotype in HD. Therefore, in order to build on the findings of these previous small-scale family studies, data on lifetime psychiatric diagnoses and symptoms were obtained for 53 sibling pairs gene positive for HD and where possible the same data for siblings gene negative for HD were also collected. This study provides a larger sample size than previously reported, uses a systematic and more thorough methodology through the use of face-to-face standardised interviews together with medical notes and focuses on the full range of psychiatric symptoms and syndromes observed in HD.

## *5.2 Methods*

The methods and clinical description of the *HD gene positive* index and sibling samples were described in Chapter 4. The number of HD gene positive siblings recruited from any single family ranged from one to four, including one sibling from 10 families, two siblings from 35 families, three siblings from four families and four siblings from one family. Using the independent sibling pair model of one affected sibling pair per family, this gave a total of 40 sibling pairs. The six extra siblings from the five families where more than two siblings gene positive for HD were recruited to the study were included in the larger all possible sibling pairs model, which gave a total of 53 sibling pairs. The demographic characteristics of these six siblings are outlined in section 5.4.1 given that they have not been included in any previous analyses and therefore were not described in Chapter 4.

The methods for ascertainment of the *HD gene negative* sample were described in section 3.2.2 and the demographic characteristics of the gene negative sample are summarised in section 5.4.1.

## *5.3 Statistical analysis*

### *HD gene positive sample*

All statistical tests were performed using the statistical package SPSS version 19 (IBM Corp, 2010) and statistical tests were considered significant at the $p<0.05$ level. Initial analyses were performed using the all-possible sibling pairs model where sibling trios were treated as three sibling pairs and the family of four siblings was counted as six possible pairs making a total of 53 sibling pairs. Although this raises the issue of the second and additional sibling

pairs in a family not being independent of the initial pair, previous research (Kendler et al., 1997, 2000) has suggested that the inclusion of sibships of up to four individuals results in comparable associations whether the non-independent sibling pairs are included or not. Where a significant result was found, the analysis was repeated using the independent sibling pair model (i.e. using just the index sibling and the sibling from the sibling sample per family). This determined if the significance still held when only the 40 independent sibling pairs were included.

*Categorical ratings:*

The kappa statistic was used to determine the concordance of categorical ratings between sibling pairs gene positive for HD for the following broad and narrow diagnostic criteria: i) any lifetime DSM-IV diagnosis (present/absent), ii) a lifetime DSM-IV diagnosis of any depressive disorder (present/absent), iii) a lifetime DSM-IV diagnosis of recurrent major depressive disorder (MDDR) (present/absent) and, iv) a lifetime DSM-IV diagnosis of any anxiety disorder (present/absent). Additionally, concordance between sibling pairs was determined for lifetime ratings of suicidality (present/absent) and for lifetime ratings of the Problem Behaviours Assessment (PBA) items; perseverative thinking, apathy, irritability and aggression (all present/absent). For the PBA, symptoms were considered present if the severity score for that item was two or more. Where a diagnosis or rating was not known for one or both of the siblings, this sibling pair was excluded from the analysis.

*Continuous ratings:*

Intra-class correlation coefficients (ICC) were used to determine the correlations between HD gene positive sibling pairs for continuous ratings, including: i) age at onset of first psychiatric impairment, ii) scores obtained on the Bipolar Affective Disorder Dimensional

Scale – Depression subscale (BADDS-D) and, iii) the Global Assessment Scale – worst ever functioning in a depressive episode (GAS). Sibling pairs were excluded from the analysis when one or both of the siblings either did not have a known rating, or for the age at onset and GAS analyses, when a sibling did not have a rating due to the fact they had no lifetime history of a DSM-IV psychiatric illness or DSM-IV depressive disorder respectively.

***HD gene negative sample:***

The mean age at the time of interview was reported and all other demographic characteristics were described in terms of frequencies and percentages. Given the small size of this sample (N=5), a descriptive approach reporting the presence/absence of any psychiatric symptoms/disorders in those individuals was adopted.

## *5.4 Results*

### 5.4.1 Demographic characteristics of the additional six siblings gene positive for HD

The demographic characteristics of the additional six gene positive siblings used in the all possible sibling pairs model are summarised in Table 5.1. Five of the six had a clinical diagnosis of HD alongside their genetic diagnosis. The mean age of the siblings was 48 years and half of the individuals were female. All were of UK/Eire Caucasian ethnicity and the majority of the sample were either married or had lived as married (83.3%). Two-thirds of the sample had A-levels as their highest level of education and the majority of the sample (66.7%) had worked as professionals.

**Table 5.1 Demographic characteristics of the additional 6 gene positive individuals.**

| **Demographics** | **Descriptives and Percentages N = 6** |
|---|---|
| **Age (years)** | |
| Mean (95% CI) | **48.0** (43.0-53.0) |
| Standard Deviation | 6.26 |
| Range | 40-59 |
| | |
| **Female** | **N (%)** (95% CI) |
| | **3 (50.0)** (10.0-90.0) |
| | |
| **Ethnic Origin** | |
| UK/Eire Caucasian | **6 (100.0)** (-) |
| | |
| **Marital status** | |
| Has married/lived as married | **5 (83.3)** (44.9-100) |
| Has never married/lived as married | **1 (16.7)** (0-53.5) |
| | |
| **Highest Level Education** | |
| A level/ HND/ BTEC | **4 (66.7)** (29.0-100) |
| Degree | **2 (33.3)** (0-71.0) |
| | |
| **Highest Lifetime Occupation** | |
| Professionals, senior officials and managers | **4 (66.7)** (29.0-100) |
| Plant & machinery operators and assemblers | **1 (16.7)** (0-53.5) |
| Armed forces | **1 (16.7)** (0-53.5) |

### 5.4.2 Familial clustering of categorical ratings

Lifetime DSM-IV diagnoses were known for 50 sibling pairs, which were from 37 different families (32 families contributed 1 sibling pair, 4 families contributed 3 sibling pairs and 1 family contributed six sibling pairs).

#### 5.4.2.1 Concordance between sibling pairs for any lifetime DSM-IV disorder

The presence/absence of a lifetime DSM-IV disorder was known for 50 sibling pairs and using this broad diagnostic category, 35 sibling pairs were concordant and 15 sibling pairs were

discordant, resulting in a fair but significant level of agreement as shown in Table 5.2 (κ = 0.302, p=0.031).

**Table 5.2 Concordance between all possible sibling pairs (N = 50 pairs) for any lifetime DSM-IV psychiatric diagnosis.**

| | **Sibling 2 No DSM-IV diagnosis** | **Sibling 2 DSM-IV diagnosis** |
|---|---|---|
| **Sibling 1 No DSM-IV diagnosis** | 8 | 6 |
| **Sibling 1 DSM-IV diagnosis** | 9 | 27 |

κ = 0.302, p=0.031

This analysis was repeated using only the 37 independent sibling pairs. As shown in Table 5.3, 26 sibling pairs were concordant and 11 sibling pairs were discordant, which resulted in a non-significant level of agreement (κ = 0.27, p=0.10).

**Table 5.3 Concordance between independent sibling pairs (N=37 pairs) for any lifetime DSM-IV psychiatric diagnosis.**

| | **Sibling 2 No DSM-IV diagnosis** | **Sibling 2 DSM-IV diagnosis** |
|---|---|---|
| **Sibling 1 No DSM-IV diagnosis** | 5 | 5 |
| **Sibling 1 DSM-IV diagnosis** | 6 | 21 |

κ = 0.27, p=0.10

### 5.4.2.2 Concordance between sibling pairs for a lifetime DSM-IV diagnosis of any depressive disorder

Associations between all the possible sibling pairs (50 sibling pairs) for a lifetime DSM-IV diagnosis of any depressive disorder, including a lifetime DSM-IV diagnosis of i) major recurrent depression (MDDR), ii) single episode major depression (MDDS) and iii) depression not otherwise specified (depression NOS), revealed a moderate and significant level of familial clustering (κ = 0.444, p=0.002) with 37 sibling pairs concordant for any depressive disorder and 13 sibling pairs discordant (Table 5.4).

**Table 5.4 Concordance between all possible sibling pairs (N=50 pairs) for a lifetime DSM-IV diagnosis of any depressive disorder**

| | **Sibling 2 No DSM-IV depression** | **Sibling 2 DSM-IV depression** |
|---|---|---|
| **Sibling 1 No DSM-IV depression** | 12 | 8 |
| **Sibling 1 DSM-IV depression** | 5 | 25 |

$\kappa$ = 0.444, p=0.002

When this analysis was repeated using only the 37 independent sibling pairs, 28 sibling pairs were concordant for any depressive disorder and 9 sibling pairs were discordant (Table 5.5), which still resulted in a moderate and significant level of familial clustering, ($\kappa$ = 0.46, p=0.004).

**Table 5.5 Concordance between independent sibling pairs (N=37 pairs) for a lifetime DSM-IV diagnosis of any depressive disorder**

| | **Sibling 2 No DSM-IV depression** | **Sibling 2 DSM-IV depression** |
|---|---|---|
| **Sibling 1 No DSM-IV depression** | 8 | 6 |
| **Sibling 1 DSM-IV depression** | 3 | 20 |

$\kappa$ = 0.46, p=0.004

### 5.4.2.3 Concordance between sibling pairs for a lifetime DSM-IV diagnosis of recurrent major depressive disorder (MDDR)

Associations between all sibling pairs for a lifetime DSM-IV diagnosis of MDDR revealed that 34 sibling pairs were concordant for MDDR (although only 2 sibling pairs were concordant for having a lifetime DSM-IV diagnosis of MDDR) and 16 sibling pairs were discordant for MDDR, which was not significant as displayed in Table 5.6 ($\kappa$ = 0.010, p=0.942). Therefore, the analysis was not repeated using the independent sibling pairs.

**Table 5.6 Concordance between all possible sibling pairs (N=50 pairs) for a lifetime DSM-IV diagnosis of recurrent major depression (MDDR).**

| | Sibling 2<br>No DSM-IV MDDR | Sibling 2<br>DSM-IV MDDR |
|---|---|---|
| **Sibling 1<br>No DSM-IV MDDR** | 32 | 6 |
| **Sibling 1<br>DSM-IV MDDR** | 10 | 2 |

$\kappa$ = 0.010, p=0.942

### 5.4.2.4 Concordance between all sibling pairs for a lifetime DSM-IV diagnosis of any anxiety disorder.

Table 5.7 displays the concordance between all possible sibling pairs (N=50) for a lifetime DSM-IV diagnosis of any anxiety disorder, which included i) panic disorder with agoraphobia, ii) panic disorder without agoraphobia, iii) agoraphobia without panic disorder, iv) social phobia and, v) anxiety disorder not otherwise specified (NOS). Twenty-eight sibling pairs were found to be concordant for an anxiety disorder and 22 sibling pairs were found to be discordant, which was not significant ($\kappa$ = -0.017, p=0.899).

**Table 5.7 Concordance between all possible sibling pairs (N=50 pairs) for a lifetime DSM-IV diagnosis of any anxiety disorder.**

| | Sibling 2<br>No DSM-IV anxiety | Sibling 2<br>DSM-IV anxiety |
|---|---|---|
| **Sibling 1<br>No DSM-IV anxiety** | 24 | 7 |
| **Sibling 1<br>DSM-IV anxiety** | 15 | 4 |

$\kappa$ = -0.017, p=0.899

### 5.4.2.5 Familial clustering of lifetime suicidality in HD

Fifty-one sibling pairs from a total of 38 families with at least two sibling pairs with ratings on lifetime suicidal behaviour were included in the following analyses.

*5.4.2.5.1 Concordance between sibling pairs for lifetime suicidal ideation*

Associations between all possible sibling pairs (51 sibling pairs) for lifetime suicidal ideation, which includes a history of suicidal thoughts with or without suicide attempts, found 33 sibling pairs to be concordant for lifetime suicidal ideation and 18 sibling pairs to be discordant, which was not significant ($\kappa = 0.261$, p=0.062) (Table 5.8).

**Table 5.8 Concordance between all possible sibling pairs (N=51 pairs) for lifetime suicidal ideation.**

| | **Sibling 2 No suicidal ideation** | **Sibling 2 Suicidal ideation** |
|---|---|---|
| **Sibling 1 No suicidal ideation** | 22 | 10 |
| **Sibling 1 Suicidal ideation** | 8 | 11 |

$\kappa = 0.261$, p=0.062

*5.4.2.5.2 Concordance between sibling pairs for lifetime suicide attempts.*

Table 5.9 demonstrates that using a more narrow definition of a history of at least one suicide attempt, 38 sibling pairs were concordant and 13 sibling pairs were discordant for lifetime suicide attempts. However, of the 38 sibling pairs that were concordant, 37 of these were concordant for no history of attempted suicide, resulting in no significant concordance ($\kappa = -0.015$, p=0.913).

**Table 5.9 Concordance between all possible sibling pairs (N=51 pairs) for lifetime suicide attempts.**

| | **Sibling 2 No suicide attempts** | **Sibling 2 Suicide attempts** |
|---|---|---|
| **Sibling 1 No suicide attempts** | 37 | 6 |
| **Sibling 1 Suicide attempts** | 7 | 1 |

$\kappa = -0.015$, p=0.913

### 5.4.2.6 Familial clustering of lifetime Problem Behaviours Assessment (PBA) items

Lifetime ratings (the presence or absence) of PBA items were available for 52 sibling pairs from 39 families and were included in the following analyses.

#### *5.4.2.6.1 Perseverative thinking*

Table 5.10 displays the concordance between siblings for a lifetime history of perseverative thinking. Thirty three siblings were found to be concordant for a history of perseverative thinking and nineteen sibling pairs were found to be discordant ($\kappa = 0.263$, p=0.053), which approached significance. When only the independent sibling pairs were used in the analysis (N=39), 24 sibling pairs were concordant for perseverative thinking and 15 were discordant, resulting in a non-significant p-value ($\kappa = 0.230$, p=0.152).

**Table 5.10 Concordance between all possible sibling pairs (N=52 pairs) for a lifetime history of perseverative thinking**

| | **Sibling 2 No perseverative thinking** | **Sibling 2 Perseverative thinking** |
|---|---|---|
| **Sibling 1 No perseverative thinking** | 20 | 7 |
| **Sibling 1 Perseverative thinking** | 12 | 13 |

$\kappa = 0.263$, p=0.053

#### *5.4.2.6.2 Apathy*

Associations between all possible sibling pairs for a lifetime history of apathy revealed that 29 sibling pairs were concordant for apathy and 23 sibling pairs were discordant, which was not significant as shown in Table 5.11 ($\kappa = 0.105$, p=0.432).

**Table 5.11 Concordance between all possible sibling pairs (N=52 pairs) for a lifetime history of apathy**

| | **Sibling 2 No apathy** | **Sibling 2 Apathy** |
|---|---|---|
| **Sibling 1 No apathy** | 10 | 15 |
| **Sibling 1 Apathy** | 8 | 19 |

$\kappa$ = 0.105, p=0.432

*5.4.2.6.3 Irritability*

Associations between all possible sibling pairs (52 sibling pairs) for a lifetime history of irritability revealed a fair yet significant level of familial clustering ($\kappa$ = 0.341, p=0.013) with 36 sibling pairs concordant for a history of irritability and 16 sibling pairs discordant (Table 5.12).

**Table 5.12 Concordance between all possible sibling pairs (N = 52 pairs) for a lifetime history of irritability**

| | **Sibling 2 No irritability** | **Sibling 2 Irritability** |
|---|---|---|
| **Sibling 1 No irritability** | 11 | 6 |
| **Sibling 1 Irritability** | 10 | 25 |

$\kappa$ = 0.341, p=0.013

When only the independent sibling pairs were analysed (N = 39 pairs), a similar fair and significant level of association between siblings for a lifetime history of irritability was found ($\kappa$ = 0.357, p=0.024). Twenty-eight sibling pairs were concordant for irritability and 11 sibling pairs were discordant (Table 5.13).

**Table 5.13 Concordance between the independent sibling pairs (N=39 pairs) for a lifetime history of irritability**

| | Sibling 2<br>No irritability | Sibling 2<br>Irritability |
|---|---|---|
| **Sibling 1<br>No irritability** | 7 | 4 |
| **Sibling 1<br>Irritability** | 7 | 21 |

$\kappa$ = 0.357, p=0.024

*5.4.2.6.4 Aggression*

For a lifetime history of aggression, 37 sibling pairs were found to be concordant and 15 sibling pairs were found to be discordant, which resulted in a moderate level of familial clustering, as shown in Table 5.14 ($\kappa$ = 0.418, p=0.003).

**Table 5.14 Concordance between all possible sibling pairs (N = 52 pairs) for a lifetime history of aggression**

| | Sibling 2<br>No aggression | Sibling 2<br>Aggression |
|---|---|---|
| **Sibling 1<br>No aggression** | 21 | 7 |
| **Sibling 1<br>Aggression** | 8 | 16 |

$\kappa$ = 0.418, p=0.003

This association between the sibling pairs for a lifetime history of aggression remained significant (albeit with a reduced Kappa value, $\kappa$ = 0.384, p=0.016) when only the independent sibling pairs (N=39 pairs) were used in the analysis (Table 5.15).

**Table 5.15 Concordance between the independent sibling pairs (N=39 pairs) for a lifetime history of aggression**

| | Sibling 2<br>No aggression | Sibling 2<br>Aggression |
|---|---|---|
| **Sibling 1<br>No aggression** | 14 | 6 |
| **Sibling 1<br>Aggression** | 6 | 13 |

$\kappa$ = 0.384, p=0.016

Tables 5.16 and 5.17 summarise the Cohen's kappa and associated p-values for the categorical ratings between all possible sibling pairs gene positive for HD and for the independent sibling pairs gene positive for HD respectively.

**Table 5.16 Summary of the concordance between all possible sibling pairs gene positive for HD for all categorical ratings.**

| Rating | N* | κ | 95% CI | *p*-value |
|---|---|---|---|---|
| Any lifetime DSM-IV diagnosis | **50** | 0.302 | 0.006-0.586 | 0.031 |
| A lifetime DSM-IV diagnosis of any depressive disorder | **50** | 0.444 | 0.189-0.699 | 0.002 |
| A lifetime DSM-IV diagnosis of MDDR | **50** | 0.010 | -0.262-0.282 | 0.942 |
| A lifetime DSM-IV diagnosis of any anxiety disorder | **50** | -0.017 | -0.274-0.240 | 0.899 |
| A history of suicidal ideation | **51** | 0.261 | -0.008-0.530 | 0.062 |
| A history of suicide attempts | **51** | -0.15 | -0.415-0.115 | 0.913 |
| A lifetime history of perseverative thinking | **52** | 0.263 | 0.004-0.523 | 0.053 |
| A lifetime history of apathy | **52** | 0.105 | -0.156-0.366 | 0.432 |
| A lifetime history of irritability | **52** | 0.341 | 0.080-0.602 | 0.013 |
| A lifetime history of aggression | **52** | 0.418 | 0.171-0.665 | 0.003 |

MDDR; Recurrent Major Depressive Disorder, CI; Confidence Interval
*Number of sibling pairs included in the analysis

**Table 5.17 Summary of the concordance between the independent sibling pairs gene positive for HD for the categorical ratings that demonstrated within-pair correlations.**

| Rating | N* | κ | 95% CI | *p*-value |
|---|---|---|---|---|
| Any lifetime DSM-IV diagnosis | **37** | 0.269 | -0.066-0.604 | 0.101 |
| A lifetime DSM-IV diagnosis of any depressive disorder | **37** | 0.460 | 0.164-0.756 | 0.004 |
| A lifetime history of irritability | **39** | 0.357 | 0.051-0.663 | 0.024 |
| A lifetime history of aggression | **39** | 0.384 | 0.094-0.674 | 0.016 |

CI; Confidence Interval
*Number of sibling pairs included in the analysis

### 5.4.3 Familial clustering of continuous variables

#### 5.4.3.1 Age at onset of psychiatric illness

From the all possible sibling pairs sample of 53 pairs, there were 27 sibling pairs with a lifetime DSM-IV diagnosis for whom the age at onset of psychiatric illness was known. The correlation between siblings for the age at psychiatric onset was weak (ICC = 0.12, p=0.223).

#### 5.4.3.2 BADDS-D

BADDS-D ratings were made for 50 sibling pairs. There was a fair but significant correlation between siblings for BADDS-D scores (ICC = 0.36, *p*=0.005). When only the sample of independent sibling pairs was analysed (N=37 pairs), the within-pairs correlation was moderate and significant (ICC = 0.47, *p*=0.002).

#### 5.4.3.3 GAS – worst ever level of functioning in a depressive episode

There were 25 sibling pairs who had a lifetime DSM-IV diagnosis of a depressive disorder and for whom GAS ratings were available. The correlation between siblings for GAS scores was very weak (ICC = 0.021, *p*=0.460).

Tables 5.18 and 5.19 summarise the intra-class correlation coefficients (ICCs) for the continuous variables: age at psychiatric illness onset, BADDS-D, and GAS - worst ever functioning in a depressive episode between all possible sibling pairs and the independent sibling pairs respectively.

**Table 5.18 Summary of the intra-class correlations (ICC) of the continuous ratings between all possible sibling pairs gene positive for HD.**

| Rating | N* | ICC | 95% CI | *P* value |
|---|---|---|---|---|
| Age at Onset of Psychiatric Illness | 27 | 0.147 | -0.225 - 0.488 | 0.223 |
| BADDS-D | 50 | 0.360 | 0.091-0.580 | 0.005 |
| GAS - WEDE | 25 | 0.021 | -0.370 – 0.405 | 0.118 |

ICC; Intra-Class Correlations, BADDS-D; Bipolar Affective Disorder Dimensional Scale – Depression subscale, GAS – WEDE; Global Assessment Scale – worst ever functioning in a depressive episode, CI; Confidence Interval
*Number of sibling pairs included in the analysis.

**Table 5.19 Summary of the intra-class correlations (ICC) of the continuous ratings between the independent sibling pairs gene positive for HD.**

| Rating | N* | ICC | 95% CI | *P* value |
|---|---|---|---|---|
| BADDS-D | 37 | 0.47 | 0.17 - 0.68 | 0.002 |

ICC; Intra-Class Correlations, BADDS-D; Bipolar Affective Disorder Dimensional Scale – Depression subscale, CI; Confidence Interval, *Number of sibling pairs included in the analysis.

## *5.5 Description of the HD gene negative sample*

The HD gene negative sample comprised five individuals from five different families recruited to the study. All individuals were aware growing up that they had a positive family history of HD and therefore were themselves at 50% risk for inheriting the disease. For three of these families where the gene negative sibling was the only sibling to not carry the gene, the gene negative sibling had taken on the responsibility of looking after their sibling(s).

### 5.5.1 Demographic characteristics of the gene negative sample

The demographics of the HD gene negative sample are summarised in Table 5.20. The mean age of the sample was 45.4 years and four of the five individuals were female. All were UK/Eire Caucasian and 80% were married or had lived as married. Two individuals had obtained a degree, one individual had O-levels as her highest level of education and two individuals had left school without any qualifications. Although two of the five individuals were now full time carers for their siblings, they were both previously service workers. One female was a carer for her sister but also held down a full-time job as a charity worker and the additional two individuals were working full-time in professional and associate professional jobs.

**Table 5.20 Demographic characteristics of the 5 gene negative individuals.**

| **Demographics** | **Descriptives and Percentages N = 5** |
|---|---|
| **Age (years)** | |
| Mean (95% CI) | 45.4 (37.9-53.0) |
| Standard Deviation | 8.62 |
| Range | 34-58 |
| | |
| | **N (%)** (95% CI) |
| **Female** | **4 (80.0)** (44.9-100) |
| | |
| **Ethnic Origin** | |
| UK/Eire Caucasian | **5 (100.0)** (-) |
| | |
| **Marital status** | |
| Has married/lived as married | **4 (80.0)** (44.9-100) |
| Has never married/lived as married | **1 (20.0)** (0-55.1) |
| | |
| **Highest Level Education** | |
| No qualifications | **2 (40.0)** (0-82.9) |
| O-levels/CSEs/ GCSEs | **1 (20.0)** (0-55.1) |
| A level/ HND/ BTEC | **0 (0.0)** (-) |
| Degree | **2 (40.0)** (0-82.9) |
| | |
| **Highest Lifetime Occupation** | |
| Professionals, senior officials and managers | **2 (40.0)** (0-82.9) |
| Technicians and associate professionals | **1 (20.0)** (0-55.1) |
| Service workers & shop & market workers | **2 (40.0)** (0-82.9) |

### 5.5.2 Description of the psychiatric histories of the HD unaffected siblings

#### 5.5.2.1 Family 005: Participant 005-2A

***Lifetime DSM-IV diagnosis:*** None

*Background:*

A 47 year old female with an HD affected older brother and older sister**.** She lives with her husband and two children and received her negative predictive test result aged 35.

*Family psychiatric history:*

The HD affected older sister has a lifetime DSM-IV diagnosis of recurrent major depression and panic disorder without agoraphobia. The HD affected older brother has a history of anxiety NOS and also has two children aged 21 and 15 years who both suffer with severe OCD (they are at 50% risk of carrying the HD gene). Her mother had HD and suffered with depression and anxiety as well as hallucinations/delusions and was admitted to a psychiatric hospital twice before she was diagnosed with HD (this information was provided by participant 005-2A and could not be verified by medical records).

*Psychiatric history:*

Summary:

Age 13: first symptoms of low mood, self-harm and obsessional symptoms.

Age 30: further period of low mood and onset of panic attacks following bereavement

Age 36: additional period of low mood following bereavement

As a teenager, she had her first symptoms of low mood and self-harmed for 2-3 years. She also had a few obsessional symptoms (mainly keeping possessions in a certain order/place), which she said gave her some control in an otherwise very uncontrollable home environment.

She had two further periods of low mood aged 30 when her Mum (who had HD) died and then aged 36 when her father passed away. She described her depressive symptoms as mainly mild and she managed to carry on with her work and everyday activities.

She also experienced panic attacks two or three times a week for three months after her mother died but again they did not interfere with her daily life and she perceived them to be a reaction to her Mother's death.

None of these periods of low mood and anxiety were severe enough to reach DSM-IV diagnosis.

*Psychiatric medication:* she was prescribed anti-depressants aged 30 after her mother died.

*Contact with psychiatric services:* none

*Suicidal behaviour:* she has never attempted suicide but as a teenager she self-harmed for 2-3 years by cutting herself with a razor blade. She said it was more for a release and was not because she did not want to live.

#### 5.5.2.2 Family 009: Participant 009-2A

***Lifetime DSM-IV diagnosis:*** *None*

*Background:*

A 45 year old female with an older sister, younger sister and non-identical twin sister all HD symptomatic. She lives and cares for her elder sister as well as her disabled husband. She also lives next door to her mother and affected twin sister, who she also sometimes has to care for as well as holding down a full-time job. She had the negative predictive test aged 40.

*Family psychiatric history:*

Her non-identical twin sister has a lifetime DSM-IV diagnosis of anxiety NOS, her eldest sister has a lifetime DSM-IV diagnosis of major depressive disorder, single episode and her younger sister has a lifetime DSM-IV diagnosis of both major depressive disorder, single episode and anxiety NOS.

*Psychiatric history:*

Summary:

No particular psychiatric history. She has the occasional down day but nothing more than that. They have a strong Christian faith as a family, which she believes has played a role in her being better able to deal mentally with her family's situation.

*Psychiatric medication: none*

*Contact with psychiatric services: none*

*Suicidal behaviour*: no lifetime history of suicidal thoughts or attempts.

**5.5.2.3 Family 021: Participant 021-2A**

***Lifetime DSM-IV diagnosis:*** *None*

*Background:*

A 34 year old, single male with an older brother, older sister and younger sister all with positive predictive test results. He was the first of his siblings to undergo genetic testing aged 18, which he found a very stressful experience.

*Family psychiatric history:*

Both of his sisters, although not yet symptomatic, have a lifetime DSM-IV diagnosis of major depressive disorder (one with a single episode and the other with recurrent episodes). The sister with a lifetime DSM-IV diagnosis of recurrent major depressive disorder also had a lifetime DSM-IV diagnosis of panic disorder without agoraphobia. His mother and maternal grandmother had HD and both appeared to suffer with depression (his mother was on anti-depressants) as well as irritability and aggression (this information was provided by participant 021-2A and could not be verified by medical records).

*Psychiatric history:*

Summary:

Age 18: onset of binge drinking

Between the ages of about 18 and 23, he would drink up to 70 units of alcohol a week but only socially and he would also occasionally take ecstacy when at a social event**.** When he was drunk he would start feeling low about money problems, relationship problems and family issues and when he was very low he would have feelings of tedium vitae and suicidal ideation. These feelings of low mood would only happen under the influence of alcohol and therefore only lasted for a few hours at the end of an evening.

*Psychiatric medication:* none

*Contact with psychiatric services:* none

*Suicidal behaviour:* When he went through this period of drinking heavily he sometimes thought that life wasn't worth living and he might harm himself when drunk but he never acted on these thoughts.

**5.5.2.4 Family 024: Participant 024-2A**

***Lifetime DSM-IV diagnoses:*** *MDDR, Anxiety NOS, Alcohol Abuse*

*Background:*

A 58 year old unaffected female who is the eldest of seven siblings. One brother has died of HD, two HD affected sisters are in a nursing home, another sister is mid-stage HD, one brother committed suicide (he did not know his genetic status) and another brother has not had the genetic test but is not yet showing any symptoms of HD. She received her negative predictive test result aged 42 years.

*Family psychiatric history:*

Of the two siblings with HD who took part in the current study, one had a lifetime DSM-IV diagnosis of recurrent major depressive disorder and panic disorder with agoraphobia and for the other, diagnosis was unknown due to the fact she was in the later stages of HD and living in a nursing home. One other sister with HD is in a low-secure psychiatric unit, one brother committed suicide and no psychiatric diagnoses were known for the other two brothers (one who died of HD and one whose genetic status is unknown).

*Psychiatric history:*

Summary:

Age 13: onset of depression and anxiety

Age 28: onset of alcohol abuse.

She has had up to 10 episodes of severe depression since she was a teenager. Her home life was very difficult as a teenager. Her parents both experienced depression and alcoholism and were violent. She had psoriasis, which greatly affected her confidence and her mother and grandmother had HD. Being the eldest, she felt she had to look after her younger brothers and sisters.

She has experienced anxiety since her teenage years and has had a difficult life since including trying to look after her siblings, having many family members die with HD, her sister who was having a psychotic episode once tried to break into her house and kill her and she lived with an abusive partner for many years.

She was around alcohol a lot as a child as both her mother and father had alcohol problems. In her late 20s/early 30s, she drank a lot, which started as being socially drinking lots and then became drinking when stressed to try and escape from what was going on in her life to later relying on alcohol to get her through the day. She thinks she drank as a result of her depression as it was a way for her to block it out. During her heaviest period of drinking, she would drink about 50cl vodka most nights a week.

*Psychiatric medication:* anti-depressant, citalopram 20mg once a day.

*Contact with psychiatric services:* none

*Suicidal behaviour:* she has had recurrent thoughts of suicide throughout her life. Once she planned for her death by sorting out all her belongings and making sure everything was in order. Then she was going to leave her house keys with the GP and take an overdose but she decided not to go through with it.

**5.5.2.5 Family 035: Participant 035-2A**

***Lifetime DSM-IV diagnoses:*** *MDDR, Panic Disorder with Agoraphobia.*

*Background:*

A 43 year old HD unaffected female with two younger sisters both with genetic and clinical HD diagnoses. She is a full-time carer for both her sisters and she received her negative predictive test result when she was 21 years old.

*Family psychiatric history:*

One sibling with HD has a lifetime DSM-IV diagnosis of recurrent major depressive disorder, panic disorder with agoraphobia and alcohol abuse and the other HD affected sibling has a lifetime DSM-IV diagnosis of single episode major depressive disorder, agoraphobia without panic disorder and alcohol abuse.

*Psychiatric history:*

Summary:

Age 16: Onset of depression and panic attacks.

Her mother was diagnosed with HD aged 31 and became quite violent. Her Dad was an alcoholic and so life around this time was very chaotic; she had to spend a lot of time looking after her Mum rather than having a typical teenage life. Aged 17, she was taken into care with her sisters, though she ended up living with her Aunt. Her sisters were subsequently fostered into the same family.

She believes she has had 10+ episodes of depression lasting longer than 2 weeks with her first episode aged 16 and her worst episode aged 19. She believes her depression had significant interference with her everyday life as she had to stop work for a while and didn't want to go out.

Onset of panic attacks happened when she was 16 but her worst episode was about 5 years ago, which lasted for about 4 months. She hasn't had an attack for about 4 years now. She said that her panic attacks had a severe interference with her everyday life as she stopped working (she found her job very stressful and although after some counselling she went back to her job, she then left it). She also found it hard to leave the house and would not drive for this time.

*Psychiatric medication:* anti-depressant, citalopram 60mg once daily.

*Contact with psychiatric services:* none

*Suicidal behaviour:* she had moments during her worst episode of depression of contemplating ending her life, but she did not act on these thoughts.

A summary of the lifetime psychiatric history of the five individuals gene negative for HD is provided in Table 5.21.

**Table 5.21 Summary of the lifetime psychiatric history of the five gene negative individuals**

| Participant | Gender | Age at HD genetic test | Age at onset of first psychiatric symptoms | Age at onset of first psychiatric impairment | Contact with psychiatric services | DSM-IV Main Diagnosis | DSM-IV Other Diagnoses | Psychiatric Medication | Family psychiatric history | Suicidal thoughts | Suicide Attempts |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **005-2A** | Female | 35 | 13 | n/a | No | None | None | Yes | Yes | No | No |
| **009-2A** | Female | 40 | n/a | n/a | No | None | None | No | Yes | No | No |
| **021-2A** | Male | 18 | 18 | n/a | No | None | None | No | Yes | Yes | No |
| **024-2A** | Female | 42 | 13 | 23 | No | MDDR | Anxiety NOS, Alcohol Abuse | Yes | Yes | Yes | No |
| **035-2A** | Female | 21 | 16 | 19 | No | MDDR | PD with agoraphobia | Yes | Yes | Yes | No |

MDDR; recurrent major depressive disorder, Anxiety NOS; Anxiety disorder not otherwise specified, PD; Panic disorder

## *5.6 Discussion*

The data presented in this chapter report the familiality of psychiatric syndromes and symptoms in siblings gene positive for HD. In addition, a description of the psychiatric history of siblings gene negative for HD from 5 of the HD families was detailed. The following discussion will compare the results found in the present study with previous family studies in the HD population as well as discussing possible explanations for the evidence of familial clustering of depression, irritability and aggression. Additionally, gene positive/gene negative comparative studies of psychiatric syndromes/symptoms in HD will be discussed.

### 5.6.1 Familiality of psychiatric disorders/symptoms in HD

The results of this study demonstrate familial influences on the psychiatric presentation of HD in a well-characterised sample of siblings gene positive for HD. In particular, evidence for familial clustering was found for any lifetime DSM-IV diagnosis ($\kappa = 0.296$, $p$=0.04) and for a lifetime DSM-IV diagnosis of any depressive disorder ($\kappa = 0.44$, $p$=0.002). When restricting the analysis to the independent sibling pairs, the significant association held for a lifetime DSM-IV diagnosis of any depressive disorder ($\kappa = 0.460$, $p$=0.004). There was no evidence for familiality of any narrower definitions of lifetime DSM-IV disorders including MDDR and any anxiety disorder as well as for suicidal behaviour.

For the lifetime ratings of the PBA items perseverative thinking, apathy, irritability and aggression, fair and moderate significant within all possible sibling-pair associations were found for the neuropsychiatric symptoms of irritability ($\kappa = 0.341$, $p$=0.013), and aggression ($\kappa = 0.418$, $p$=0.003) respectively. These associations remained fair and significant when just

the independent siblings were included in the analysis (κ = 0.357, *p*=0.024 and κ = 0.384, *p*=0.016 respectively). No further significant associations were found, although there was a non-significant trend for a lifetime history of perseverative thinking (κ = 0.263, *p*=0.053) when the all possible sibling-pairs were used.

The correlations between siblings for key psychiatric ratings found a moderate and significant correlation between all-possible sibling pairs for the frequency and severity of depressive episodes as measured by the depression subscale of the BADDS (ICC = 0.360, *p*=0.005). This significance held when just the independent sibling pairs were included in the analysis (BADDS-D: ICC = 0.47, *p*=0.002). The age at onset of psychiatric illness and the level of functioning in a depressive episode were not significantly correlated between siblings.

### 5.6.2 Previous family studies in HD

These findings support previous HD studies (outlined in section 5.1.1) suggesting that familial factors play a role in the presence and course of psychiatric disorders in the HD population. Of the few familiality studies that have been previously conducted in the HD population, the majority have focused on the more severe psychiatric disorders including psychosis and schizophrenia-like symptoms (Lovestone et al., 1996; Tsuang et al., 1998; Tsuang et al., 2000). Given that there was only one individual in the present sample that had a lifetime DSM-IV diagnosis of a psychotic disorder, it was not possible to investigate the familiality of psychotic disorders.

The findings in this study for familial aggregation of depressive disorders and the frequency and severity of depressive episodes builds on Folstein and colleagues (1983) previous work in HD families where HD affected relatives of five probands with HD and affective disorder were significantly more likely to have affective disorder than the HD relatives of the five probands with HD and no affective disorder (Folstein et al., 1983).

Familial factors were also found to influence the presence/absence of irritability and aggression in the current study. There have been no previous HD family studies of irritability and aggression; however, in the non-HD population, aggression and anti-social behaviour have been demonstrated to run in families (Jary and Stewart, 1985; McCartney et al., 1990; Rowe et al., 1992; Miles and Carey, 1997). Possible hypotheses to account for these findings in the current study that the presence and course of depression, irritability and aggression seem to aggregate in certain HD families will be discussed below.

There have been no previous family studies of apathy and perseverative thinking in the HD population. The absence of evidence for familiality of apathy and perseverative thinking in the current study could be as a result of the fact that these neuropsychiatric symptoms (unlike depression and anxiety) seem to correlate with disease progression. A longitudinal analysis of an Apathy subscale and Irritability subscale as well as its constituent symptoms demonstrated highly significant linear effects for all seven items for the Apathy subscale as well as the perseverative preoccupations item of the Irritability subscale, with these symptoms increasing in severity over time (Thompson et al., 2012). Therefore, if the presence of these symptoms is strongly influenced by the duration of HD, given that siblings

were often in different stages of disease (due in part to their different ages), it is perhaps not surprising that these symptoms did not appear to correlate between siblings.

A pedigree has been described demonstrating an association between OCD and pathological gambling with HD (De Marchi et al., 1998). Although there were no individuals in the current study with a lifetime DSM-IV diagnosis of OCD, no evidence was found for family clustering of any anxiety disorder. In the non-HD population, in contrast to the findings in this study, family studies have demonstrated a three-fold increased risk in the development of anxiety disorders in first-degree relatives of patients with panic disorder (Maier et al., 1993), generalised anxiety disorder (GAD) and specific phobias (Hettema et al., 2001), which increases to a 17 times increased disease risk for panic disorder with an age at onset before 20 years (Goldstein et al., 1997). Heritability estimates for anxiety disorders from twin studies range from approximately 30% for GAD and simple phobias, to 48% for panic disorder and 67% for agoraphobia (Kendler et al., 1999; Hettema et al., 2001). Given that only just over a third of the index sample and a quarter of the sibling sample had a lifetime diagnosis of an anxiety disorder (38% and 25% respectively), it is possible that the sample size of individuals with a history of an anxiety disorder was not large enough to detect any familiality (of the 28 sibling pairs that were concordant for a lifetime diagnosis of any anxiety disorder, only four of these were concordant for a lifetime diagnosis). Therefore, it would be recommended for this study to be replicated in a larger number of sibling pairs with a lifetime DSM-IV diagnosis of an anxiety disorder to confirm the findings of this study.

### 5.6.3 Possible explanations for the familiality of psychiatric syndromes/symptoms in HD

The aetiology of psychiatric symptoms/syndromes in HD is undoubtedly complex. However, the results of this study have provided useful information regarding the fact that the presence and course of depression and irritability and aggression appear to run in HD families. Given that irritability in HD may sometimes be secondary to the presence of a depressive disorder (Craufurd and Snowden, 2014), it is possible that the evidence for familiality of irritability/aggression is consequent to the finding that the presence and course of depression is also familial in HD. There are several possible hypotheses to account for the demonstration of familiality in the current study.

It has been proposed (Folstein et al., 1983) that genetic heterogeneity at the HD locus may account for the familiality of psychiatric disorders/illness. However, this theory now seems unlikely since the discovery that HD is caused by a CAG repeat expansion in gene *IT15* on the short arm of chromosome 4 (HD Collaborative Research Group, 1993) and that the probability of developing psychiatric symptoms is independent of the CAG repeat length (Naarding et al., 2001; Vassos et al., 2008). There may, however, be as yet undetected differences in the HD gene, which alter the effects of the CAG repeat expansion (Lovestone et al., 1998).

It could be that a gene predisposing to depression, irritability and/or aggression is in linkage disequilibrium with the HD gene. However, this has yet to be demonstrated by research and it seems increasingly likely the genetic basis of psychiatric disorders is complex and

multifactorial and that no single gene is necessary and sufficient for their onset (Lohoff et al., 2010).

It is possible that shared environmental factors contribute to the familiality of depression, irritability and/or aggression in HD. Significant life events and stressors are known contributors to the aetiology of depression (Kendler et al., 1999b) and individuals from HD families likely experience a great deal of psychological stress. It is possible that some HD family environments are more harmful and stressful than others and/or that coping mechanisms to deal with the stressful life events differ between families and consequently contributes to the familial aggregation of such psychiatric symptoms.

In the non-HD population, genetic effects are considered the most important contributor to familial aggregation (Sullivan et al., 2000) and twin studies in depression suggest that shared environmental factors are small or non-existent (McGuffin et al., 1996; Sullivan et al., 2000). Also, in the non-HD population, it has been proposed that in adults, shared environmental factors are negligible in promoting similarity in aggression among family members whereas heritability plays a much more significant role (Miles and Carey, 1997). It is therefore also possible that in the HD population, the evidence for familial aggregation of depression, irritability and aggression could be due to a shared genetic predisposition.

This more plausible explanation is that the presence and course of depression, irritability and/or aggression may cluster in families because genes predisposing to psychiatric illness are more likely to be expressed in the presence of the HD gene. For example, in the case of

depression, if someone is carrying genes that cause hyperactivity of the hypothalamic pituitary adrenal (HPA) axis (which is one of the most consistent biological findings of major depression in the non-HD population, Pariante and Lightman, 2008) and one of the neuropathological changes associated with HD is also hyperactivity of the HPA axis (Heuser et al., 1991; Leblhuber et al., 1995; Aziz et al., 2009, and van Duijn et al., 2010), it is possible that together, this interaction results in sufficient disruption of the HPA axis to contribute to the development of depression, which may not have otherwise occurred had the HD gene and its effects not been present. Reduced serotonin signalling could in a similar way account for the familiality of irritability/aggression. Low levels of the neurotransmitter serotonin (5-HT) have been associated with impulse aggression in studies of humans and animals (Linnoila and Virkkunen, 1992; Seo et al., 2008). In mouse models of HD, serotonin levels have been found to be decreased by up to 50% compared to non-HD mice by age 12 weeks (Reynolds et al., 1999). Therefore, if some HD families have a genetic predisposition to reduced serotonin signalling and one of the effects of the HD gene is also decreased levels of serotonin, then this interaction may result in the emergence of an irritable/aggressive phenotype.

To further understand the aetiology of psychiatric disorders in the HD population, the inclusion of gene negative siblings from the HD families included in the current study provide a useful control sample to correct for the environmental stress experienced by HD family members and to assess the importance of the *HD* gene in the psychopathology of HD.

### 5.6.4 HD gene negative/gene positive comparative studies

In the present study, of the five gene negative siblings recruited and interviewed, four had a psychiatric history but only two individuals had symptoms severe enough to reach a formal DSM-IV diagnosis. Both of these individuals had MDDR as their main lifetime psychiatric diagnosis with one individual having additional lifetime DSM-IV diagnoses of anxiety disorder NOS and alcohol abuse and the other individual had an additional lifetime DSM-IV diagnosis of panic disorder with agoraphobia. Also, both individuals had at least one sibling with HD who also had a lifetime DSM-IV diagnosis of MDD with a co-morbid anxiety disorder. Although, the sample size of five is small, the proportion of the gene negative sample with a lifetime DSM-IV disorder is higher than that reported in the European general population study, ESEMeD (the European Study of the Epidemiology of Mental Disorders (Alonso et al., 2004), where the lifetime DSM-IV prevalence rate was 14% for any mood disorder, 13.6% for any anxiety disorder and 4.1% for alcohol abuse). It is also useful to compare the prevalence rates of all lifetime DSM-IV diagnoses for the gene negative siblings with the gene positive siblings (see Table 5.22).

**Table 5.22 Summary of all lifetime DSM-IV diagnoses for the gene positive individuals of the index and sibling samples and the gene negative siblings.**

| | Index sample<br>N = 50 | Sibling sample<br>N = 40 | Gene negative siblings<br>N = 5 |
|---|---|---|---|
| | **N (%)**<br>95% CI | **N (%)**<br>95% CI | **N (%)**<br>95% CI |
| Any DSM-IV Mood Disorder | **28 (56.0)**<br>42.2-69.8 | **26 (65.0)**<br>50.2-79.8 | **2 (40.0)**<br>0-82.9 |
| Any DSM-IV Anxiety Disorder | **19 (38.0)**<br>25.6-51.4 | **10 (25.0)**<br>11.6-38.4 | **2 (40.0)**<br>0-82.9 |
| Alcohol Abuse | **3 (6.0)**<br>0.0-12.6 | **3 (7.5)**<br>0.0-15.7 | **1 (20.0)**<br>0-55.1 |
| Psychotic Disorder NOS | **1 (2.0)**<br>0.0-5.9 | **0 (0.0)**<br>- | **0 (0.0)**<br>- |

NOS; not otherwise specified
Where individuals have more than one lifetime DSM-IV diagnosis, they are included in more than one category

The finding in the current study that the lifetime frequency of any anxiety disorder and alcohol abuse was higher in the gene negative than the gene positive individuals and that the gene positive individuals had a higher lifetime frequency of any mood disorder, replicates findings by Julien et al., (2007). In this comprehensive study, Julien and colleagues assessed lifetime and current psychiatric histories in 204 individuals at risk for HD (89 were HD gene carriers and 115 were non-gene carriers). At the time of their semi-structured psychiatric interview, both participants and interviewers were blind to the individuals' gene status. Lifetime rates of DSM-III diagnoses did not differ significantly between the gene carriers and non-gene carriers with regards the prevalence of both major psychiatric disorders and sub-threshold psychiatric disturbances. However, the non-carriers had a higher lifetime prevalence than the gene carriers for any DSM-III anxiety disorder (25% versus 17%) and alcohol dependence (6% versus 3%) whereas the gene carriers had a higher lifetime prevalence of any affective disorder (23% versus 15%).

Another study (Berrios et al., 2002) using formal diagnostic criteria and where both the interviewer and participants were blinded to their genetic status found no significant differences between the gene positive and gene negative individuals for the prevalence of lifetime psychiatric diagnoses (31.3% and 27.3% respectively). However, a non-significant trend towards higher depression scores on the Beck Depression Inventory (BDI) for the gene positive group was found. Gene carriers were also found to have significantly higher levels of irritability than the non-gene carriers, which supports previous findings suggesting that irritability is an important component of the psychiatric presentation in pre-motor manifest individuals (Duff et al., 2007). Baxter et al (1992) also found no significant differences for any

formal lifetime psychiatric diagnoses between a sample of 52 chorea-free individuals, who were either “more” or “less” likely to develop HD.

Other studies that have compared the prevalences of psychiatric disorders/symptoms in gene positive and gene negative individuals have looked at current prevalence rates only, with equivocal findings (Kirkwood et al., 2002a; Kirkwood et al., 2002b; Soliveri et al., 2002; Duff et al., 2007; van Duijn et al., 2008). Some of these studies have found that HD gene carriers have significantly higher levels of current psychiatric symptoms (in particular irritability and hostility) than non-gene carriers (Kirkwood et al., 2002a; Duff et al., 2007). Others have found no significant differences between the gene positive and gene negative individuals for current psychiatric syndromes/symptoms (Kirkwood et al., 2002b; Soliveri et al., 2002; van Duijn et al., 2008), although in two of these three studies, the gene positive individuals had more current DSM-IV psychiatric disorders (van Duijn et al., 2008) and higher depression and anxiety levels (Soliveri et al., 2002) than the gene negative individuals.

This methodology, although useful in determining current psychiatric status in at-risk gene carriers for HD and whether there are any correlations between psychiatric symptomatology and estimated time to disease onset in the gene positive individuals, does not allow for conclusions to be drawn as to whether gene positive individuals experience more (or less) psychiatric syndromes/symptoms over their lifetime than gene negative individuals. Indeed, although the study by Julien et al., (2007) found no significant differences in terms of lifetime prevalence of psychiatric disorder, the gene positive individuals did report a higher prevalence of current affective symptoms.

Furthermore, all of these studies, except the one by van Duijn and colleagues (2008), have used rating scales to measure psychiatric symptoms rather than formal diagnostic criteria. These scales (such as the BDI, Hamilton rating scale for depression and anxiety, the Minnesota Multiphasic Personality Inventory, and the Symptom Checklist 90-Revised) are undoubtedly useful for identifying the more subtle psychiatric symptoms observed in HD (such as irritability, aggression and apathy). However, given the overlap of certain psychiatric symptoms and certain symptoms of HD, it is difficult to be sure that the scales are measuring the psychiatric rather than the HD symptomatology. The difficulties associated with using depression rating scales in HD will be discussed further in Chapter 6.

Additionally, unlike the current study and those by Soliveri et al (2002) and van Duijn et al (2008), all of the other gene positive/gene negative comparative studies discussed here used unrelated individuals, which does not control for shared environmental and non-HD shared genetic factors in the aetiology of psychiatric disorders/symptoms.

#### 5.6.4.1 Age at onset of psychiatric illness in the gene negative siblings

An interesting result from the current study was the finding that unlike the gene positive siblings, the age of onset of the first psychiatric symptoms and impairment in the gene negative siblings was much more similar to that observed in the general population (Alonso et al., 2004; Kessler et al., 2005). Whereas the median age at onset for depressive disorders and anxiety disorders was 42 and 41 years respectively for the gene positive siblings in the index sample and 34 and 37 years respectively for the gene positive siblings in the sibling sample (see section 4.4.2), for the two gene negative siblings with lifetime DSM-IV

diagnoses, their age at onset of first psychiatric impairment was aged 19 and 23 years and for the two other gene negative individuals with a psychiatric history but no lifetime DSM-IV diagnosis, their age at onset of first psychiatric symptoms was 13 and 18 years. This is suggestive of a role for the HD gene in contributing to the older age at onset of psychiatric disorders/symptoms in the HD population. The possibility that the aetiology of psychiatric syndromes/symptoms is different in the HD population whereas HD gene negative individuals experience a more "typical" psychiatric illness as seen in the non HD population would also fit with the findings in Chapter 4. These results suggested that depression and anxiety disorders may be phenotypically different in HD with between 25% and 42% of DSM-IV lifetime diagnoses of depressive and anxiety disorders comprising NOS diagnoses (see section 4.4.1) and also differences in the proportion of individuals experiencing particular depressive symptoms as rated on the OPCRIT between the HD MDDR sample and the non-HD MDRG sample (see section 4.5.7). If the aetiology of psychiatric disorders is different in HD, then it would not be surprising for the phenotype to be different too.

The results from the current study demonstrate familial influences on the psychiatric presentation of HD (most notably the presence and course of depression and the presence of irritability and aggression) in a well-characterised sample of siblings gene positive for HD. The finding that psychiatric symptoms may also be frequent in the gene negative siblings suggests that the familial influences may be unrelated to the HD gene and not secondary to having HD. Other shared genetic and shared environmental factors are likely to contribute, which are not necessarily mutually exclusive.

## *5.7 Summary and Limitations*

The data presented in this chapter have built on previous research investigating the familiality of psychiatric symptoms in HD by using an increased sample size, a gold standard methodology to elicit an accurate psychiatric history and by investigating the full range of psychopathology in HD. The main findings of the chapter are summarised below:

*Familiality of psychiatric syndromes/symptoms in HD*

- Using the all possible sibling pairs model, between fair and moderate familial clustering was found for a lifetime history of any DSM-IV diagnosis ($\kappa = 0.302$, $p=0.031$), any depressive disorder, ($\kappa = 0.444$, $p=0.002$) (including the frequency and severity of depressive episodes, BADDS-D, ICC=0.36, $p=0.005$), irritability ($\kappa = 0.341$, $p=0.013$) and aggression ($\kappa = 0.418$, $p=0.003$).
- When using the independent sibling pairs only, the significant associations remained for a lifetime history of any depressive disorder ($\kappa = 0.46$, $p=0.004$) (including the frequency and severity of depressive episodes, BADDS-D, ICC = 0.47, $p=0.002$), irritability ($\kappa = 0.357$, $p=0.024$), and aggression ($\kappa = 0.384$, $p=0.016$).
- No significant familiality was found for a lifetime history of anxiety disorders, apathy, perseverative thinking or for any other lifetime psychiatric ratings.

*Gene negative siblings:*

- Two of the five gene negative siblings had a lifetime history of DSM-IV disorders, with both having a main DSM-IV diagnosis of MDDR.

- Both of these individuals had at least one sibling with HD who also had a lifetime DSM-IV diagnosis.
- Three of the five individuals had a lifetime history of suicidal ideation but none of the sample had ever made a previous attempt at suicide.
- The age at onset of first psychiatric symptoms and first impairment in the gene negative siblings was very similar to the non-HD population and much earlier than the gene positive siblings in this study.

*Aetiology of psychiatric syndromes/symptoms in HD*

- The aetiology of psychiatric symptoms/syndromes in HD is undoubtedly complex and multifactorial.
- However, it is likely that the familiality observed for depression (and maybe irritability and aggression) cannot be entirely explained by the HD gene and that other shared genetic factors and shared environmental factors contribute, which are not necessarily mutually exclusive.

The results should be interpreted with a degree of caution given the significant findings were only moderate levels of association and the 95% confidence intervals were very large. The sample size of this study is modest but is nearly twice as large as any known previous sibling study in HD. The findings reported here require replication in a larger sample of siblings with HD. Alternatively, by focusing on recruiting probands with HD and a specific co-morbid psychiatric disorder (perhaps depression given the findings from this study) as well as probands and no psychiatric history together with the probands' first-degree relatives, this

methodology may increase the power to detect familial influences on the psychiatric phenotype in HD.

Multiple comparisons were not corrected for in view of the small sample sizes and the exploratory nature of the study. Nevertheless, when using a more stringent p-value cut-off of $p<0.01$, the moderate within-pair associations for a lifetime DSM-IV diagnosis of any depressive disorder ($p=0.004$) as well as the correlation between sibling pairs for the severity and frequency of depressive episodes (BADDS-D, $p=0.002$) are still classified as significant. The small sample size also meant that it was not possible to perform multi-variate analyses to investigate, for example, female-female sibling pairs versus male-male sibling pairs and early age at psychiatric onset versus later age at psychiatric onset sibling pairs. This would be interesting for future studies to investigate further.

Further limitations of the study include the fact that the reporting of all psychiatric history was retrospective, which could have led to some inaccurate details being provided. However, in order to minimise this, information about an individual's psychiatric history was gathered from as many different sources as possible including: the patients, carer, other family members, GP casenotes and HD casenotes. A prospective study, although ideal in terms of providing the most reliable information, would take a considerable length of time and also would be expensive.

The additional rater was not blinded to the participants' sibling status when making ratings from the vignettes for consensus diagnoses. In future studies, this would be an important

factor to address as it could have resulted in psychiatric diagnoses of siblings being biased. However, given that consensus ratings were made with the input of a third rater who was blinded to the participant's sibling status where necessary, this should not have led to biased ratings being made.

It was particularly difficult to recruit the HD gene negative sample, as many of the siblings who were not showing any symptoms of HD did not know their genetic status rendering it impossible to assign them to either the gene positive or gene negative sample. Also, recruitment of the gene negative sibling was reliant on the gene positive sibling passing on information about the study, which limited recruitment of this sample. It is also possible that those individuals gene negative for HD that did take part in the study were those that were particularly interested in research/mental health research (perhaps due to their own psychiatric history) and therefore led to a sample bias. However, these issues regarding recruitment of the gene negative individuals are difficult to avoid (Tibben et al., 1992) and this group of individuals still provide a very useful sample for better understanding the aetiology of psychiatric symptoms of HD.

The evidence that depression, irritability and aggression seem to cluster in HD families has implications for clinical practice, research and nosology. It is important that an individual's family history of psychiatric disorders is recorded to identify possible increased risks. Future research should focus on confirming the results of this study with the prospect of investigating possible genetic risk variants for psychiatric disorders/symptoms in HD. It is crucial that when research is carried out on the psychopathology of HD that the scales used

are measuring what they are supposed to i.e. the presence of psychiatric symptoms rather than the presence of HD symptoms. This is important if research into the psychiatric phenotype of HD is to progress and this forms the content of the following chapter, Chapter 6: The validation of self-report measures of depression in HD.

# CHAPTER 6: VALIDATION OF SELF-REPORT MEASURES OF DEPRESSION IN HD

This chapter will discuss the use of self-report depression rating scales in HD. It will outline the rationale for the study and the recruitment, methodology and results concerned with validating self-report measures of depression in HD. This will be followed by a discussion of the results obtained and their implications.

## *6.1 Introduction*

The data presented in chapter 4 confirm the association between HD and psychiatric disorders, of which depressive disorders are most prevalent (Julien et al., 2007; van Duijn et al., 2007; Reedeker et al., 2012). It is also apparent that the reported prevalence rates of depression in HD vary greatly due mainly to methodological differences including: the use of different rating scales, varying definitions of depression (depressed mood, depressive symptoms or depressive disorder), the use of different time scales (point, period or lifetime prevalence rates), and study populations at different stages of disease. Given that depression is common in HD, it is significantly associated with reduced quality of life (Ho et al., 2009) and functional decline (Marder et al., 2000) yet is relatively treatable, it is important that depression is accurately measured in this population.

Ideally, depressive disorder is diagnosed according to the gold standard that is the criteria of the major classification systems, the Diagnostic and Statistical Manual, Fifth Edition (DSM-V) and the International Classification of Diseases, Tenth Edition (ICD-10). These formal diagnoses are best accomplished by a comprehensive clinical interview and examination.

However, this thorough, yet time consuming and expensive method is often not feasible in clinical practice and research. Consequently, self-report rating scales have become a popular, cheap and convenient alternative method for measuring the clinical construct of depression and have been used for screening purposes, diagnostic purposes as well as for measuring change in severity of depression over time.

There are over 30 scales in the English language that have been designed to assess the presence of depression (Snaith, 1993). Depression rating scales are often selected arbitrarily and administered on the assumption that they all measure the same symptoms of depressive disorder. However, some scales place greater emphasis on particular areas of psychopathology than others, necessitating careful consideration of the most valid rating scale for a particular population. This is particularly the case in HD, where a diagnosis of depression is complicated greatly by considerable overlap between the core symptoms of depression and core symptoms of HD. Symptoms that are part of the operational diagnostic criteria for depressive disorder such as decreased interest or pleasure (Levy et al., 1998; Naarding et al., 2009), fatigue or loss of energy, significant weight change or change in appetite (Kremer, 2002; Aziz et al., 2008), change in sleep (Hansotia, 1985; Silvestri et al., 1995), change in activity (Starkstein et al., 1992; Dubois et al., 1998) and reduced concentration or indecisiveness (Sprengelmeyer et al., 1995) can all be observed in non-depressed HD patients.

Self-report by HD patients is also complicated by dysarthria and progressive cognitive impairment, with one study demonstrating that inter-rater agreement between HD patients

and caregivers for the presence of depressed mood was highest for those patients whose cognition was most intact (Chaterjee et al., 2005). Additionally, HD patients have been demonstrated to persistently and selectively underestimate their degree of executive dysfunction by 26% (Ho et al., 2006).

Another important consideration when measuring depression in HD patients is the cognitive complexity of scales (measured in terms of length of items, readability, linguistic problems related to syntax and structure, and number of items) (Shumway et al., 2004). Self-report measures of depression differ in terms of their cognitive complexity, and in HD patients with cognitive difficulties the more complex scales are likely to limit comprehension and reduce measurement accuracy (Shumway et al., 2004). However, self-report measures of depression are important and widely-used tools in research and practice and it is therefore necessary that such measures of depression are validated in a sample of the target population in which they are to be used.

As yet, depression rating scales have not been validated in patients with HD even though they have been used in various research and clinical settings. For example, the Beck Depression Inventory has been used in many studies (Berrios et al., 2002; Holl et al., 2010; Downing et al., 2012; Smith et al., 2012; Epping et al., 2013), including the European Huntington's Disease Network REGISTRY study, a longitudinal, multi-centre, multinational observational study with more than 10 000 participants enrolled (Handley et al., 2011). However, without sensitivity (patients with depression who test positive) and specificity (patients without depression who test negative) being calculated for any depression rating

scale in the HD population, it is unknown whether they can be utilised as accurate measures of the presence/absence of depression in this population. Consequently, the aim of this study is to assess the concurrent validity of three self-report measures of depression in a sample of individuals with manifest HD against a gold-standard interview measure and ICD-10 operational diagnostic criteria.

## *6.2 Methods*

### 6.2.1 Selection of scales

After a thorough review of the literature, the rating scales were selected for this study based on the following criteria: i) their current use in HD or other neurological disorders, and ii) their potential utility in HD due to their item content (that is minimising the overlap between HD and depressive symptoms). Therefore, this study evaluated the validity of the Beck Depression Inventory-II, BDI-II (Beck et al., 1996), the Hospital Anxiety and Depression Scale, HADS (Zigmond and Snaith, 1983) and the Depression Intensity Scale Circles, DISCs (Turner-Stokes et al., 2005) in measuring depression presence or absence in HD when compared with the Schedules for Clinical Assessment in Neuropsychiatry, SCAN (Wing et al., 1990).

The BDI is a 21 item self-report rating scale that was designed to provide a quantitative assessment of the severity of depression in the past week (Beck et al., 1961). Each item is scored 0-3, with a total score range from 0-63. The following cut-off scores have been suggested to interpret the BDI (Beck et al., 1961): minimal depression = 0-9; mild depression = 10-18, moderate depression = 19-29 and severe depression = 30-63. It is one of the most widely used self-report measures for depression in clinical practice and was the initial

measure of depression used by the European Huntington's Disease REGISTRY study. The BDI has been validated for use as a screening instrument for depression in patients with Parkinson's Disease (Leentjens et al., 2000), multiple sclerosis (Sullivan et al., 1995) and in stroke patients (Aben et al., 2002). It has high internal consistency and high test-retest reliability in a range of patient groups (Beck et al., 1988). The revised version of the BDI, the BDI-II (Beck et al., 1996, Appendix Biii pg. 264), was developed in response to the publication of the DSM-IV. This resulted in the BDI-II introducing new items relating to agitation, concentration difficulties and loss of energy, which replaced items in the BDI concerning hypochondria, changes in body image and difficulty working. Additionally, the items involving loss of sleep and appetite were altered to reflect any change in appetite and sleep. Consequently, the BDI-II rather than the BDI was selected to be validated in this study. Like the BDI, each item is scored 0-3 to give a total range from 0-63. However, the BDI-II is designed to assess the presence and severity of depression in the past two weeks and has the following standardised cut-offs (Beck et al., 1996): minimal depression = 0-13; mild depression = 14-19, moderate depression = 20-28 and severe depression = 29-63. The BDI-II contains several items relating to somatic symptoms and has high overall cognitive complexity (Shumway et al., 2004).

The HADS is a 14 item self-administered rating scale that consists of two sub-scales assessing the presence and severity of depression and anxiety (seven items for each subscale) over the past week (Zigmond and Snaith, 1983, Appendix Biv pg. 269). Each item is scored 0-3 with the total score being the sum of the 14 items (range from 0-42) and for each subscale, the score is the sum of the respective seven items (range from 0-21). In the authors' original

study, Zigmond and Snaith (1983) recommended a score of 8 or more on each subscale to indicate possible depression/anxiety. The scale was designed to diminish the effects of somatic illness and consequently does not include physical or cognitive symptoms, although it also does not include the more severe symptoms of depression such as suicidal ideation. The depressive symptoms instead focus on the emotional experiences of depression and anhedonia (Zigmond and Snaith, 1983). The HADS has been validated as a useful screening instrument for depression in stroke patients (Aben et al., 2002) and in chronic fatigue syndrome (Henderson and Tannock, 2005). It has good internal consistency and test-retest reliability (Mykletun et al., 2001) and its overall cognitive complexity was rated as medium (Shumway et al., 2004). Both the total HADS as a global measure of mood as well as just the depression sub-scale of the HADS were validated in this study.

The DISCs is a simple screening and severity measure for depression in patients with cognitive or communicative deficits (Turner-Stokes et al., 2005, Appendix Bv pg. 272). It is a 6-point graphic rating scale (score range 0-5) portraying six circles with an increasing proportion of grey shading, which is designed to improve accuracy of assessment of mood in patients who may find more cognitively complex assessment tools difficult to complete. It assesses someone's current mood state by asking them how sad or depressed they feel today and a cut-off of 2 or more is used to identify cases of depression. The DISCs has been validated as a simple screening tool for depression in patients with cognitive or communicative deficits following acquired brain injury (Turner-Stokes et al., 2005). It also has excellent test-retest reliability (Turner-Stokes et al., 2005).

### 6.2.2. Participants and setting

Fifty patients with a clinical and genetic diagnosis of HD were recruited from the HD service, Birmingham, UK. All suitable participants received information about the research project (Appendix Bi, pg. 258) during their routine HD clinic appointment and those interested in taking part opted into the study by returning a reply to slip to JDS (Appendix Bi, pg. 260). Patients were excluded from the study if they were sufficiently cognitively impaired to prevent them from giving informed consent, were less than 18 years of age or were not fluent in English. Participants gave written informed consent for the study (Appendix Bi, pg. 261), which was approved by the Solihull Local Research Ethics Committee (reference: 06/Q2706/38) and their GP was informed of their participation in the study (Appendix Bi, pg. 262). All participants were assessed at their homes in a single session lasting approximately an hour and a half.

### 6.2.3. Demographic information

Information was obtained on a variety of demographic variables (see Appendix Bii, pg. 263), including: date of birth, gender, ethnicity, years of education, and age at HD motor symptom onset.

### 6.2.4 Neuropsychiatric assessment

Psychiatric assessment was performed using section 6 (depressed mood and ideation), section 7 (thinking and concentration, energy and interests) and section 8 (bodily functions) of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN, Wing et al., 1990). The SCAN is a widely used semi-structured interview aimed at assessing, measuring and classifying the psychopathology associated with major psychiatric disorders for DSM-IV or

ICD-10 diagnoses (see section 3.4.5.2). For the purpose of this study, the presence of current depressive disorder was made according to the standardised operational diagnostic criteria of the ICD-10, which was considered the gold standard for this study. Structured vignettes were written for each participant using information obtained from the psychiatric interview and all ratings were made independently by JDS and KGS to ensure that consensus was reached. Participants also completed the BDI-II, HADS and DISCs by themselves during the home visit.

### 6.2.5. Statistical analysis

The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated using the recommended cut-off points for each scale as well as for all the cut-offs in the mid-range of the scales in order to determine the optimal cut-off for the scales. The optimal cut-off score is the point at which the scale best discriminates 'caseness' in the population. This is determined by the cut-off with the maximal sum of sensitivity and specificity. Receiver Operating Characteristics (ROC) curves were obtained by plotting the sensitivity against 1-specificity for each score on each depression rating scale. The "area under the curve" (AUC) provides an indication of the discriminative property of a scale and this was also calculated for each rating scale. The analyses were conducted using SPSS version 14.0 (SPSS Inc, 2005).

## *6.3 Results*

### 6.3.1 Demographic characteristics

Fifty patients with motor manifest HD participated in this study and Table 6.1 summarises the demographic characteristics of the sample. The mean age of the sample was 51.2 years; approximately half of the participants were female (48%); the mean number of years of education was 12.26 years; and, all of the participants were UK/Eire Caucasian (100%). The mean age at disease onset was 44.12 years and the mean number of years since disease onset was 6.78 years.

**Table 6.1 Demographic characteristics of the 50 participants**

| **Demographics** | **Descriptives and Percentages N=50** |
|---|---|
| **Age (years)** | |
| Mean (95% CI) | 51.2 (48.3-54.1) |
| Standard Deviation | 10.4 |
| Range | 22-67 |
| | |
| **Education (years)** | |
| Mean (95% CI) | 12.3 (11.8-12.8) |
| Standard Deviation | 1.8 |
| Range | 9-17 |
| | |
| **Age at disease onset (years)** | |
| Mean (95% CI) | 44.1 (41.2-47.0) |
| Standard Deviation | 10.6 |
| Range | 19-62 |
| | |
| **Duration of illness (years)** | |
| Mean (95% CI) | 6.8 (5.8-7.9) |
| Standard Deviation | 3.8 |
| Range | 2-14 |
| | |
| **Female N (%)** | 24 (48.0) |
| | |
| **Ethnic Origin N (%)** | |
| UK/Eire Caucasian | 50 (100.0) |

CI: Confidence Interval

### 6.3.2 Performance of the depression rating scales

Using the SCAN, six out of 50 patients met ICD-10 criteria for current mild depressive disorder, five met criteria for current moderate depressive disorder and one met criteria for current severe depressive disorder to give an overall prevalence of 24% (12/50). The average and range of scores obtained on each depression rating scale for the depressed and non-depressed patients are displayed in Table 6.2. As expected, the depression rating scales resulted in more cases of depression than formal diagnoses obtained from the SCAN (see Table 6.3).

**Table 6.2. Depression rating scales: properties and basic statistics**

| Depression rating scale | Range | Items | Depressed patients (N=12) Mean (S.D., range) | Non-depressed patients (N=38) Mean (S.D., range) |
|---|---|---|---|---|
| **BDI-II** | 0-63 | 21 | 26.08 (13.97, 11-58) | 8.84 (8.89, 0-29) |
| **HADS** | 0-42 | 14 | 21.25 (6.90, 14-36) | 7.55 (7.82, 0-32) |
| **HADS-D** | 0-21 | 7 | 11.17(2.72, 7-17) | 3.50 (3.94, 0-13) |
| **DISCs** | 0-5 | 1 | 2.83 (0.83, 1-4) | 0.79 (0.81, 0-3) |

Using the ICD-10 diagnoses as the gold standard, sensitivity, specificity, positive and negative predictive values and the areas under the curves were calculated for the standard cut-off scores for the BDI-II, HADS, HADS-D and DISCs (Table 6.3). The sensitivity, specificity, positive and negative predictive values were also calculated for all cut-off scores in the mid-range for each depression rating scale (Tables 6.4, 6.5, 6.6 and 6.7). Figure 6.1 displays these results in the form of a ROC curve.

**Table 6.3. Performance of the depression rating scales using standard cut-offs.**

| Depression measure | Cut-off | Depression cases | AUC | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|
| **SCAN** | | 12 (24%) | Gold Standard | | | | |
| **BDI-II** | 13/14 | 21 (42%) | 0.856 | 0.83 | 0.71 | 0.48 | 0.93 |
| **HADS** | 14/15 | 16 (32%) | 0.900 | 0.75 | 0.82 | 0.56 | 0.91 |
| **HADS-D** | 7/8 | 16 (32%) | 0.923 | 0.92 | 0.87 | 0.69 | 0.97 |
| **DISCs** | 1/2 | 18 (36%) | 0.943 | 0.92 | 0.82 | 0.61 | 0.97 |

AUC – Area Under Curve, PPV – Positive Predictive Value, NPV – Negative Predictive Value

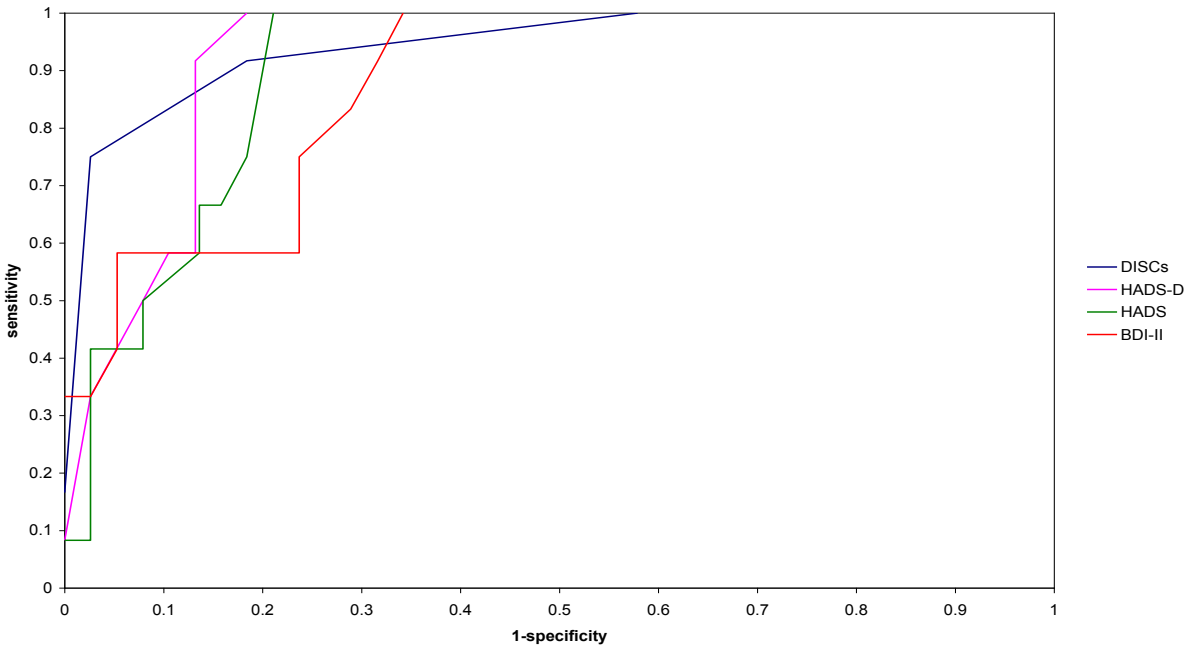



**Fig 6.1 Receiver Operating Characteristics (ROC) curves for the depression rating scales**

#### 6.3.2.1. BDI-II

From the ROC curve, it is clear to see that with the lowest AUC of 0.856, the BDI-II performed least well in discriminating between depressed and non-depressed patients. Although the standard cut-off for the BDI-II is 13/14, this study found an optimal cut off of 10/11 (sensitivity 1.00, specificity 0.66) for the BDI-II, where a score of 11 or more is indicative of depression presence and a score of 10 or less indicates the absence of

depression (see Table 6.4). At this optimal cut-off with perfect sensitivity and NPV, the BDI-II makes an excellent screening measure for depression. However, this is at a cost to the specificity of the scale, which means that many non-depressed patients are misdiagnosed by the BDI-II as having depression. For diagnostic purposes, a high specificity and PPV are required and with the PPV never exceeding 0.50, the BDI-II does not meet this criterion for the HD population.

**Table 6.4.** Sensitivity, specificity, positive and negative predictive values at different cut-off scores for the BDI-II.

| **Cut-off** | **10/11** | **11/12** | **12/13** | **13/14*** | **14/15** | **15/16** | **16/17** | **17/18** | **18/19** |
|---|---|---|---|---|---|---|---|---|---|
| Sensitivity | 1.00 | 0.92 | 0.83 | 0.83 | 0.75 | 0.58 | 0.58 | 0.58 | 0.58 |
| Specificity | 0.66 | 0.68 | 0.71 | 0.71 | 0.76 | 0.76 | 0.76 | 0.76 | 0.76 |
| PPV | 0.48 | 0.48 | 0.48 | 0.48 | 0.50 | 0.44 | 0.44 | 0.44 | 0.44 |
| NPV | 1.00 | 0.96 | 0.93 | 0.93 | 0.91 | 0.85 | 0.85 | 0.85 | 0.85 |

BDI-II, Beck Depression Inventory-II; PPV, positive predictive value; NPV, negative predictive value.
--Maximum sum of sensitivity and specificity
*Standard cut-off of BDI-II

### 6.3.2.2 HADS

Overall, the HADS as a global measure of mood performed better than the BDI-II with an AUC of 0.900. At the standard cut-off of 14/15 (sensitivity 0.75, specificity 0.82), the sensitivity of the scale was not as high as any of the other measures (see Table 6.5). However, at the optimal cut-off of 1 point lower at 13/14, the sensitivity becomes perfect whilst retaining good specificity (sensitivity 1.00, specificity 0.79). Like the BDI-II, the HADS makes a much better screening than diagnostic measure. Although at higher cut-off scores the specificity improves, the PPV remains low and the sensitivity drops off markedly.

**Table 6.5.** Sensitivity, specificity, positive and negative predictive values at different cut-off scores for the HADS.

| Cut-off | 13/14 | 14/15* | 15/16 | 16/17 | 17/18 | 18/19 | 19/20 | 20/21 |
|---|---|---|---|---|---|---|---|---|
| Sensitivity | 1.00 | 0.75 | 0.67 | 0.67 | 0.67 | 0.58 | 0.50 | 0.50 |
| Specificity | 0.79 | 0.82 | 0.84 | 0.86 | 0.86 | 0.86 | 0.92 | 0.92 |
| PPV | 0.60 | 0.56 | 0.57 | 0.62 | 0.62 | 0.58 | 0.67 | 0.67 |
| NPV | 1.00 | 0.91 | 0.89 | 0.89 | 0.89 | 0.86 | 0.85 | 0.85 |

HADS, Hospital Anxiety and Depression Scale; PPV, positive predictive value; NPV, negative predictive value.
--Maximum sum of sensitivity and specificity
*Standard cut-off of HADS

#### 6.3.2.3. HADS-D

When only the depression subscale of the HADS is analysed, the self-report measure performs even better at discriminating between depressed and non-depressed patients, with an AUC of 0.923. At the standard cut-off of 7/8 (sensitivity 0.92, specificity 0.87), it is the best scale at discriminating 'caseness' in the population with both high sensitivity and specificity (see Table 6.6). The optimal cut-off, however is 6/7 where the sensitivity increases to the maximum of 1.00 and the specificity remains good at 0.82. The HADS-D only reaches the specificity and PPV required for a diagnostic test at a cut-off 12/13. This is however, at the cost of a very low sensitivity (0.33), meaning that many depressed patients would be missed.

**Table 6.6.** Sensitivity, specificity, positive and negative predictive values at different cut-off scores for the HADS-D.

| Cut-off | 6/7 | 7/8* | 8/9 | 9/10 | 10/11 | 11/12 | 12/13 | 13/14 |
|---|---|---|---|---|---|---|---|---|
| Sensitivity | 1.00 | 0.92 | 0.92 | 0.58 | 0.58 | 0.50 | 0.33 | 0.08 |
| Specificity | 0.82 | 0.87 | 0.87 | 0.87 | 0.90 | 0.92 | 0.97 | 1.00 |
| PPV | 0.63 | 0.69 | 0.69 | 0.58 | 0.64 | 0.67 | 0.80 | 1.00 |
| NPV | 1.00 | 0.97 | 0.97 | 0.87 | 0.87 | 0.85 | 0.82 | 0.78 |

HADS-D, Hospital Anxiety and Depression Scale – depression section; PPV, positive predictive value; NPV, negative predictive value.
--Maximum sum of sensitivity and specificity, *Standard cut-off of HADS-D

#### 6.3.2.4 DISCs

With an AUC of 0.943, the DISCs performed best overall in detecting depression in HD patients, although this difference is unlikely to be clinically relevant. The standard cut-off of 1/2 (sensitivity 0.92, specificity 0.82) was also the optimal cut-off (see Table 6.7). At a cut-off at 2/3 (sensitivity 0.75, specificity 0.97), the PPV is also high at 0.90, which would mean that the DISCs is the only self-report rating scale that could be considered a useful screening and diagnostic measure.

**Table 6.7.** Sensitivity, specificity, positive and negative predictive values at different cut-off scores for the DISCs.

| **Cut-off** | **0/1** | **1/2*** | **2/3** | **3/4** |
|---|---|---|---|---|
| Sensitivity | 1.00 | 0.92 | 0.75 | 0.17 |
| Specificity | 0.42 | 0.82 | 0.97 | 1.00 |
| PPV | 0.35 | 0.61 | 0.90 | 1.00 |
| NPV | 1.00 | 0.97 | 0.93 | 0.79 |

DISCs, Depression Intensity Scale Circles; PPV, positive predictive value; NPV, negative predictive value.
--Maximum sum of sensitivity and specificity
* Standard cut-off of DISCs

## *6.4. Discussion*

It is important in terms of clinical management and research that unpleasant affective states as symptoms can be distinguished from depression as a clinical syndrome. In this way, self-report rating scales play an extremely important role as quick, cheap and easy to use measures of depression. However, in HD, diagnostic distinction can be confounded by the presence of somatic complaints as well as cognitive impairment and dysarthria. This was the first study to date that has validated self-report rating scales for depression in the HD population, despite their common use in research and clinical practice.

Of all the self-report rating scales validated in this study, the BDI-II was the one with highest overall cognitive complexity and contained the greatest number of items relating to somatic symptoms. The fact that the BDI-II was found to be the least suitable scale for discriminating between depressed and non-depressed HD patients confirms the criticism of the use of such rating scales in the HD population. However, it is possible that the use of the BDI-II with certain items of the scale removed would improve the psychometric properties of the scale. For example, a Rasch analysis of the BDI-II in stroke survivors found that the removal of five items from the original 21 item scale that did not demonstrate acceptable goodness-of-fit to the Rasch model (items 10 (crying), 16 (changes in sleeping pattern), 17 (irritability), 18 (changes in appetite) and 21 (loss of interest in sex)), improved the reliability and validity of the scale (Lerdal et al., 2014). In a neurorehabilitation sample, a Rasch analysis of the BDI-II resulted in three items being deleted from the original BDI-II (item 16 (changes in sleeping pattern), 18 (changes in appetite) and 21 (loss of interest in sex) in order for the scale to have good overall fit to the Rasch model (Siegert et al., 2010).

It was anticipated that the HADS would be a good instrument at detecting depression in HD patients, owing to the fact it was designed for use with physically ill patients and omits somatic items. The results discussed in an earlier chapter (see section 4.5.7) demonstrated that HD individuals with MDDR were significantly less likely to experience certain somatic symptoms (diurnal variation, increased appetite and middle insomnia) as part of their depressive symptomatology when compared to a non-HD population sample with MDDR. These results suggest that such somatic symptoms common to both HD and depressive disorder may be more associated with HD symptomatology than depression and therefore,

the HADS, which excludes these items may have good face validity in the HD population. However, there is still one item on the scale (item 8, "I feel as if I am slowed down"), which could relate to the commonly observed symptom of bradykinesia in HD and result in inflated scores. Additionally, whereas the BDI-II is more reflective of operational diagnostic criteria for major depressive disorder (MDD), the HADS focuses on the depressive symptoms of mood and anhedonia and consequently omits two core items of MDD (suicidal ideation and excessive and inappropriate guilt). However, the HADS performed better than the BDI-II at discriminating depressed from non-depressed HD patients as shown by the larger AUC and without including the anxiety subscale, the sensitivity and specificity of the scale were further improved.

The purpose of including the DISCs in this study was to use a simple, graded scale that may be more accessible for those patients with more severe cognitive and/or communicative deficits. The results confirm that a score ≥2 accurately predicted 'cases' of depression according to ICD-10 criteria. Perhaps surprisingly, the DISCs had the highest overall AUC and was the only scale that performed well as both a screening and diagnostic instrument.

The results of this study compare favourably to research on the use of depression rating scales in other neurological disorders with associated somatic symptoms. Leentjens et al. (2000) concluded that the psychometric properties of the BDI are not ideal for individuals with Parkinson's disease, which also holds true for the Huntington's population. The discriminant property of the BDI-II in the current study was found to be very similar to that determined by Leentjens et al (2000) in their evaluation of the BDI in Parkinson's Disease

patients, with AUCs of 0.856 and 0.857 respectively. Sullivan and colleagues (1995) concluded that the BDI should be used with caution in individuals with MS due to high false negative rates. Kang and colleagues (2013) recommended the use of the HADS over the BDI in screening for depression in a post-stroke population.

The optimal cut-off scores in this study for the BDI-II and HADS-D were lower than the recommended cut-off scores for primary care patients with major depression (Beck et al., 1996; Zigmond and Snaith, 1983). This reflects findings in other studies of patient populations with somatic symptoms. For example, Aben et al (2002) and Kang et al (2013) in screening for depression in post-stroke patients, found the HADS-D to be optimal at a cut-off of 6/7. In patients with Parkinson's Disease, for screening purposes, a cut-off on the BDI of 8/9 (Leentjens *et al.,* 2000) and 6/7 on the BDI-II (Williams et al., 2012) have been recommended.

The predictive validity of the DISCs was even greater in the HD population than in patients with acquired brain injury (ABI), the population for which it was initially designed (HD: sensitivity 0.92, specificity 0.82; ABI: sensitivity 0.60, specificity 0.87, Turner-Stokes et al., 2005). Few studies have been carried out on the reliability and validity of the DISCs; however, a single-item screening question has been demonstrated to be as valid as the HADS in screening for depression in individuals with chronic back pain (Reme et al., 2004). From the results obtained in this study, it would be useful for the DISCs to be validated in other patient groups such as people with Parkinson's disease.

With the use of any rating scale, there will always be a trade-off between sensitivity and specificity. The optimal cut-off point of a scale should depend on the purpose for which it is to be utilised. Given the evidence that depression can exacerbate functional decline and reduce quality of life in HD patients, it could be argued that it would be better to choose a lower cut-off where most 'cases' can be identified even at the cost of a relevant number of false positives. Additionally, because self-report rating scales give a dimensional rather than categorical representation of mood, they should be used as indicators of a probable psychiatric 'case' rather than giving a definitive diagnosis. This is confirmed by the findings from this study as all scales performed much better as screening than diagnostic measures.

There will also be various settings such as clinical trials where a scale is needed to detect changes in severity of depression over time. Such as scale needs to contain some items that are unstable over time and are sensitive to mild, moderate and severe depression (Kellner, 1992). The DISCs is unlikely to be suitable at detecting change over time given that it only has a score range of 0-5, the HADS does not contain items that accurately assesses severe depression and the BDI-II measures attitudes and cognitions, which are typically stable over time among depressed patients (Cusin et al., 2010). For this purpose, the development of a scale using an iterative process whereby various interview questions are tested in the target population, and the data obtained then used to determine which items to test further and which to discard, should allow for the development of a valid rating scale able to detect changes in symptom severity. This is the purpose of the Functional Rating Scale Taskforce for pre-Huntington's Disease (FuRST-pHD) who are in the process of developing a rating scale

aimed at assessing depression, anxiety and apathy in prodromal and early HD (Vaccarino et al., 2011).

Higher rates of current depression in HD patients than would be expected in the general population were also reported in this study. This is in keeping with the findings in chapter 4 (see Table 4.4 in section 4.4.1.2) where the lifetime prevalence rate for DSM-IV major depressive disorder was up to three times as high as those reported in general population studies (index sample=42%, sibling sample=42.5%, National Comorbidity Survey Replication, NCS-R=16.9% (Kessler et al., 2005) and the European Study of the Epidemiology of Mental Disorders, ESEMeD=12.8% (Alonso et al., 2004)). Sixty percent of participants in this HD sample reported themselves as having current feelings of low mood, although only 24% fulfilled the criteria for formal ICD-10 diagnosis. In the 2007, Adult Psychiatric Morbidity Survey in the UK (see section 4.6.1), only 2.3% of the sample met ICD-10 diagnostic criteria for a current depressive episode (a further 9.0% had a current ICD-10 diagnosis of a mixed anxiety and depressive disorder). However, the figure of 24% is comparable to other point prevalence rates of major depression in HD. Caine and Shoulson (1983) reported that 20.8% of their small sample of HD patients had current depression according to DSM-III (a further 25.0% were experiencing dysthymia), Julien et al (2007) also using DSM-III found a current prevalence rate of 15% for major depression in a sample of pre-symptomatic individuals and van Duijn et al (2008) reported a DSM-IV 12-month prevalence rate of 17.9% for major depressive disorder in a sample of 140 mutation carriers.

### *6.5. Summary and limitations*

This chapter has discussed the validation of self-report depression rating scales in HD and provides evidence that the somatic items of depression add little value to the differential diagnosis of depression in HD. The main findings are as follows:

- The depression subscale of the HADS with a high sensitivity and specificity at a cut-off of 6/7 was the most suitable scale for discriminating between depressed and non-depressed patients in the HD sample.
- The BDI-II performed the least satisfactorily of all scales at detecting "cases" of depression in the HD sample but if the low specificity of the scale can be accepted, then a cut off of 10/11 should be used.
- The high predictive validity of the DISCs using a cut-off of 1/2 makes this an ideal instrument to use in HD patients with more complex cognitive and communicative difficulties.
- The self-report rating scales should not be used as diagnostic instruments for depression and following screening, the identification of a possible 'case' requires further investigation.

Limitations of the study arise from the modest sample size and it is therefore important for the findings to be replicated with a larger sample size, which would also enable the sample to be stratified by severity of HD and depression. The majority of depressed patients had either mild or moderate depression and consequently the scales were not so rigorously tested in patients with severe depression. As already indicated, the HADS does not include items associated with more severe depression including suicidal ideation, somatic symptoms

and psychotic symptoms and therefore may prove to have lower validity in patients who are severely depressed.

Additionally, those patients with severe cognitive deficits were excluded from this study, owing to their presumed inability to consistently respond meaningfully and reliably, thus limiting the generalisability of these results to the entire HD population. HD individuals with depression may be under-represented in this sample given that very depressed individuals are less likely to be invited to take part in research and all participants were registered with the HD service in Birmingham and consequently, any patients presenting with low mood are likely to be followed up closely with intervention prescribed as necessary. Some may also criticise the use of ICD-10 diagnoses obtained from the SCAN interview as a gold standard, owing to the fact that five of the criteria for depression concern somatic items (decreased energy, diminished ability to think or concentrate, change in psychomotor activity, sleep disturbance and change in appetite). However, the use of a semi-structured interview allowed for the depressive symptoms only to be rated if they were clearly associated with low mood rather than the temporal course of HD (see section 4.6.3.5), which may have led to underreporting of certain items and therefore possible underdiagnosis of depression in this sample.

The sample consisted entirely of HD symptomatic individuals. However, it is possible that in pre-symptomatic individuals, the absence of motor symptoms and fewer cognitive difficulties may be less likely to result in spuriously raised scores on the scales. Therefore,

self-report depression rating scales also need to be validated in the pre-symptomatic HD population.

The following chapter (chapter 7) is the final chapter. It will summarise the key findings of the studies, discuss the limitations and implications of these results and make suggestions for further research.

# CHAPTER 7: MAIN FINDINGS AND FINAL CONCLUSIONS

This final chapter will summarise the main findings and final conclusions of the investigations into the psychiatric phenotype of Huntington's disease (HD) presented in this thesis. The implications of the findings and limitations of the work will then be discussed followed by suggestions for future research.

## *7.1 Main findings*

Psychiatric symptoms have long been recognised as part of the clinical phenotype of Huntington's disease (Huntington, 1872). Given the presence of neuropsychiatric symptoms is known to cause more distress to both patients and caregivers than the motor and cognitive aspects of the disease (Craufurd and Snowden, 2002) and they contribute to reduced quality of life (Ho et al., 2009) as well as functional (Hamilton et al., 2003) and cognitive decline (Nehl et al., 2001; Smith et al., 2012), further investigation into the aetiology of psychiatric symptoms in HD is warranted.

Previous studies investigating possible associations between the behavioural changes in HD and the HD gene have demonstrated no relationship between the presence and severity of psychiatric symptoms and the length of the trinucleotide repeat (Weigell-Weber et al., 1996; Naarding et al., 2001; Vassos et al., 2007). However, other studies have demonstrated clustering of psychiatric symptoms/syndromes in some HD families, suggesting that familial factors may influence the psychiatric phenotype in HD (Heathfield, 1967; Folstein et al., 1983; Lovestone et al., 1996; Tsuang et al., 1998; De Marchi et al., 1998; Tsuang et al., 2000; Correa et al., 2006). Nevertheless, these previous studies used small sample sizes (often only

describing one or two family pedigrees), have had methodological problems and have mainly focused on the familial association between HD and psychosis. These limitations led to the two main aims of this thesis as well as three secondary aims, and the main findings from this study associated with these aims are summarised below.

### 7.1.1 Main Aims

#### 7.1.1.1 First Aim

*To determine whether a broad range of psychiatric syndromes and symptoms aggregate in families affected with HD by conducting a systematic, standardised psychiatric assessment on a large sample of sibling pairs with HD.*

This thesis reported on the familiality of psychiatric syndromes and symptoms in siblings gene positive for HD using gold-standard methodology and the largest sample to date. Evidence was found for familial aggregation of the presence of depressive disorders, irritability and aggression as well as the frequency and severity of depressive episodes. Previous familiality studies in HD have focused on psychotic-like symptoms, which was not possible in the current study as only one individual had a lifetime diagnosis of a psychotic disorder. The results from this study support the single previous study published over 30 years ago suggesting that affective disorders may cluster in some HD families (Folstein et al., 1983) and this is the first study to report that familial factors may influence the presence of irritability and aggression in HD.

No evidence of familiality was found for anxiety disorders, suicidal behaviour, apathy, perseverative thinking, age at onset of psychiatric symptoms, or level of functioning in a depressive episode.

#### 7.1.1.2 Second Aim

*To further improve current understanding of the relative role the HD gene, other genetic factors and psychosocial factors may play in explaining the increased prevalence of psychiatric symptoms in HD. This will be achieved by administering the psychiatric assessment to unaffected siblings who have had a negative HD genetic test.*

Of the five gene negative siblings from five different families who participated in this study, all with a psychiatric history in their HD relatives, four had experienced psychiatric symptoms, three had a history of suicidal ideation and two had lifetime DSM-IV diagnoses. The frequency of psychiatric disorders was higher in the gene negative sample than prevalence rates reported in large general population epidemiological studies. When compared to the gene positive HD samples, the frequency of lifetime DSM-IV depressive disorders was higher in the HD gene positive samples than the gene negative sample whereas the frequency of lifetime DSM-IV anxiety disorders and alcohol abuse was higher in the gene negative sample. The age at onset of psychiatric symptoms in the gene negative individuals was more similar to that observed in general population studies than that found in the gene positive siblings. Taken together, these findings suggest that the familial influences on the psychiatric presentation of HD cannot be entirely explained by the HD gene.

### 7.1.2 Secondary Aims

#### 7.1.2.1 First Aim

*To assess and determine the lifetime prevalence rates of a broad range of psychiatric symptoms and syndromes defined using DSM-IV criteria in a large sample of unrelated individuals with HD.*

This thesis reported a systematic investigation of the psychiatric phenotype in HD using a battery of standardised assessment measures, including gold-standard semi-structured interview methodology. Depressive disorders were the most frequent psychiatric illness in the HD sample with lifetime DSM-IV prevalence rates of 56% for the index sample and 65% for the sibling sample. This was followed by anxiety disorders with a lifetime DSM-IV prevalence rate of 38% for the index sample and 25% for the sibling sample. This finding is in keeping with previous HD studies suggesting that the prevalence of depressive and anxiety disorders is over-represented in the HD population when compared to the general population. However, contrary to some previous HD studies, there were no HD individuals in the current study with a lifetime DSM-IV diagnosis of bipolar disorder or obsessive compulsive disorder (OCD).

#### 7.1.2.2 Second Aim

*To compare the depression phenotype in this HD sample with that in a large sample of individuals with unipolar depression without HD.*

This was the first study to compare the depression phenotype in HD with a non HD sample. The non-HD sample of individuals with major recurrent depressive disorder (MDDR) used in this study was an ideal comparative sample given that the same assessment measures were used in the neuropsychiatric assessment of both samples and both samples were recruited systematically. The main finding from this investigation was that the depression phenotype in HD may be different to that in the non-HD population. When compared to the non-HD MDDR sample, individuals with a lifetime DSM-IV diagnosis of MDDR in the HD sample had a significantly older age at onset of depression, experienced significantly more frequent

episodes of depression (and episodes of shorter duration, although this finding approached significance), experienced significantly less impairment of functioning during their worst episode of depression and were significantly less likely to experience core biological symptoms in episodes of depression. These findings suggest that the HD gene, whether directly and/or indirectly through the psychosocial stresses associated with having HD, influences the presentation and course of depression in these individuals.

#### 7.1.2.3 Third Aim

*To validate the use of self-report depression rating scales in HD so that depression can be more accurately assessed in this population.*

This was the first study to validate the use of self-report depression rating scales in the HD population despite their widespread use in research and clinical practice. The scales were validated against a gold standard interview, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), which was used to assess the presence and severity of clinical symptoms associated with depressive disorder for ICD-10 diagnosis. The results demonstrated that the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D, Zigmond and Snaith, 1983) at a cut-off of a score of 7 or more was the most valid self-report measure at discriminating between depressed and non-depressed individuals with HD. Interestingly, the Beck Depression Inventory-II (BDI-II, Beck et al., 1996), which is the most commonly used self-report measure of depression in the HD population was the least useful at detecting “cases” of depression in the HD sample.

## *7.2 Final conclusions*

In conclusion, investigations into the psychiatric phenotype of HD as presented in this thesis have found evidence to suggest that familial factors (most likely genetic factors other than the HD gene) contribute to the lifetime presence and course of depression, irritability and aggression in HD. Although the HD gene cannot alone account for the high prevalence of psychiatric disorders/symptoms in HD given the significant proportion of HD family members gene negative for HD who also have a lifetime psychiatric history, having the HD gene does appear to influence the presentation and course of psychiatric symptoms, most notably the age at onset of psychiatric illness and the depression phenotype.

## *7.3 Implications*

The results of this study have important implications both in terms of clinical management and treatment of individuals with HD and psychiatric disorders as well as those HD family members gene negative for HD.

### 7.3.1 Clinical management of individuals with HD

The evidence from this study for the clustering of depression, irritability and aggression in some HD families, emphasises the requirement for an individual's psychiatric family history to be taken to inform of possible increased risks. The high lifetime prevalence of psychiatric disorders including depressive and anxiety disorders as well as neuropsychiatric symptoms including irritability, aggression, perseverative thinking and apathy observed in this sample highlights the need for HD individuals to be regularly screened for psychiatric illness. Furthermore, a significant proportion of individuals with a lifetime history of depression

and/or anxiety had a “not otherwise specified” (NOS) diagnosis, where DSM-IV criteria were not met for a specific disorder. Recognition of individuals with HD and NOS diagnoses is important as they may require different clinical management than those HD individuals with more typical depression/anxiety disorders.

The fact that many individuals experienced onset of their psychiatric symptoms prior to motor onset emphasises the importance of assessing for the presence of psychiatric syndromes/symptoms throughout the prodromal phase. HD individuals also need to be regularly screened for suicidal ideation. Effective screening is the first step in reducing the morbidity associated with psychiatric symptoms in HD. For depression, it is recommended that the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) at a cut-off score of 7 or more is used in the HD population and the Depression Intensity Scale Circles (DISCs) is used at a cut-off of 2 or more to screen for depression in those individuals with more severe communicative deficits. Use of these quick, cheap yet valid screening tools in HD could be particularly useful given the recent evidence suggesting that depression is under-treated in HD (Epping et al., 2013; van Duijn et al., 2014). For those individuals who score above the recommended cut-offs on the scales, further assessment for formal psychiatric diagnosis according to DSM-V/ICD-10 is recommended.

### 7.3.2 Treatment implications for individuals with HD

The findings from this study suggest that the depression phenotype and therefore possibly the aetiology of depression is different in HD than in the non-HD population. This has important treatment implications as it could be that in order to treat depression successfully

in individuals with HD, different treatments are required. Additionally, for those individuals with depression NOS, an important question arises as to whether these individuals should be treated in the usual way with anti-depressants or if other treatment methods including non-pharmacotherapy would be more beneficial. Further research is needed to evaluate this.

### 7.3.3 Psychiatric illness in gene negative individuals

Evidence in this study that individuals within HD families who are gene negative for HD also suffer from psychiatric illness more frequently than the general population highlights that this is also an important population in which to regularly screen for psychiatric symptoms/syndromes. Such screening would be important throughout the lifespan and not just around the time of genetic testing.

## *7.4 Limitations*

Limitations pertaining to the methodology of chapters 4, 5 and 6 were discussed at the end of each relevant chapter (sections 4.7, 5.6 and 6.5). The following section details the main limitations of this body of research.

### 7.4.1 Modest sample size

The main limitation of the current investigations was the modest sample size, which limited the power to detect significant relationships within the data. More specifically, low rates of specific psychiatric diagnoses such as recurrent major depressive disorder (MDDR) in the samples may have reduced the power to detect differences/similarities between the samples. As a result of the modest sample size and exploratory nature of the study, multiple comparisons were not corrected for. However, this sample was particularly difficult to

recruit given that HD is a rare disorder and only families where at least two siblings were aware of their genetic status and were gene positive for HD were invited to take part. Nevertheless, within the given time frame, 102 individuals were interviewed throughout the UK for the familality study and a further 50 individuals were recruited and assessed for the study validating depression rating scales in HD. The gene negative sample was particularly difficult to recruit given that the gene positive siblings were typically responsible for passing the information on to their gene negative sibling(s), which due to the memory problems and apathy frequently experienced by individuals with HD meant that the gene positive siblings were often not contacted. Additionally, in many of the families recruited to the study, which comprised 3 or more siblings, the additional siblings, although not showing any symptoms of HD, were often unaware of their genetic status and therefore it was not possible to include them in the study.

### 7.4.2 Reporting of lifetime psychiatric history

The reporting of an individual's psychiatric history was retrospective and therefore could have led to some inaccuracies in the data. However, information was gathered from numerous different sources including a caregiver where possible and case notes in order to try and minimise this and a prospective study would not have been possible in the time frame. Additionally, although lifetime psychiatric ratings were made, lifetime only represents an individual's psychiatric history up until their age at interview for the study. Therefore, the data collected is not a complete representation of an individual's lifetime psychiatric history as it is possible that an individual will experience first onset or further episodes of psychiatric illness post-interview.

### 7.4.3 Potential sample biases

Although sibling pairs were recruited to the study solely on the basis that both siblings were gene positive for HD, it is possible that those individuals with a psychiatric history were better known to their HD Consultant and were therefore more likely to be recruited to the study. Similarly, for the study validating rating scales of depression, it is possible that there was a recruitment bias towards HD individuals with a history of depression. Conversely, those individuals with more severe psychiatric symptoms such as severe depression or psychosis were likely to be underrepresented in the study because they are less likely to respond to an invitation to take part in research and also, the study population was nearly all out-patient. It is also possible that the gene negative sample was biased towards individuals with psychiatric illness as they may be more interested in taking part in research/mental health research.

## *7.5 Future research*

Further research into the psychiatric phenotype of HD is required in larger samples. For assessing the lifetime psychiatric phenotype of HD, a sample of consecutive, unrelated individuals gene positive for HD should be recruited. For replication of the familiality study, it is likely that collaboration is required to achieve the necessary larger sample sizes (for example with the sibling HD populations investigated at the Baltimore Huntington Disease Center, USA and the Huntington Disease Medical Genetics Clinic, Vancouver, Canada for the familiality of the age at onset of motor symptoms, Rosenblatt et al., 2001). Alternatively, focusing on recruiting families of probands gene positive for HD with a specific lifetime DSM-IV diagnosis such as depressive disorders as well as families of probands with no psychiatric

history and then determining the frequency of depressive disorders in the first degree relatives, should help increase the power to detect familial influences on the depression phenotype in HD.

Further research into the contribution of other biological and environmental factors to the psychiatric phenotype of HD is warranted. Longitudinal studies to identify possible environmental precipitants and modifiers of psychiatric illness in HD would be valuable. To identify possible biological risk factors, the search for genetic modifiers of the psychiatric phenotype in HD will likely prove an interesting area for future research. Genetic modifiers of HD (i.e. a gene or genes other than the HD gene that cause variation in the expression of HD) likely act at different stages of the disease and affect different HD phenotypes, including its psychiatric presentation (Gusella and MacDonald, 2009). The investigation of possible genetic risk variants for psychiatric disorders/symptoms in HD undoubtedly requires large scale collaboration. For example, genome-wide association studies (GWAS), often require more than 10 000 participants (Collins and Sullivan, 2013).

Given the difficulties with identifying genetic risk variants of complex, psychiatric disorders in the non-HD population (Collins and Sullivan, 2013), it may be useful to first improve the phenotypic definition of specific psychiatric symptoms/disorders in HD such as depressive and anxiety disorders in order to define relatively homogenous subgroups. Administration of the semi-structured interview, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), which rates the presence and severity of items associated with major psychiatric disorders, to a large sample of individuals with for example HD and MDD or HD and panic

disorder, may following factor analysis, yield groupings of correlated symptoms, which represent symptom dimensions that result from the action of a contributory gene or group of genes.

Additionally, research could focus on the identification of possible biological endophenotypes, which are an internal phenotype, not obvious to the unaided eye that bridge the gap between behavioural phenotype and genotype (Hasler et al., 2004). The use of such quantitative, biological markers may more likely reflect single gene effects than the clinical phenotype and therefore improve the ability to identify the role of genes other than the HD gene in the psychiatric presentation of HD (Hasler et al., 2004). In terms of depression in HD, possible biological enophenotypes could include indicators of HPA axis dysregulation and measures of brain structural changes such as hypometabolism in the orbital inferior prefrontal cortex.

Qualitative studies may prove useful in gaining greater insight into the psychiatric phenotype of syndromes such as apathy and NOS diagnoses and may enable the development of measurement tools specifically for use in the HD population. This would prove useful not only in clinical practice but also in research settings such as end points for clinical trials. An improved understanding of the aetiology of psychiatric syndromes/symptoms in HD may also help in understanding the causes of psychiatric illness in the non-HD population.

### *7.6 Summary*

This thesis has presented the findings of an investigation into the psychiatric phenotype of HD using gold standard methodologies. Evidence has been found to support the suggestion that some HD families have a predisposition to developing psychiatric disorders and the results suggest that the familial influences cannot be entirely explained by the HD gene. Additionally, evidence was found to suggest that psychiatric disorders are more prevalent in individuals with HD than in the general population and that the depression phenotype may be different in HD than in the non-HD population. This was the first study to validate the use of self-report depression rating scales in HD, with the recommendation that the depression subscale of the HADS at a cut-off of 6/7 be used for screening purposes in the HD population. These findings have important implications for the clinical management and treatment of individuals with HD as well as for gene negative individuals. Further research in larger samples to determine the biological and psychosocial underpinnings of psychiatric syndromes/symptoms in HD is required.

# APPENDICES

## *A Appendices for Chapter 3*

### Ai Participant information sheets, reply slip, HDA website advertisement, consent forms, GP letter

**PARTICIPANT INFORMATION SHEET – GENE POSITIVE SIBLING**

**RESEARCH INTO SIBLINGS WITH HUNTINGTON'S DISEASE**
**VERSION 2: Wednesday 15th October 2008**

- **INTRODUCTION**

I am a member of a research team working in the Department of Neuropsychiatry at The Barberry (formerly the Queen Elizabeth Psychiatric Hospital), Birmingham. We are currently conducting a study investigating the clinical features of siblings with Huntington's Disease. To help you decide whether or not you wish to take part in this study, please read the following information carefully, which explains why this study is being carried out and what participation entails. Please take your time to decide and if you wish, discuss the study with your family, friends or General Practitioner.

- **PURPOSE OF THE RESEARCH**

It is known that people with Huntington's Disease typically experience disordered movements, thinking and behaviour. However, it is less well known why these symptoms vary in presentation and age at onset from one person to the next. We are interested in looking at brothers or sisters with HD in order to try and identify which particular symptoms may have a familial (genetic and/or environmental) basis. This research will significantly improve our understanding of Huntington's Disease and will help improve the treatment needs of people with HD. The results could also guide future research in terms of identifying genes that predispose someone with HD to develop particular symptoms and also in the development of new and better treatments.

- **HOW WILL WE DO THIS?**

We would like to interview families where at least two brothers or sisters have Huntington's Disease – whether already symptomatic or not yet symptomatic but have had a positive predictive test. Within these families, we would also like to recruit any brothers or sisters who have had a negative predictive test and therefore **do not** have Huntington's Disease. This will help us better understand which symptoms may co-occur with Huntington's Disease and which are unrelated to having the HD gene.

- **WHAT DOES TAKING PART INVOLVE?**

We hope to recruit a sample of 80-100 brothers or sisters with Huntington's Disease as well as any willing unaffected siblings. Participation in this study involves:

1. An assessment of your movements, thinking and day-to-day functional capabilities (1/2 hour).

2. An interview asking you about any psychiatric symptoms you may have experienced (1 hour).

3. Completing 2 questionnaires (1/4 hour).

We will only need to see you once for this study and this visit will be arranged at a suitable time for you in your home or another place convenient for you.

With your permission, we would also like to look at your medical records in strict confidence.

We would also like to contact any of your brothers or sisters who have Huntington's Disease (whether symptomatic or not) or who have had a negative predictive test. This contact would be via a letter, which we would ask you to send to your brother or sister, and they would be under no obligation themselves to take part.

- **WHAT ARE THE BENEFITS OF TAKING PART? ARE THERE ANY RISKS?**

There may be no direct benefits from taking part in the study. However, your help will be of great value in allowing us to learn more about Huntington's Disease and may lead to improvements in the clinical management of HD patients and enable the development of more effective treatments.

There are no specific risks arising from your participation in this study given that this is an observational study.

We may check with your doctors involved in your care to ensure it would be appropriate for you to take part in this study.

- **DO I HAVE TO TAKE PART?**

Your participation in this research project is <u>voluntary.</u> It is up to you to decide whether or not to take part. If you do decide to take part, you will be asked to sign a consent form. If you decide to take part you are free to withdraw from the study at any time without giving reason. A decision to withdraw at any time, or a decision not to take part in the study, will not affect your medical treatment or the standard of care you receive.

- **WHAT WILL HAPPEN TO THE RESULTS OF THIS STUDY?**

At the end of the study, the results will be analysed and the results will be published in Scientific Journals. In addition, the results will be presented at conferences and to specialists working in the Huntington's Disease field. The anonymised data will be stored for five years after the end of the study in a locked cabinet.

- **CONFIDENTIALITY**

All information collected from you will be kept strictly confidential and stored in locked filing cabinets with access restricted to the investigators involved in the study. The information obtained will also

be entered onto a secure computer database for analysis, but evaluation and publication of the results will be carried out anonymously. **None of your personal data will be made public.**

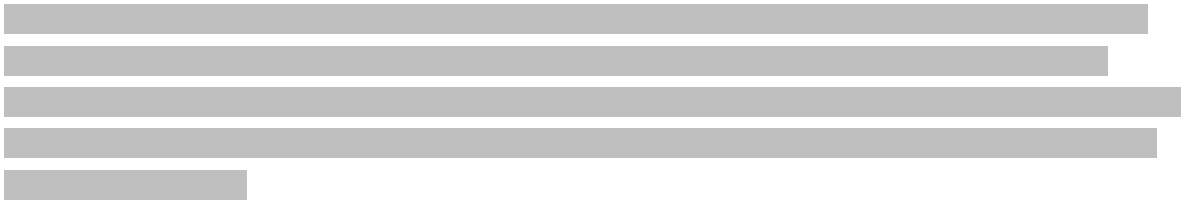
- **WILL MY GENERAL PRACTITIONER (GP) KNOW THAT I AM INVOLVED IN THIS STUDY?**

Should you agree to take part in this study, it is important that your GP is kept informed of your participation and he/she will also be sent a copy of this information sheet.

- **WHO IS ORGANISING AND FUNDING THE RESEARCH?**

The study is being organised by Dr. Hugh Rickards MD FRCPsych and Jenny Keylock BSc MSc in the Department of Neuropsychiatry at The Barberry, Birmingham. Birmingham and Solihull Mental Health Foundation Trust are sponsoring the research project.

- **WHAT IF I HAVE ANY CONCERNS?**



**PARTICIPANT INFORMATION SHEET – GENE NEGATIVE SIBLING**

**RESEARCH INTO SIBLINGS WITH HUNTINGTON'S DISEASE**
**VERSION 2: Wednesday 15th October 2008**

- **INTRODUCTION**

I am a member of a research team working in the Department of Neuropsychiatry at The Barberry (formerly the Queen Elizabeth Psychiatric Hospital), Birmingham. We are currently conducting a study investigating the clinical features of siblings with Huntington's Disease. To help you decide whether or not you wish to take part in this study, please read the following information carefully, which explains why this study is being carried out and what participation entails. Please take your time to decide and if you wish, discuss the study with your family, friends or General Practitioner.

- **PURPOSE OF THE RESEARCH**

It is known that people with Huntington's Disease typically experience disordered movements, thinking and behaviour. However, it is less well known why these symptoms vary in presentation and age at onset from one person to the next. We are interested in looking at brothers or sisters with HD in order to try and identify which particular symptoms may have a familial (genetic and/or environmental) basis. This research will not only help improve the treatment needs of people with HD but will also guide future research in terms of identifying genes that predispose someone with HD to develop particular symptoms and also in the development of new and better treatments.

- **HOW WILL WE DO THIS?**

We would like to interview families where at least two brothers or sisters have Huntington's Disease – whether already symptomatic or not yet symptomatic but have had a positive predictive test. Within these families, we would also like to recruit any brothers or sisters who have had a negative predictive test and therefore **do not** have Huntington's Disease. This will help us better understand which symptoms may co-occur with Huntington's Disease and which are unrelated to having the HD gene.

- **WHAT DOES TAKING PART INVOLVE?**

We hope to recruit a sample of 80-100 brothers or sisters with Huntington's Disease as well as any willing unaffected siblings. Participation in this study involves:
1. An interview asking you about any psychiatric symptoms you may have experienced (1 hour).
2. Completing 2 questionnaires (1/4 hour).

We will only need to see you once for this study and this visit will be arranged at a suitable time for you in your home or another place convenient for you.
With your permission, we would also like to look at your medical records in strict confidence.

- **WHAT ARE THE BENEFITS OF TAKING PART? ARE THERE ANY RISKS?**

There may be no direct benefits from taking part in the study. However, your help will be of great value in allowing us to learn more about Huntington's Disease and may lead to improvements in the

clinical management of HD patients and enable the development of more effective treatments. There are no specific risks arising from your participation in this study given that this is an observational study.

- **DO I HAVE TO TAKE PART?**

Your participation in this research project is voluntary. It is up to you to decide whether or not to take part. If you do decide to take part, you will be asked to sign a consent form. If you decide to take part you are free to withdraw from the study at any time without giving reason. A decision to withdraw at any time, or a decision not to take part in the study, will not affect your medical treatment or the standard of care you receive.

- **WHAT WILL HAPPEN TO THE RESULTS OF THIS STUDY?**

At the end of the study, the results will be analysed and the results will be published in Scientific Journals. In addition, the results will be presented at conferences and to specialists working in the Huntington's Disease field. You will also be sent information regarding the outcome of the study. The anonymised data will be stored for five years after the end of the study in a locked cabinet.

- **CONFIDENTIALITY**

All information collected from you will be kept strictly confidential and stored in locked filing cabinets with access restricted to the investigators involved in the study. The information obtained will also be entered onto a secure computer database for analysis, but evaluation and publication of the results will be carried out anonymously. **None of your personal data will be made public.**

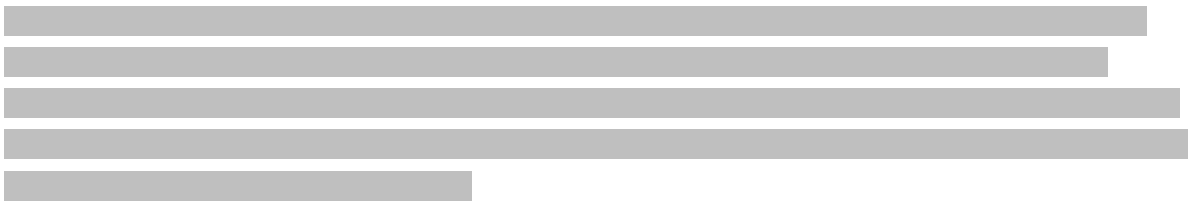
- **WILL MY GENERAL PRACTITIONER (GP) KNOW THAT I AM INVOLVED IN THIS STUDY?**

Should you agree to take part in this study, it is important that your GP is kept informed of your participation and he/she will also be sent a copy of this information sheet.

- **WHO IS ORGANISING AND FUNDING THE RESEARCH?**

The study is being organised by Dr. Hugh Rickards MD FRCPsych and Jenny Keylock BSc MSc in the Department of Neuropsychiatry at The Barberry, Birmingham. The research project is being sponsored by the Birmingham and Solihull Mental Health Foundation Trust.

- **WHAT IF I HAVE ANY CONCERNS?**



**REPLY SLIP**

**RESEARCH INTO SIBLINGS WITH HUNTINGTON'S DISEASE**
**Version 2: Wednesday 15th October 2008**

Once you have thought about the information provided in the participant information sheet, please would you kindly fill out your name, address and telephone number and indicate which of the three statements below best refers to you. Please return your response in the pre-paid envelope provided to Jenny Keylock. If you have misplaced the envelope, the address is also printed at the top of the Patient Information sheet.

**Name:**_____

**Telephone number:**_____

**Address:**_____

_____

_____

**Post code:**_____

Please tick the appropriate box below. I have read and understood the patient information sheet dated Wednesday 15 October 2008, version 2 and:

1. I am interested in taking part ☐

Best days and times to call you: _____

2. I require more information about the study before deciding whether to take part ☐

3. I am not interested in taking part ☐

In the case of (1) and (2) only, you will be contacted within 2 weeks in order to clarify any queries you may have and if you are still interested in taking part to arrange an appointment.

**Many thanks for taking the time to read this information and for completing the reply slip.**

**HUNTINGTON'S DISEASE ASSOCIATION (HDA) WEBSITE**

**RESEARCH INTO SIBLINGS WITH HUNTINGTON'S DISEASE**
**Version 2: Wednesday 15th October 2008**

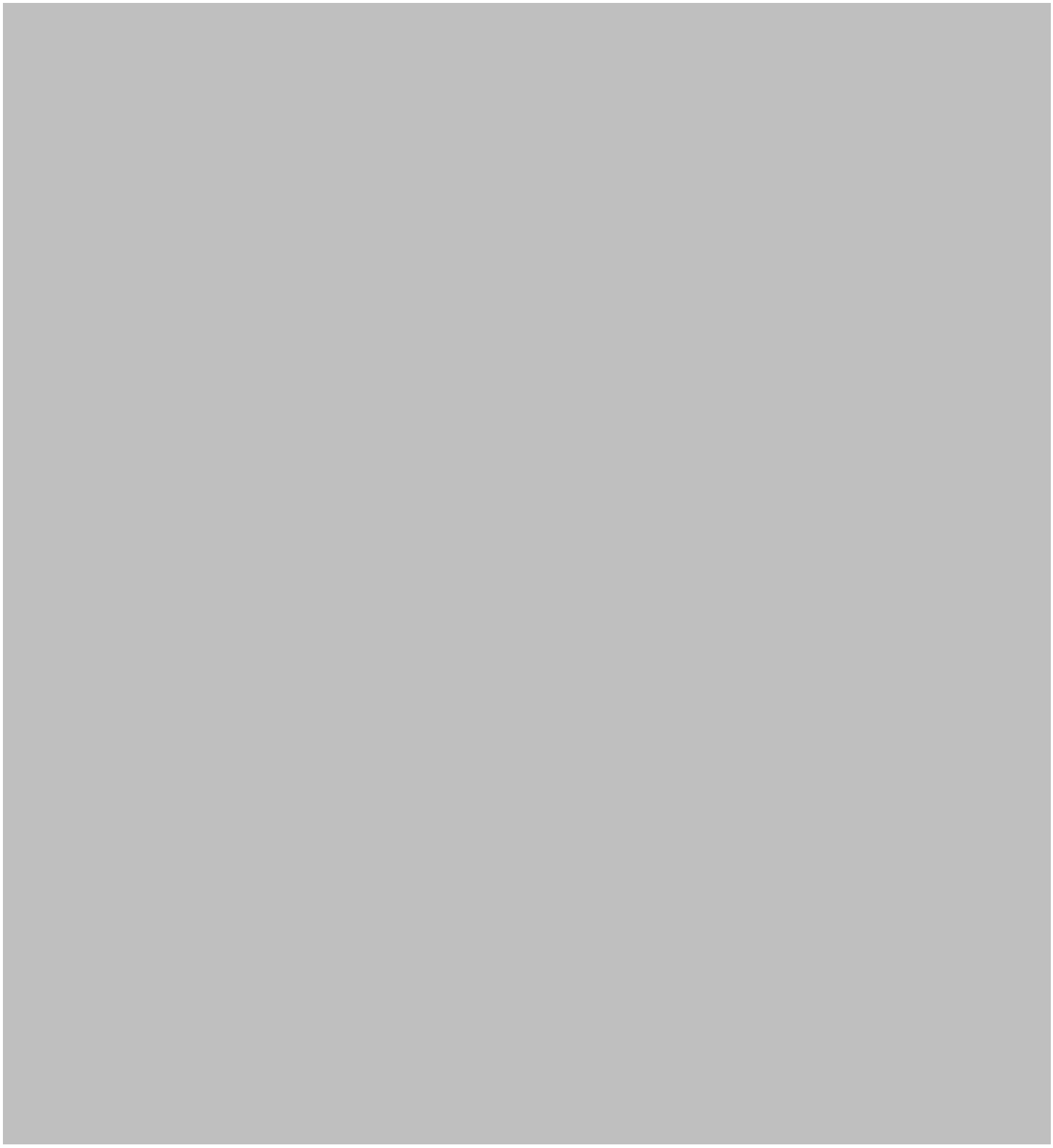
A study is currently underway in the United Kingdom investigating the clinical features of siblings with Huntington's disease (HD). The purpose of the study is to better understand why the symptoms of HD vary in presentation and age at onset from one person to the next and if any particular symptoms cluster in families affected with HD.

We would like to interview families where at least two brothers or sisters have HD – whether already symptomatic or not yet symptomatic but have had a positive predictive test. Also, if within these families there are any siblings who have had a negative predictive test and therefore **do not** have HD, we would be very interested in interviewing these family members too.

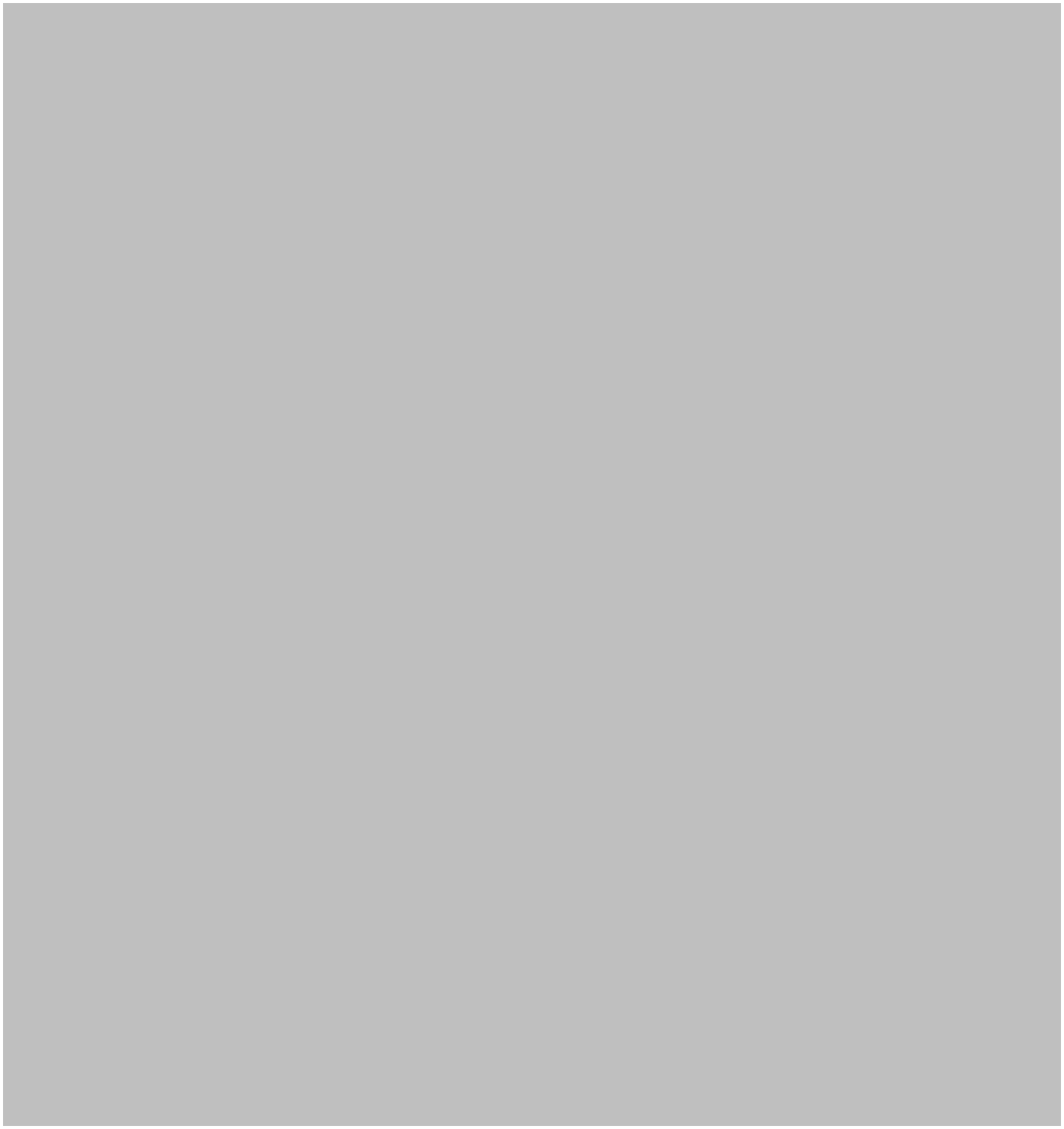
Participation in this study involves a single clinical assessment lasting approximately 2 hours, arranged at a suitable time for you in your home or another place convenient for you. The assessment consists of:

- An assessment of your movements, thinking and day-to-day functional capabilities.
- An interview about any psychiatric symptoms you may have experienced.
- Two self-report questionnaires.

**CONSENT FORMS**



**Healthy sibling consent sheet**



**GP LETTER**

**RESEARCH INTO SIBLINGS WITH HUNTINGTON'S DISEASE**
**VERSION 1: MONDAY 12TH MAY 2008**

Date

Dear Dr.

Re: **Patient name and Date of Birth**

**Patient address**

Your patient …….. has agreed to participate in a study investigating the familiality of clinical symptoms in Huntington's Disease. This study involves a single clinical assessment at the participant's home and is observational only. A copy of the information sheet has been enclosed.

The supervisor for the trial is Dr. Hugh Rickards, Consultant Neuropsychiatrist at the address above and the trial has been approved by the Multi-Centre Research Ethics Committee. If you require any further information about the study, please contact Jenny Keylock, the Chief Investigator on the number at the foot of the patient information sheet.

Yours sincerely,

Jenny Keylock

Research Psychologist

Enc. Patient information sheet

## Aii Demographic information

**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**

**DEMOGRAPHIC INFORMATION**

**Date of Birth:** ☐☐ ☐☐ ☐☐☐☐

**Gender:**
**1=male**
**2=female** ☐

**Ethnicity:_____**

**Index participant** ☐ **Affected sibling** ☐ **Unaffected sibling** ☐

**Years of education:_____**

**Highest level of qualification:_____**

**Currently employed:_____**

**Main occupation:_____**

**Age at symptom onset:_____**

**Address:_____**

**_____**

**_____**

**Telephone:_____**

**GP details:_____**

**_____**

**_____**

**Place of birth:_____**

**Any illnesses other than HD: Yes ☐ No ☐**

**Description:_____**

**_____**

**Currently on any medication? Yes ☐ No ☐**

**Medication description and dose:_____**

**_____**

**_____**

**Currently smokes:**

**No ☐ Yes ☐ Ex-smoker ☐**

**If ex-smoker, time of last cigarette:_____**

**Weight:_____**

**Height:_____**

## Aiii Clinical Assessment of Huntington's disease: UHDRS motor assessment, UHDRS cognitive assessment, Total Functional Capacity Scale

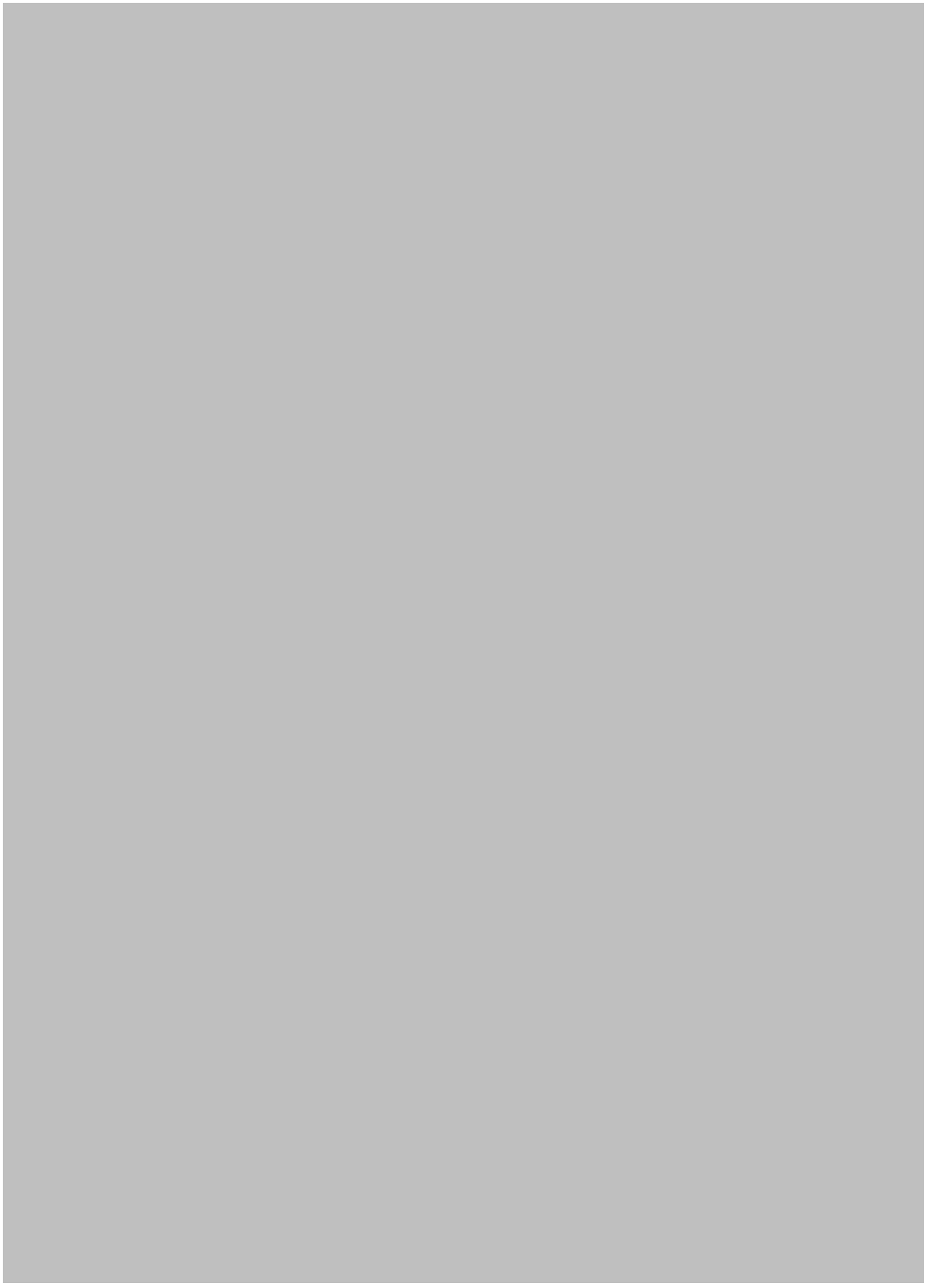
**UHDRS MOTOR ASSESSMENT (Huntington Study Group, 1996)**

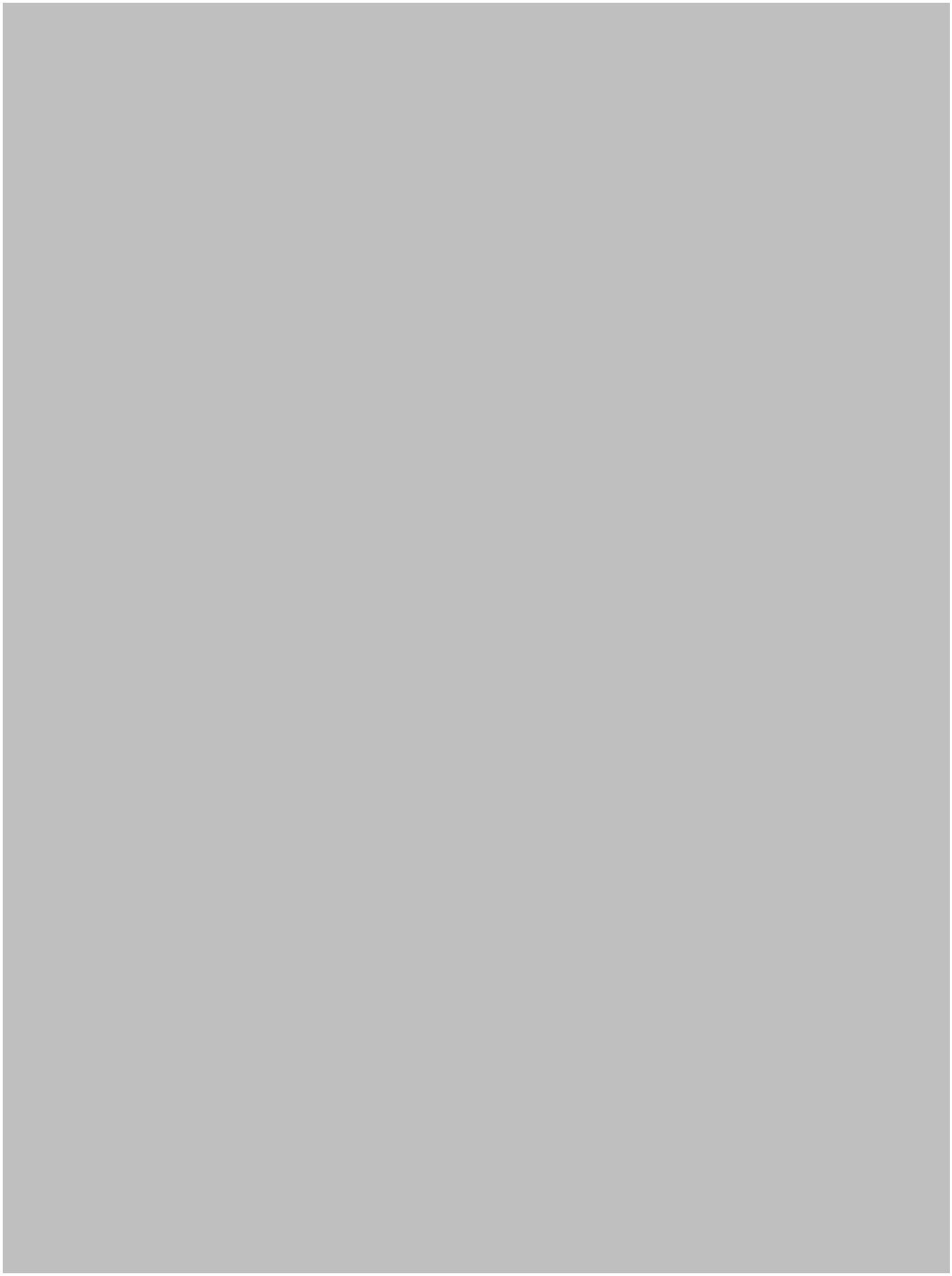
**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**

**UHDRS MOTOR ASSESSMENT**

**Total Motor score:** | | | |





**UHDRS COGNITIVE ASSESSMENT (Huntington Study Group, 1996)**

**Participant's initials:_____**

**Participant's no.:_____ Date data obtained:_____**

**UHDRS VERBAL FLUENCY TEST**

**TOTAL NUMBER OF WORDS** | |

| | *0- 30 SECONDS* | *30-60 SECONDS* |
|---|---|---|
| **F** | | |
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**SUBTOTAL** | | **INTRUSIONS** | | **PERSEVERATIONS** | |

*0-30 SECONDS* *30-60 SECONDS*

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**SUBTOTAL** **INTRUSIONS** **PERSEVERATIONS**

*0-30 SECONDS* *30-60 SECONDS*

**S**

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|---|---|
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**SUBTOTAL** **INTRUSIONS** **PERSEVERATIONS**

**<u>UHDRS COGNITIVE ASSESSMENT</u> (HUNTINGTON STUDY GROUP, 1996)**

**Participant's initials:_____**

**Participant's no.:_____ Date data obtained:_____**

**UHDRS SYMBOL DIGIT TEST**

**TOTAL NUMBER OF CORRECT ANSWERS** | | |

**<u>UHDRS COGNITIVE ASSESSMENT</u> (Huntington Study Group, 1996)**

**STROOP TEST – COLOUR NAMING**

**Participant's initials:_____**

**Participant's no:_____** **Date data obtained:_____**

**<u>UHDRS COGNITIVE ASSESSMENT</u> (Huntington Study Group, 1996)**

**STROOP TEST – WORD READING**

**UHDRS COGNITIVE ASSESSMENT (Huntington Study Group, 1996)**

**STROOP TEST – INTERFERENCE**

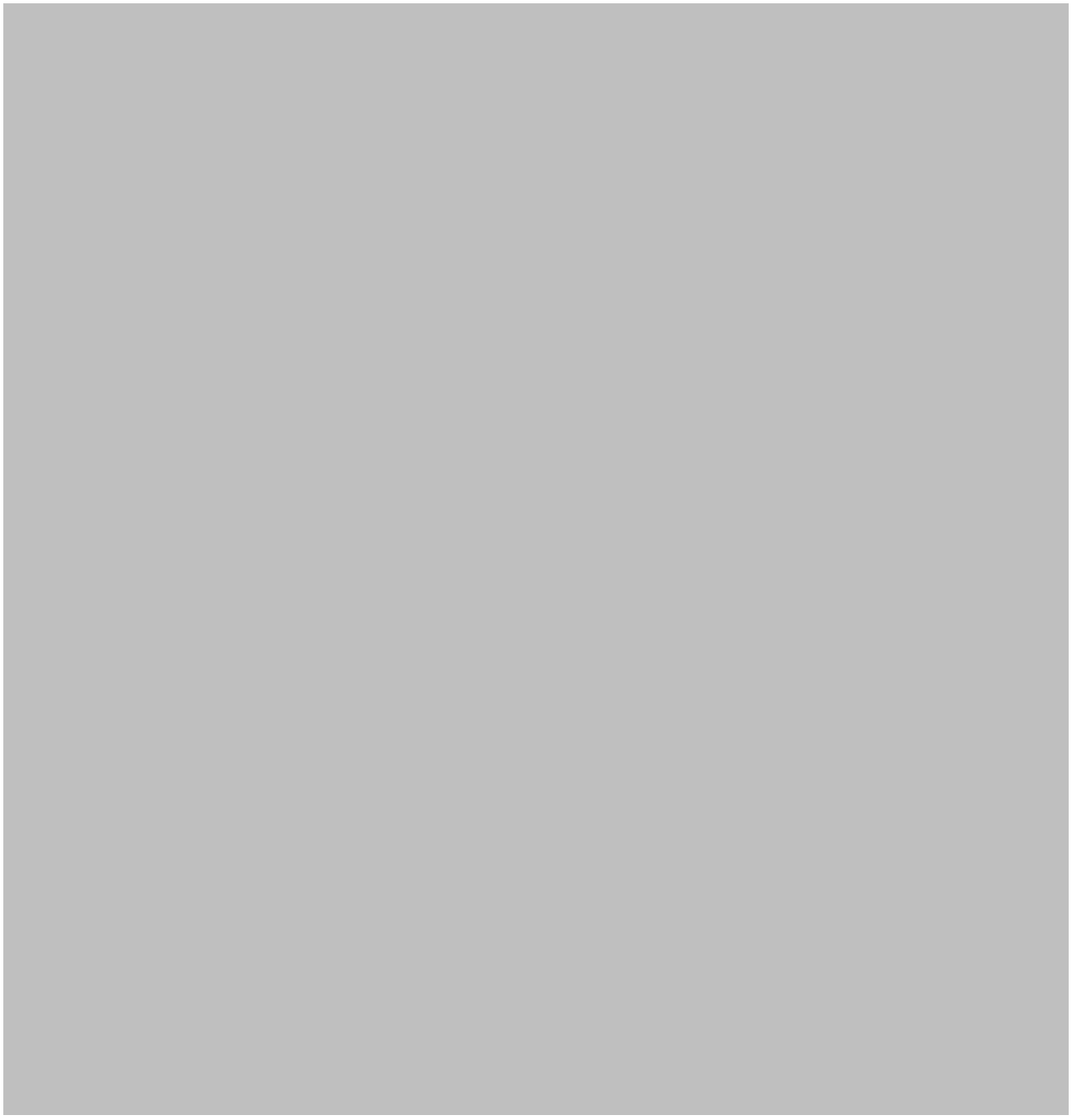
**<u>TOTAL FUNCTIONAL CAPACITY SCALE</u> (Shoulson and Fahn, 1979)**

**Participant's initials:_____**

**Participant's no.:_____ Date data obtained:_____**

**TOTAL FUNCTIONAL CAPACITY**

**TOTAL SCORE** | | |



## Aiv Brief screen of psychiatric history

**BRIEF SCREEN OF PSYCHIATRIC HISTORY**

**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**

Have you ever experienced mental health problems in your life, even if very mild?

| | Y/N | Sought help from GP/other health professional | Received counseling | Prescribed medication | Seen psychiatrist/ hospital admission | Current symptoms |
|---|---|---|---|---|---|---|
| Anxious or panic attacks | | | | | | |
| Feeling very low in spirits, depression or low mood? | | | | | | |
| Feeling much too high in spirits or elated or very irritable without reason, manic depression or bipolar disorder | | | | | | |
| Experiencing things that are difficult to explain or understand like hearing voices or seeing things, psychosis or schizophrenia | | | | | | |
| OCD – checking things you know you have done, keeping things in a special order, repeatedly cleaning things. | | | | | | |
| Eating disorders | | | | | | |
| Other | | | | | | |

## Av Psychiatric consensus rating form

**Study ID _____** **Initials _____** **DOB____**

**Rater ____** **Date _____**

**Main Diagnosis**

| DSM-IV | ICD- |
|---|---|
| | |

**Other diagnosis**

| DSM-IV | ICD- |
|---|---|
| | |

| DSM-IV | ICD- |
|---|---|
| | |

| DSM-IV | ICD- |
|---|---|
| | |

| DSM-IV | ICD- |
|---|---|
| | |

**BADDS Dimension Scores:**

**M** ___ ___ ___

**D** ___ ___ ___

**P** ___ ___ ___

**I** ___ ___ ___

**Gas scores**

**Lifetime worst ever episode** ___

**Lifetime worst in depressive episode** ___

**Lifetime worst in manic episode** ___

**Past week** ___

**Section 2 features ___** **Mood Congruence ___** **Near Section 2 ___**

**No. Episodes:** **Mania ___** **Depression ___** **Anxiety ___**

**Longest Duration:** **Mania ___** **Depression ___** **Anxiety ___**

**<u>Age of onset: any psychiatric disorder</u>**

**Symptom ___** **Impairment ___** **Contact ___** **Admission ___**

**First Depression ____** **First Mania ____** **First Psychosis ____**

**First anxiety/panic/phobia ____** **First obsessional illness ____**

**First Eating disorder ____** **First alcohol or substance ____**

**Suicidal ideation ___** **Rapid Cycling ___** **Puerperal ____**

**Age onset irritablilty _____** **Age onset aggression _____**

**Age onset perseveration _____** **Age onset apathy _____**

## Avi OPerational CRITeria checklist (OPCRIT)

**OPCRIT:** modified 63 item version

**MODIFIED OPCRIT – SYMPTOM CHECKLIST**

**Study ID _____**

| | **DEPRESSIVE SYMPTOMS** | **LE** | **WE** |
|---|---|---|---|
| 1 | Dysphoria | | |
| 2 | Loss of pleasure | | |
| 3 | Diurnal variation (mood worse am) | | |
| 4 | Suicidal ideation | | |
| 5 | Excessive self reproach | | |
| 6 | Poor concentration | | |
| 7 | Slowed activity | | |
| 8 | Loss of energy/tiredness | | |
| 9 | Poor appetite | | |
| 10 | Weight loss | | |
| 11 | Increased appetite | | |
| 12 | Weight gain | | |
| 13 | Initial insomnia | | |
| 14 | Middle insomnia | | |
| 15 | Early morning waking | | |
| 16 | Excessive sleep | | |
| 17 | Diminished libido | | |
| 18 | Agitated activity | | |

| | **MANIC SYMPTOMS** | **LE** | **WE** |
|---|---|---|---|
| 19 | Elevated mood | | |
| 20 | Irritable mood | | |
| 21 | Thoughts racing | | |
| 22 | Pressured speech | | |
| 23 | Distractibility | | |
| 24 | Excessive activity | | |
| 25 | Increased self-esteem | | |
| 26 | Reckless activity | | |
| 27 | Reduced need for sleep | | |
| 28 | Increased sociability | | |

| PSYCHOTIC SYMPTOMS | | LE | WE |
|---|---|---|---|
| 29 | 3rd person auditory hallucinations | | |
| 30 | Running commentary voices | | |
| 31 | Abusive/accusatory/persecutory voices | | |
| 32 | Other (non-affective) hallucinations | | |
| 33 | Non-affective visual hallucinations | | |
| 34 | Non-affective hallucination in other modality | | |
| 35 | Thought echo | | |
| 36 | Thought insertion | | |
| 37 | Thought broadcast | | |
| 38 | Thought withdrawal | | |
| 39 | Delusions of passivity | | |
| 40 | Delusions of influence | | |
| 41 | Primary delusional perception | | |
| 42 | Persecutory delusions | | |
| 43 | Bizarre delusions | | |
| 44 | Other primary delusions | | |
| 45 | Bizarre behaviour | | |
| 46 | Catatonia | | |
| 47 | Speech difficult to understand | | |
| 48 | Incoherent | | |
| 49 | Positive formal thought disorder | | |
| 50 | Negative formal thought disorder | | |
| 51 | Restricted affect | | |
| 52 | Blunted affect | | |
| 53 | Inappropriate affect | | |
| 54 | Perplexity | | |

| PSYCHOTIC AFFECTIVE SYMPTOMS | | LE | WE |
|---|---|---|---|
| 55 | Grandiose delusions | | |
| 56 | Delusions of guilt | | |
| 57 | Delusions of poverty | | |
| 58 | Nihilistic delusions | | |
| 59 | Mood congruent 3rd person Auditory Hallucinations | | |
| 60 | Mood congruent 2nd person Auditory Hallucinations | | |
| 61 | Mood congruent Visual Hallucinations | | |
| 62 | Mood congruent hallucinations in other modality | | |
| 63 | Other secondary delusions | | |

## Avii The Bipolar Affective Disorder Dimensional Scale, version 3.0 (BADDS 3.0)

### General information

The Bipolar Affective Disorder Dimension Scale (BADDS) has been developed in order to address some of the disadvantages of a purely categorical approach to diagnostic classification of Bipolar Spectrum Disorders.

BADDS is a dimensional rating scheme that retains and builds upon current categorical classifications. It is intended for use in clinical samples from populations over-represented by Bipolar Spectrum illness. It was not developed for use in general population samples.

BADDS has been under development since 1996 and has now been used by a variety of researchers within our group on more than 1100 cases. It has proved to be user friendly and has excellent reliability, even on sets of diagnostically challenging cases.

BADDS comprises 4 dimensions: M: Mania; D: Depression; P: Psychosis; I: Incongruence. Each dimension is rated using integer scores on a 0 – 100 scale. Ratings are made after review of all available clinical data on a subject (eg. case records, semi-structured psychiatric interview and information from an informant) and can be performed as a simple addition to the conventional consensus lifetime psychiatric diagnostic procedures already in use by many research groups. Each rating reflects a mixture of severity and frequency of clinical features. Guidelines are provided that define anchor points in the rating scales and specify how ratings should be made.

**BADDS: General rating guidelines**

1) Do not rate a dimension if there is insufficient information - just leave the dimension blank.

2) Use all available information to make the best judgement for each rating.

3) It is expected that when used for research BADDS will be used within the accepted framework of the lifetime best-estimate consensus diagnostic procedure.

4) All ratings should be made using integers in the range 0 - 100.

5) Ratings for M and D are a mixture of severity and frequency. Generally the severity of the most severe episode identifies a range in which the rating will be made and the frequency determines the score assigned within the range. In assigning a rating, start at the lowest score in the range and then add points according to any relevant psychopathology over and above that of the most severe episode according to the following guidelines:

a) In general each additional episode *of that level of severity* will add a score of 2 in a 20 point range and 1 in a 10 point range.

b) Scores in the identified severity range can and should be modified according to severity and duration of total episodes – but with a substantial down-weighting for episodes of lower severity.

c) For episodes that are one level of severity lower than the rating range, add 0.25 points for each episode of lower severity for a score in a 10 point range and 0.5 points for each episode of lower severity for a score in a 20 point range.

d) For episodes that are more than one level of severity lower than the rating range the total adjustment should not normally exceed 1 or 2 points.

6) For the P and I dimensions anchor points are given in these guidelines. Judgment is used to assign scores between anchor points.

7) Under very exceptional circumstances a score can be rated outside the severity range. However, this should always be agreed by at least two raters and the rating should lie in the interval 0 - 100. Such a rating should be indicated by an asterisk (*) following the rating for that dimension. An example of the applicability of this rule is the rating up of an episode in which the balance of evidence clearly suggests a severe illness that is not adequately supported by the documented evidence *because of poor documentation*. Another example would be the rating down of an episode if the balance of evidence strongly suggests that the formal evidence clearly over-represents the clinical significance of the episode.

**1) Mania dimension (M)**

The rating reflects severity and frequency.
Use ICD10 to define symptom and duration criteria for hypomanic and manic syndromes.
Sub-hypomanic features in the ranges 1 - 19 and 20 - 39 should be rated using judgement according to the balance of number and duration of symptoms.
No impairment criterion is used for hypomania.
The impairment criteria for mania are one or more of:

Disrupts work or social life more or less completely
Markedly inappropriate overspending that is reckless within the context of the subject's financial position
Fights
Lost job
Police involvement
Family split up
Received specific treatment (including dose increase of mood stabilizer) *for acute mania*
Psychotic features

*Incapacitating mania* refers to a severe manic episode that includes the presence of one or more of the following features: incoherence, disorientation, loss of contact with reality (which includes psychotic features), frenzied or bizarre psychomotor activity. *NB: Being admitted on a Section is an example of incapacitating mania.*
Mixed episodes are rated on the M dimension. If *all* manic episodes are mixed, add "m" to the rating (eg. 65m).

***Key points and ranges on the M dimension***

| | |
|---|---|
| 0 | No manic features. |
| 1 - 19 | Mild sub-hypomanic features. Elation/irritability and less than 3 symptoms. |
| 20 - 39 | Sub-hypomanic features. Elation/irritability and 3+ symptoms for at least 1 day. |
| 40 - 59 | Hypomanic features. At least one hypomanic episode. |
| 60 - 79 | Manic features. At least one manic episode. |
| 80 - 100 | Severe manic features. At least one episode of incapacitating mania. |

*NB: a) if * enter as .01, e.g., 65* = 65.01*
*b) if m enter as .02, e.g., 65m = 65.02*
*c) if both * and m enter as .03, e.g., 65*m = 65.03)*

**2) Depression (D)**

Rating reflects severity and duration.
Use ICD10 to define depressive syndromes. This includes 10 symptoms of depression that count for the purposes of diagnosis:

A Depressed mood
Loss of interest/pleasure
Loss of energy

B Suicidal ideation
Pathological guilt
Loss of confidence/self esteem
Loss of concentration
Slowed activity
Change of appetite or weight
Change in sleep pattern

Depression severity: Mild - 4+ symptoms (2+ from A); moderate - 6+ symptoms (2+ from A); severe - 8+ symptoms (3 from A). Refer to ICD10 for full definition of syndromes and symptoms.
Duration criterion for Major Depressive Episode is 2 + weeks. If 1- 2 weeks, classify as Minor Depression.
Rate depression as severe if (a) ICD10 criteria fulfilled, or (b) criteria for major depression are fulfilled and there has been a serious suicide attempt, ECT treatment or hospital admission for depression.
Minor depression refers to at least 1 week of low mood accompanied by 2 or more depression items or to brief episodes that would otherwise meet criteria for Major Depression.
Incapacitating depression refers to severe major depression that includes presence of one or more of the following features: stupor; mutism; loss of contact with reality (including psychotic features). *NB: Being admitted on a Section is an example of incapacitating depression.*
If psychotic features are present, a depressive episode can be rated as incapacitating if the minimum criteria for major depression are satisfied (ie. 4 items).

***Key points and ranges on D dimension***

| | |
|---|---|
| 0 | No features of depression during lifetime. . |
| 1 – 19 | Sub-Minor depression. |
| 20 - 39 | Minor depression. |
| 40 - 49 | Mild major depression. |
| 50 - 59 | Moderate major depression. |
| 60 - 79 | Severe depression. |
| 80 - 100 | Incapacitating depression |

*NB: a) if * enter as .01, e.g., 65* = 65.01*

**3) Psychotic features (P)**

Psychotic features refers to delusions, hallucinations, positive formal thought disorder, catatonia or grossly disorganized behaviour (but see exclusions below).
Ratings on this dimension exclude stupor or excitement during an affective episode or positive formal thought disorder during mania.
Lifetime occurrence of psychotic features is rated.
Near psychotic schizotypal features refers to the following DSMIV schizotypal items: ideas of reference; odd beliefs or magical thinking that influences behaviour and is inconsistent with sub-cultural norms; unusual perceptual experiences including bodily illusions; odd thinking and speech; suspiciousness or paranoid ideation; behaviour or appearance that is odd eccentric or peculiar. Depersonalization and derealization are not classified as near psychotic features.
The period of illness considered refers to all affective and non-affective periods of psychopathology. Rating should take account of both number and duration of episodes with and without psychotic features. If in doubt, "rate up" the psychotic features. Examples:

If there have been two 1 week long affective psychotic episodes and a 1 year non-psychotic depressive episode, rate 60 (ie. approx. 2/3 of illness *episodes*).

If there have been nine 1 month non-psychotic affective episodes, one 1 month psychotic affective episode and 4 years of chronic hallucinations outside affective episodes, rate 80 (ie. approx. 80% of illness *duration*).
The Uncertain category (P = 1) is used for situations in which insufficient information is available to determine if sign or symptom meets criteria for near psychotic feature.

***Key points and ranges on P dimension***

| | |
|---|---|
| 0 | Absent. |
| 1 | Uncertain. |
| 2 - 9 | Near psychotic features: occasional at low end of range, frequent at high end of range. Occurrence of true psychotic symptoms should not be rated in this range. |
| 10 - 20 | Brief clear-cut psychotic symptom that are not a prominent feature of illness.<br>10 – Single.<br>20 – Multiple. |
| 21 – 100 | Psychotic symptoms that are a prominent feature in one of more episodes of illness.<br>25 - present for 25% of illness.<br>50 - present for 50% of illness.<br>75 - present for 75% of illness.<br>100 - prominent psychotic features present throughout illness. |

**4) Mood incongruence (I)**

- DSMIV definitions of congruence and incongruence are used.
- Rate incongruence of lifetime occurrence of psychotic features.
- For convenience, the set of psychotic symptoms recognized as having special weight in the diagnosis of schizophrenia and schizoaffective disorder (thought echo, insertion, withdrawal or broadcasting; passivity experiences; hallucinatory voices giving running commentary, discussing subject in third person or originating in some part of the body; bizarre delusions; catatonia) are denoted in the guidelines as the "S set".
- If Psychosis Features dimension, P < 10, leave I blank.

**Key points on I dimension**

| | |
|---|---|
| 0 -40 | Psychotic symptoms occur only during affective episodes and do not include any of the S set.<br>Rating 0 – virtually completely mood congruent.<br>Rating 20 – approximate balance between mood congruent and incongruent.<br>Rating 40- virtually completely mood incongruent |
| 43 | Psychotic symptoms occur only during affective episodes and include one or more of the S set which have not definitely been present for 2 weeks. |
| 47 | Psychotic symptoms occur only during affective episodes and include one or more of the S set which have definitely been present for 2 weeks. |
| 50 - 59 | Psychotic symptoms probably present for at least 2 weeks either side of an affective episode.<br>Rating 50 – on at least one occasion.<br>Ratings of 51-59 used to reflect recurrence and/or certainty. |
| 60 - 100 | Psychotic symptoms definitely present for at least 2 weeks either side of an affective episode.<br>Rating 60 – on at least one occasion.<br>Rating 80- on many occasions.<br>Rating 100 – Psychotic symptoms predominate illness and occur chronically outside (or in absence of) affective episodes. |

## Aviii The Global Assessment Scale (GAS)

**GAS:**

Rate the subject's level of functioning in the worst episode of depression by selecting the lowest range that describes his functioning on a hypothetical continuum of mental health illness. For example, a subject whose "behaviour is considerably influenced by delusions" (range 21-30) should be given a rating in that range even though he has "major impairment in several areas" (range 31-40). Use intermediary levels when appropriate (eg. 35, 58, 63). Rate actual functioning independent of whether or not subject is receiving, and may be helped by, medication or some other form of treatment.

| | |
|---|---|
| 100 – 91 | No symptoms, superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his warmth and integrity. |
| 90 – 81 | Transient symptoms may occur, but good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, "everyday" worries that only occasionally get out of hand. |
| 80 – 71 | Minimal symptoms may be present but no more that slight impairment in functioning, varying degrees of "everyday" worries and problems that sometimes get out of hand. |
| 70 – 61 | Some mild symptoms (eg. depressive mood and mild insomnia) OR some difficulty in several areas of functioning, but generally functioning pretty well, has some meaningful interpersonal relationships and most untrained people would not consider him "sick". |
| 60 – 51 | Moderate symptoms OR generally functioning with some difficulty (eg few friends and flat affect, depressed mood and pathological self-doubt; euphoric mood and pressure of speech, moderately severe antisocial behaviour). |
| 50 – 41 | Any serious symptomatology or impairment in functioning that most clinicians would think obviously requires treatment or attention (eg. suicidal preoccupation or gesture, severe obsessional rituals, frequent anxiety attacks, serious antisocial behaviour, compulsive drinking). |
| 40 – 31 | Major impairment in several areas, such as work, family relations, judgement, thinking or mood (eg. depressed woman avoids friends, neglects family, unable to do housework), OR some impairment in reality testing or communication (eg. speech is at times obscure, illogical or irrelevant), OR single serious suicide attempt. |
| 30 – 21 | Unable to function in almost all areas (eg. stays in bed all day), OR behaviour is considerably influenced by either delusions or hallucinations, OR serious impairment in communication (eg. sometimes incoherent or unresponsive) or judgement (eg. acts grossly inappropriately). |

20 – 11 Needs some supervision to prevent hurting self or others, or to maintain minimal personal hygiene (eg. repeated suicide attempts, frequently violent, manic excitement, smears faeces), OR gross impairment in communication (eg. largely incoherent or mute).

10 – 1 Needs constant supervision for several days to prevent hurting self or others, or makes no attempt to maintain minimal personal hygiene.

## Aix Problem Behaviours Assessment for Huntington's disease (PBA-HD)

**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**

**SHORT BEHAVIOURAL ASSESSMENT FORM**

This assessment is a modified version of the Problem Behaviours Assessment Scale for Huntington's disease (PBA-HD) (Craufurd et al., 2001), which will measure whether the neuropsychiatric symptoms of irritability, aggression, apathy and perseverative thinking have ever been experienced by the patient. If the symptom has been present, record the date at onset of first symptoms and then rate the frequency and severity of that behavior during the worst episode using the general guidelines below.

**General rating guidelines:**

| Severity | Frequency |
|---|---|
| 0 = absent | 0 = never/almost never |
| 1 = slight, questionable | 1 = seldom (less than once/week) |
| 2 = mild (present, not a problem) | 2 = sometimes (up to 4 times a week) |
| 3 = moderate (symptom causing problem) | 3 = frequently (most days/5,6 or 7 times a week) |
| 4 = severe (almost intolerable for carer) | 4 = daily/almost daily for most (or all) of day |

Rate 9 if not known or not applicable

**IRRITABILITY:** **Severity** **Frequency**

If present, date of

(This item is used to rate the ease at which the subject loses his/her temper, rather than the degree to which the self-control is lost once the subject is angry (the latter is rated in the next item). It should also be used to record irritable moods, which might have developed into an angry outburst if the carer had not acted with increased tact or discretion).

*Suggested prompts:*

- Have you ever found yourself feeling irritable, bad-tempered, moody or 'cranky'?
- Do you think you get cross more easily than you used to?
- (if yes to above) How does this affect people around you? Do you think they treat you differently when you are like that?

0 no more irritable than the average person
1 questionable or trivial; within normal limits but worse than he/she used to be
2 definitely more irritable than is reasonable but not to an extent which causes significant problems or distress for other household members; rate 2 if subject appeared to be in a bad mood, but rater considered that subject might have become angry if not treated with tact.
**3** Subject very irritable and loses temper over trivial matters; household members have to be careful what they say and do to avoid problems; rate 3 if subject's appearance and behaviour are suggestive of angry mood, such that outbursts would almost certainly have occurred if care had not been taken to placate subject or keep out of his/her way.
4 Subject very irritable and looses temper without any obvious reason at all; living with him/her is like walking on eggshells.

**ANGRY OR AGGRESSIVE BEHAVIOUR:** **Severity** **Frequency**

If present, date at ☐ ☐

*Suggested prompts:*

- Have you found yourself having any emotional or angry outbursts?
- Have you had times when you have lost control of your temper?
- Have you hit, shoved or thrown things or expressed your temper in a physical way?
- Have you used threats or hostile words?

0 normal

1 questionable

2 verbal outbursts which are outside socially acceptable limits but do not cause significant problems or distress for other household members; for example, rate 2 if subject becomes angry with self or inanimate objects when confronted with frustrating situations due to disability, such as failure when attempting to rewire a plug.

3 Temper tantrums are severe enough to cause distress for other household members and/or practical difficulties caring for subject; rate 3 when verbal hostility or anger is directed towards another person (e.g. shouting, sarcastic name-calling, use of foul or abusive language). Also, rate 3 if there are explicit verbal threats of violence to another person, or behaviour causing a justifiable fear of personal violence (e.g. subject approaches too close, raises fist, mild pushing). Also, rate 3 for violence towards property.

4 Subject has temper tantrums so severe that relationship with carers is compromised, creating risk that subject will be rejected; rate 4 if there has been any kind of actual physical assault (includes pushing, shoving, hitting, biting, scratching, kicking) or threatening behaviour involving weapons.

**LACK OF INITIATIVE (APATHY):** **Severity** **Frequency**

If present, date at

*Suggested prompts:*

- Have you found that you have lost interest in things that used to be important to you? Are you just as interested as always in trying new things, starting new projects?
- Do you have to be pushed to get started on chores that need doing? Do you leave it to friends to take the initiative for organising social activities? Do you sit around a lot doing nothing?

0 symptom absent
1 questionable
2 subject no longer tries new things; may need gentle prompting to initiate hobbies or pastimes which he/she usually enjoys; make less effort to keep up with friends and relatives; tends to put off household tasks which were previously part of normal daily routine and may need gentle prompting to do these things.
3 Needs quite overt prompting to take part in hobbies or pastimes which he/she used to enjoy, or to carry out routine daily household tasks; makes little or no effort to keep in touch with friends and leaves it to other to initiate any social contacts; able to take part in (and apparently enjoy) conversation, but tends to follow and is less likely to initiate a change of subject.
4 No longer performs any household chores, even if prompted repeatedly; never initiates activities, and displays no interest in hobbies or pastimes; markedly impoverished speech, rarely initiates new topics of conversation except in relation to own needs; active choices limited to selecting TV programmes to watch, and perhaps switching on or changing channel to do this.
8 unable to assess because condition too advanced (e.g. mute and immobile)

(This item will usually be rated 9 (data missing) in the absence of a reliable informant)

**PERSEVERATIVE THINKING OR BEHAVIOUR:** **Severity** **Frequency**

If present, date at ☐ ☐ ☐

*Suggested prompts:*

- Have you found yourself getting stuck on certain ideas or actions?
- Have your family or friends complained that you are getting obsessed about something or going on about it more than you should, or doing something over and over again?

0 symptom absent
1 questionable
2 mild perseverative behaviours or abnormal preoccupations are present but do not interfere with everyday life or cause significant distress for subjects or carers; rate 2 if carer reports that subject tends to come out with comments, which refer to an earlier topic of conversation, or when rater observes perseverative phenomena during examination (e.g. continues tandem walking after test is completed).
3 Abnormal preoccupations or repetitive behaviours occupy a significant proportion of subject's attention and cause distress for subject or practical problems for carers; for example, rate 3 if carers report that subject will not let matter drop after an argument, and keeps returning to the same contentious issue all day, or has repetitive behaviours (see below) which cause some interference with everyday care.
4 Abnormal preocuupations occupy most of subject's attention for several days at a time, causing major problems or distress for subjects and carers, or subject cannot be diverted from repetitive behaviours (pacing, smoking, repeatedly visiting the toilet), which interfere significantly with everyday care.
8 unable to assess because condition too advanced (e.g. mute and immobile)

(This item will usually be rated 9 (data missing) in the absence of a reliable informant)

# *B Appendices for Chapter 6*

## Bi Participant information sheet, reply slip, consent form, GP letter

**PARTICIPANT INFORMATION SHEET**

**VALIDITY OF DEPRESSION RATING SCALES IN HUNTINGTON'S DISEASE**
**VERSION 2: Friday 7th July 2006**

**Patient Information Sheet**

**Validity of Depression Rating Scales in Huntington's Disease**

- **Invitation to take part in a research study**

You are invited to take part in a research study investigating the validity of self-report rating scales in measuring depression severity in persons with Huntington's Disease. To help you decide whether or not you wish to take part in this study, please read the following information carefully, which explains why this study is being carried out and what participation entails. Please take your time to decide and if you wish, discuss the study with your family, friends or General Practitioner.

- **Purpose of the study**

The purpose of this study is to assess the validity of three simple self-report measures of depression severity in a sample of individuals with Huntington's Disease. An accurate diagnosis of depression can be especially difficult to make in the setting of Huntington's Disease because many symptoms of depression such as fatigue, loss of appetite, weight loss and sleep disturbance may also be seen in non-depressed Huntington's Disease patients. Therefore, this study aims to determine the most sensitive self-rating scale that will provide a quick, cost-effective means for clinicians to more accurately diagnose and therefore treat depression and to monitor any changes in depression severity.

- **Why have I been chosen?**

Participants in this study will all have a clinical diagnosis of Huntington's Disease, which has been confirmed by a genetic test. It is not necessary for you to have depression in order to participate in this study. Fifty to eighty participants are needed to take part in this study so that we can reliably determine which rating scale is most accurate in diagnosing depression severity. You have been invited to take part in this study because you have Huntington's Disease and you are registered with the HD service based at the Queen Elizabeth Psychiatric Hospital.

- **Do I have to take part?**

No. Your participation in this research project is voluntary. Before deciding whether or not to take part you should read this leaflet very carefully and ask if there is anything you do not understand or if you want further information. If you do decide to take part, you will be asked to sign a consent form indicating that you understand what the study involves. You will then be given a copy of this information sheet and a signed consent form to keep. **You are also free to withdraw from the study at any time and without giving reason. This potential withdrawal does not affect your current clinical care and treatment.** If you decide not to take part, again you do not have to give any reason for your decision and it will not affect your continuing clinical treatment.

- **What does participation involve?**

Participation in the study entails a single clinical assessment, which depending on your preference will either take place at your home at a time convenient to you or in the out-patient clinic at the QEPH, Birmingham. The assessment will first involve measuring your movements, thinking, and functional capabilities similar to the consultations which you already undergo in the Huntington's disease clinic. This will be followed by an assessment of your mood including a semi-structured interview and three simple self-report depression rating scales. The total assessment will take approximately an hour and a half to complete.

- **Are there any risks attached to this study?**

There are no specific risks arising from your participation in this study given that it is an observational study.

- **What are the possible benefits of taking part?**

There may be no direct benefits from taking part in the study. However, it is hoped that results from this study will have important implications for the management of Huntington's Disease through improvements in diagnosing severity of depression.

- **What will happen to the results of this study?**

At the end of the study, the results will be analysed and a report will be written for a medical journal. You will also be sent information regarding the outcome of the study. The anonymised data will be stored for five years after the end of the study in a locked cabinet.

- **Confidentiality**

All information collected from you will be kept strictly confidential and stored in locked filing cabinets with access restricted to the investigators involved in the study. The information will also be entered onto a secure computer database for analysis, but you will not be identified when the results are reported.

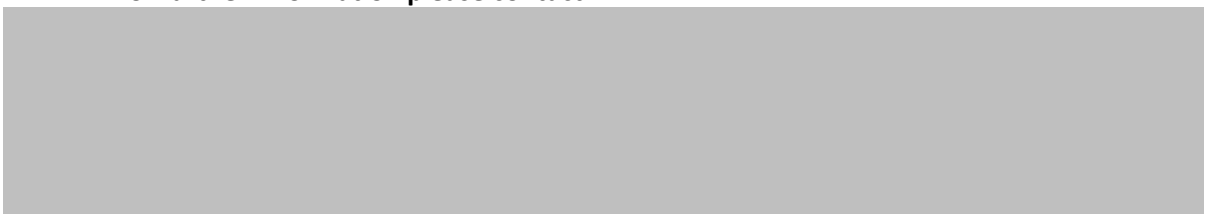
- **Will my General Practitioner (GP) know that I am involved in this study?**

Should you agree to take part in this study, it is important that your GP is kept informed of your participation and he/she will also be sent a copy of this information sheet.

- **Who is organising and funding the research?**

The study is being organised by Dr. Hugh Rickards MD MRCPsych and Jenny Keylock BSc MSc in the department of neuropsychiatry at the Queen Elizabeth Psychiatric Hospital, Birmingham. The research project is being sponsored by the Birmingham and Solihull Mental Health Trust.

- **For further information please contact**



- **What if I have any concerns?**

If you have any concerns or questions about this study or the way it has been conducted, you should contact the supervisor Dr. Rickards, or you may contact the Queen Elizabeth Psychiatric Hospital or Birmingham and Solihull Mental Health Trust complaints department.

**REPLY SLIP**

**VALIDITY OF DEPRESSION RATING SCALES IN HUNTINGTON'S DISEASE**
**VERSION 2: FRIDAY 7TH JULY 2006**

**Please would you kindly indicate which of the statements below refers to you and return your response in the pre-paid envelope provided to Jenny Keylock. If you have misplaced the envelope, the address is also printed at the top of the Patient Information sheet.**

**Name:_____**

**Telephone number:_____**

**Address:_____**

**_____**

**_____**

**Post code:_____**

I have read and understood the patient information sheet dated Friday, July 7th 2006, version 2 and:

1. I am interested in taking part ☐
2. I require more information about the study before deciding ☐
3. I am not interested in taking part ☐

In the case of (1) and (2) only, you will be contacted within 3 weeks in order to clarify any queries you may have and to arrange an appointment.

**Many thanks for taking the time to read this information and for completing the reply slip.**

**PATIENT CONSENT SHEET**

**VALIDITY OF DEPRESSION RATING SCALES IN HUNTINGTON'S DISEASE**
**VERSION 2: FRIDAY 7TH JULY 2006**


Chief Investigator

Dr. Hugh Rickards MB ChB MD MRCPsych M Med Sci

Research Assistant

Jenny Keylock BSc MSc


Please initial boxes

1. I have read and understood the patient information sheet 'Validity of Depression Rating Scales in Huntington's Disease, version 2 07/07/2006'. I have had the opportunity to ask questions and have had sufficient time to decide whether to participate in the study. ☐

2. I understand that participation is voluntary and that I am free to withdraw from the study at any time without giving reason and without affecting my continuing medical treatment. ☐

3. I agree to the publication of any findings that arise from this study so long as my anonymity is preserved. ☐

4. I understand that my GP will be informed that I am taking part in this study. ☐

Patient's signature_____

Patient's name_____ Date_____

Researcher's signature_____

Researcher's name_____ Date_____

**GP LETTER**

**VALIDITY OF DEPRESSION RATING SCALES IN HUNTINGTON'S DISEASE**

**VERSION 1: MONDAY 15TH MAY 2006**

Date

Dear Dr.

Re: **Patient name and Date of Birth**

**Patient address**

Your patient . . . . . .has agreed to participate in a study to validate self-report severity measures of depression in Huntington's disease patients. This study, based at the Queen Elizabeth Psychiatric Hospital, Birmingham involves a single clinical assessment and is observational only. A copy of the information sheet has been enclosed.

The supervisor for the trial is Dr. Hugh Rickards, Consultant Neuropsychiatrist at the address above and the trial has been approved by the local Research Ethics Committee. If you require any further information about the study, please contact Jenny Keylock, trial administrator on the number at the foot of the patient information sheet.

Yours sincerely,

Jenny Keylock

Research Psychologist

Enc. Patient information sheet

## Bii Demographic Information

**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**

**DEMOGRAPHIC INFORMATION**

**Date of Birth:** ☐☐ ☐☐ ☐☐☐☐

**Gender:** ☐

**1=male**

**2=female**

**Ethnicity:_____**

**Years of education:_____**

**Age at symptom onset:_____**

## Biii Beck Depression Inventory-II

**Participant's initials:_____**

**Participant's no.:_____ Date data obtained:_____**

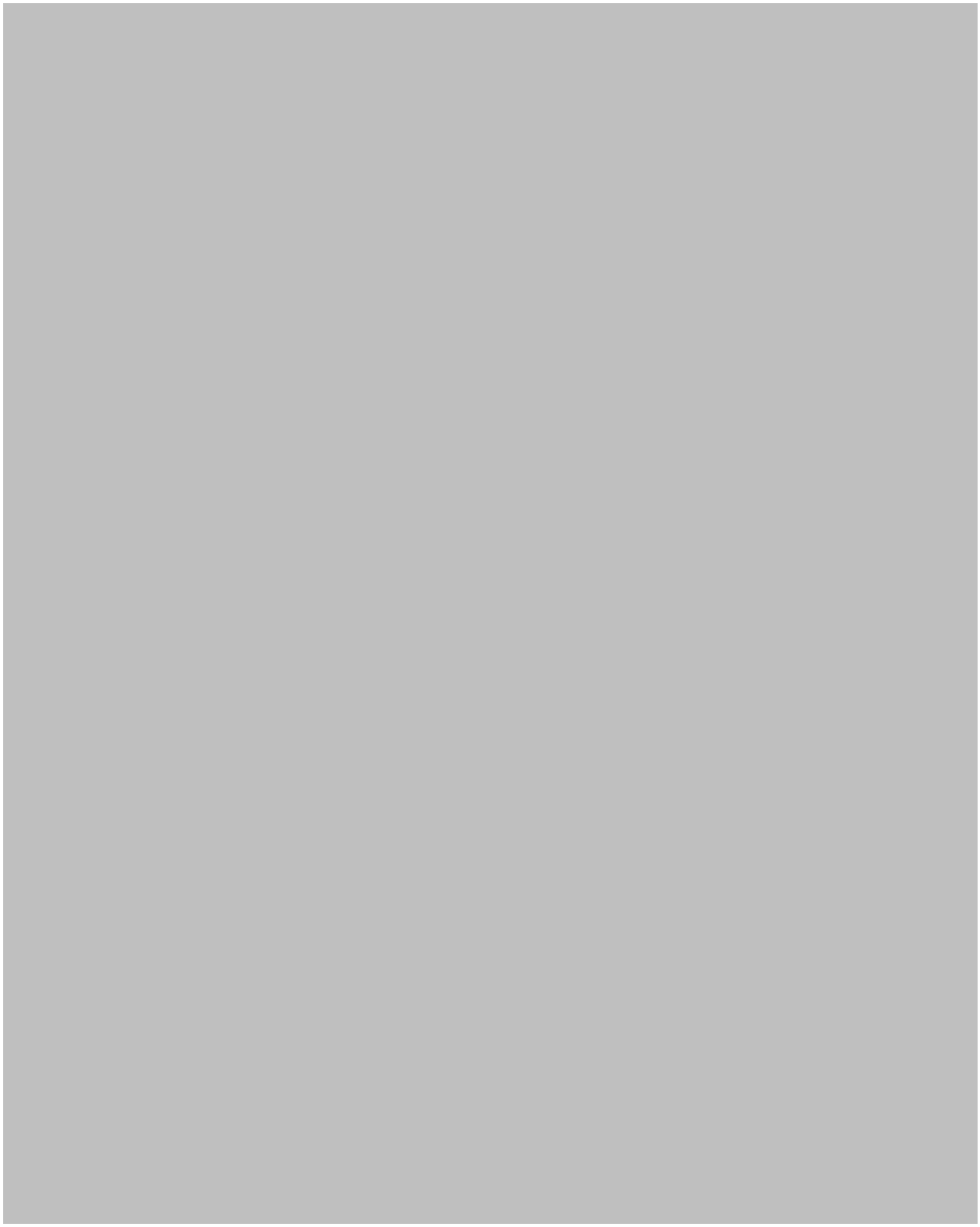
**BECK DEPRESSION INVENTORY-II**

**This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including item 16 (Changes in Sleep Pattern) or Item 18 (Changes in Appetite).**

**Total score:** | | |

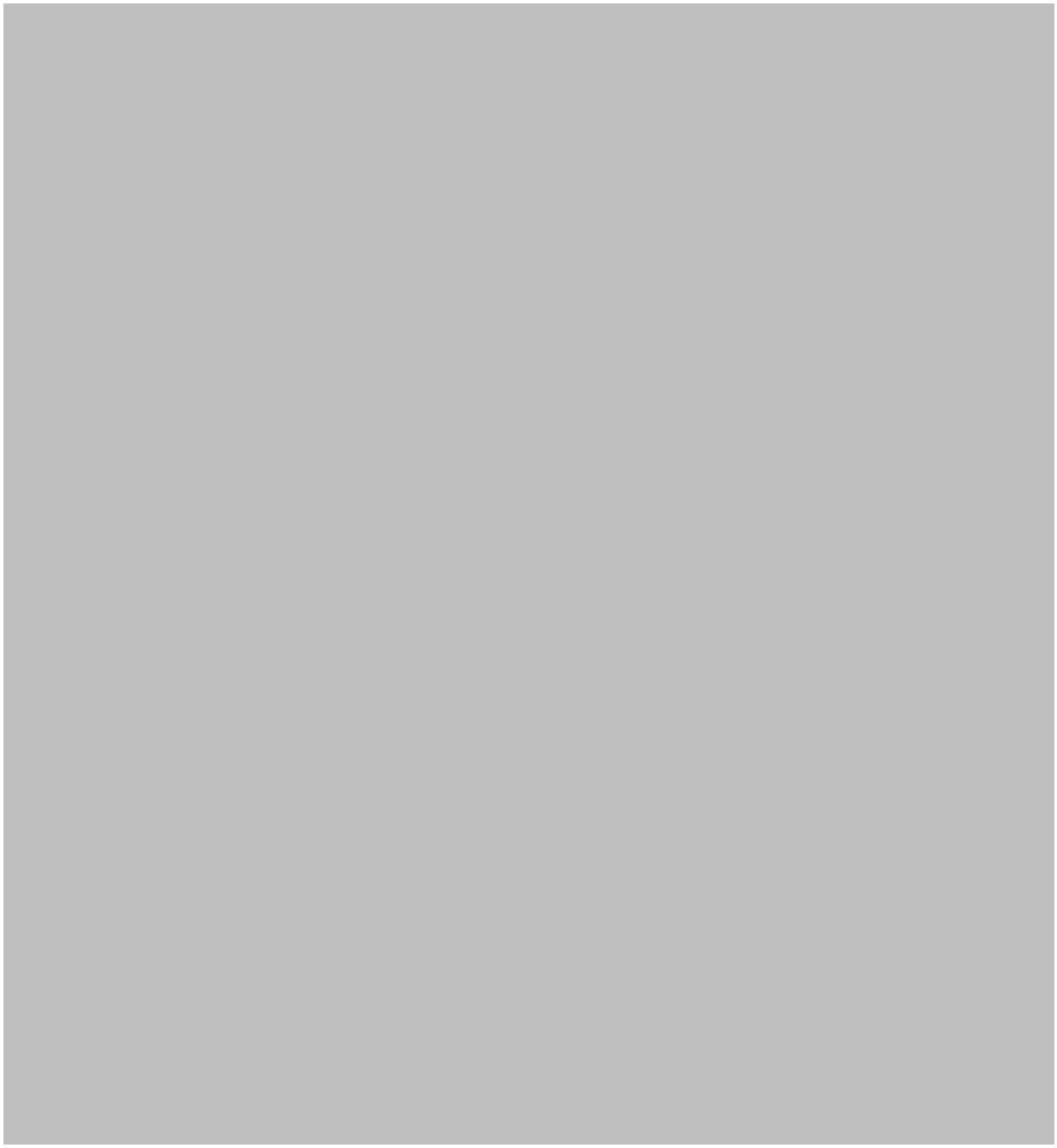
**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**



**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**



**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**

**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**

## Biv The Hospital Anxiety and Depression Scale (HADS)

**Participant's initials:_____**

**Participant's no.:_____ Date data obtained:_____**

**HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)**

**Please read each item carefully and tick the box next to the response, which best represents how you have been feeling in the past week. Please select only one answer for each group and try not to take too long over your replies.**

| | | |
|---|---|---|
| **1.** | **I feel tense or wound up:** | |
| | Most of the time | |
| | A lot of the time | |
| | From time to time, occasionally | |
| | Not at all | |

| | | |
|---|---|---|
| **2.** | **I still enjoy the things I used to enjoy:** | |
| | Definitely as much | |
| | Not quite so much | |
| | Only a little | |
| | Hardly at all | |

| | | |
|---|---|---|
| **3.** | **I get a sort of frightened feeling as if something awful is about to happen:** | |
| | Very definitely and quite badly | |
| | Yes, but not too badly | |
| | A little, but it doesn't worry me | |
| | Not at all | |

| | | |
|---|---|---|
| **4.** | **I can laugh and see the funny side of things:** | |
| | As much as I always could | |
| | Not quite so much now | |
| | Definitely not so much now | |
| | Not at all | |

| | | |
|---|---|---|
| **5.** | **Worrying thoughts go through my mind:** | |
| | A great deal of the time | |
| | A lot of the time | |
| | From time to time, but not too often | |
| | Only occasionally | |

**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**

| **6.** | **I feel cheerful:** | |
|---|---|---|
| | Not at all | |
| | Not often | |
| | Sometimes | |
| | Most of the time | |

| **7.** | **I can sit at ease and feel relaxed:** | |
|---|---|---|
| | Definitely | |
| | Usually | |
| | Not often | |
| | Not at all | |

| **8.** | **I feel as if I am slowed down:** | |
|---|---|---|
| | Nearly all the time | |
| | Very often | |
| | Sometimes | |
| | Not at all | |

| **9.** | **I get a sort of frightened feeling like 'butterflies' in the stomach:** | |
|---|---|---|
| | Not at all | |
| | Occasionally | |
| | Quite often | |
| | Very often | |

| **10.** | **I have lost interest in my appearance:** | |
|---|---|---|
| | Definitely | |
| | I don't take as much care as I should | |
| | I may not take quite as much care | |
| | I take just as much care as ever | |

| **11.** | **I feel restless as if I have to be on the move:** | |
|---|---|---|
| | Very much indeed | |
| | Quite a lot | |
| | Not very much | |
| | Not at all | |

**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**

| **12.** | **I look forward with enjoyment to things:** | |
|---|---|---|
| | As much as I ever did | |
| | Rather less than I used to | |
| | Definitely less than I used to | |
| | Hardly at all | |

| **13.** | **I get sudden feelings of panic:** | |
|---|---|---|
| | Very often indeed | |
| | Quite often | |
| | Not very often | |
| | Not at all | |

| **14.** | **I can enjoy a good book or radio or TV program** | |
|---|---|---|
| | Often | |
| | Sometimes | |
| | Not often | |
| | Very seldom | |

**Bv The Depression Intensity Scale Cirlces (DISCs)**

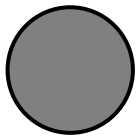
**Participant's initials:_____**

**Participant's no.:_____** **Date data obtained:_____**

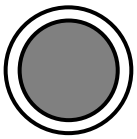
**DEPRESSION INTENSITY SCALE CIRCLES (DISCs)**

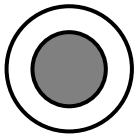
This is a scale for measuring sadness or depression. The grey circles show how sad or depressed you feel. The bottom circle shows no sadness or depression. The top circle shows sadness or depression as bad as it can be. As you go from the bottom to the top circle you can see that sadness or depression is becoming more and more severe. Which of these circles shows best how sad or depressed you feel today?

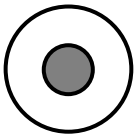
**Participant's score:** ☐

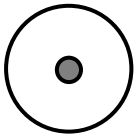


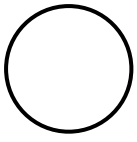
**Most severe depression**











**No Depression**

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