Objective Assessment Of The Neuropsychiatric Symptoms In Huntington's Disease

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. . . . . to Orlaith and Conor

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Abbreviations

AES Apathy evaluation scale – Clinician

BDNF Brain derived neurotrophic factor

BIS-11 Barrett impulsivity scale

BISBAS Behavioural inhibition scale behavioural activation scale

CT Computed tomography

EDSST Extra-dimensional set shift task

fMRI Functional magnetic resonance imaging

HD Huntington's disease

HTT Huntingtin protein

HTT The gene responsible for Huntington's disease

IGT Iowa gambling task

MSN Medium spiny neuron

PBA Problem behaviours assessment

PBAs Problem behaviours assessment (short form)

PET Positron emission tomography

PSLT Probabilistic selection learning task

PVF Phonemic verbal fluency

SCOPI Schedule of compulsions, obsessions, and pathological impulses

SDMT Symbol digit modalities task

TMS Total motor score from the UHDRS

UHDRS Unified Huntington's disease rating scale

UPPS P Urgency, pre-meditation, perseverance, sensation-seeking scale

VAS Visual analogue scale

VBM Voxel based morphometry

Abstract

Huntington's disease (HD) is a progressive neurodegenerative disorder, caused by a repeat expansion in the HTT gene, carried on chromosome 4. HD causes motor symptoms (chorea, dystonia and an eye movement disorder), cognitive decline (impairments in social cognition, memory and executive function) and neuropsychiatric disorders. The commonest neuropsychiatric problems are apathy, depression and irritable behaviour, whilst disinhibited behaviour and perseveration are also frequently reported later in the disease course. The neuropsychiatric symptoms are common in HD and have significant, deleterious effects on quality of life and function, yet the underlying cognitive processes and neurobiology remain unclear. This study addresses the gap in knowledge: we have used a battery of established and novel tasks to delineate the specific cognitive processes leading to neuropsychiatric disorders in HD.

53 patients, with a confirmed genetic test for HD were recruited from the South Wales HD service, and 26 controls were recruited from both gene negative family members and local advertising. Subjects completed gold standard measures of neuropsychiatric symptoms in HD: Problem Behaviours Assessment- short form (PBA), Apathy Evaluation Scale (AES), Behavioural Inhibition Scale Behavioural Activation Scale (BISBAS), Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behaviour Scale (UPPSP), Barratt Impulsiveness Scale (BIS), Mini International Neuropsychiatric Interview (MINI); in addition to a battery of novel and established tasks measuring depressive cognition, planning, learning, reward value, reward-effort calculation, option generation, susceptibility to provocation, reactive aggression, delay discounting and response inhibition. We compared performance between groups and then used regression models, generalised linear models and generalised linear mixed models to study the cognitive processes underlying the neuropsychiatric symptoms in HD.

We found that apathy in HD is predicted by a selective deficit in learning from aversive stimuli, in addition to impairments in executive dysfunction and option generation, whilst reward value and reward-effort calculations do not make major contributions to apathy in HD. Impulsivity in HD is associated with impairment on tasks measuring inhibition of pre-potent responses and cognitive impulsivity, with relative preservation of delay discounting and risk-taking. HD participants also had higher scores on some questionnaire measures of impulsive behaviour: the UPPS P Negative Urgency scale, Barratt Impulsiveness scale and the inhibitory subscale of the BISBAS. Irritability in HD is related to enhanced negative anticipatory emotional reactivity, but

not with measures of impulsive behaviour or reactive aggression. The data on mood disorders suggests that suicidal ideation is associated with executive dysfunction and over-estimate of performance. Reward and effort measures did not significantly contribute to mood symptoms in HD.

This study has demonstrated an entirely novel cognitive mechanism leading to apathetic behaviour, and the finding of relatively preserved reward and effort in apathy and mood disorders is also novel. We have replicated previous findings of an executive function deficit leading to apathy. The data on impulsivity with regard to response inhibition and delay discounting is consistent with the known pattern of striatal degeneration in HD. Irritability in HD is not related to impulsive or reactive aggression, but to measures of negative mood induction. The data do not support anhedonia or negative cognitive bias as contributory mechanisms to mood disorders in HD, but executive dysfunction and over-estimate of performance are related to suicidal behaviour. This work demonstrates that the cognitive processes leading to neuropsychiatric symptoms in HD are consistent with the known degeneration in cortico-striatal circuits. The selective preferential degeneration in the indirect compared with the direct pathway is consistent with impaired learning from punishment, but not reward which we found in association with apathy in HD, whilst the dorso-ventral progression of striatal degeneration is consistent with the finding of preserved delay discounting, but impaired pre-potent response inhibition.

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Chapter 1

Introduction

1.1 Introductory Remarks

Chapter 1 describes the molecular biology and neurobiology of Huntington's disease in humans, the clinical features of Huntington's disease and finally the antecedents of neuropsychiatric symptoms in other disorders. Chapter 2 describes the materials and methods used in the completion of this work. Chapters 3-6 describe the experimental work, comparing task performance between a cohort of cases carrying the repeat expansion for Huntington's disease, and healthy controls on assessments designed to probe the hypothesised cognitive processes underpinning apathy, impulsive behaviour, irritability and depressed mood in Huntington's disease. Chapter 7 gives an overview of what we have found, and describes this in the context of the wider literature.

Huntington's disease was first described in detail by George Huntington in 1872. His report documents the motor features of the disease, but also comments on the psychiatric symptoms, such as disinhibited behaviour, and the inherited nature of the condition. Despite this, the illness was referred to as 'Huntington's chorea' for most of the 20th century, reflecting the comparative lack of interest in the clinical and scientific community regarding the behavioural changes associated with the disease. This thesis focusses on these behavioural changes, as the cognitive processes and neurobiology underlying the neuropsychiatric symptoms in Huntington's disease remain relatively obscure.

1.2 Introductory Review

This introductory review aims to give an overview of Huntington's disease: describing the epidemiology of the condition; the nature of the underlying genetic changes; the molecular biology of the gene product, including how it functions in health and the changes known in the diseased state; the neurological structures and systems affected in Huntington's disease, with a particular emphasis on cortico-striatal circuitry and the limbic system; the clinical symptoms experienced by sufferers of Huntington's disease; and finally an overview of the cognitive processes and neurobiology associated with neuropsychiatric symptoms in other neurodegenerative and psychiatric disorders.

1.3 Epidemiology of Huntington's disease

HD is a rare genetic disorder, predominantly affecting the central nervous system. Estimates of prevalence and incidence have been hampered in the past by several factors: prior to the discovery of the gene, it was difficult to know if the choreiform movement disorder experienced by patients represented HD or a phenocopy, it is now thought that a number of cases diagnosed as 'senile chorea' were in fact late onset HD(1, 2) moreover the stigma associated with carrying an inherited condition, may preclude many from coming forward for genetic testing. Despite this, a number of attempts have attempted to capture the prevalence and incidence of Huntington's disease from the 1930's onwards(3). Two recent systematic reviews(3, 4) give a comprehensive account of the incidence(4) and prevalence(3) of the disease. Given the nature of HD as a genetic disorder, small sample sizes are even more likely to be misleading owing to the possibility of a cluster of cases from a common founder: in both systematic reviews the smallest population included is >75000 strong. There are two major features arising from the epidemiological work. First there is marked geographical variability in the prevalence: studies in predominantly caucasian populations in Western Europe, Oceania and North America (the North American studies have a high degree of heterogeneity) report rates of between 0.35 and 17.27 cases per 100 000, with mean prevalence of 7.33 in North America, 3.60/100 000 in Western Europe, 6,68/100 000 in UK and 5.63/100 000 in Oceania; whilst in Asia, the mean prevalence is 0.40. Secondly, regardless of the geographical region, the prevalence appears to be rising with time. This may reflect the improved availability of genetic testing, better clinical care, or an increased willingness of sufferers to come forward for testing. The incidence review, included 8 papers in the meta analysis. In keeping with the prevalence studies, the incidence is markedly higher in Europe, North America and

Canada (rates 0.11-0.76 new diagnoses per 100 000 per year), compared with 0.046-0.16/100 000 new diagnoses per year in Asia. The lower incidence and prevalence in Asia may reflect fewer founders (although there is a de novo mutation rate in the HD gene(5)), or protective genetic loci which remain, as yet, unknown.

1.4 Molecular Biology

1.4.1 Genetic Description

HD has been recognised as an inherited disorder, since George Huntington's initial description. However, it was only in 1983, that linkage analysis allowed identification of likely gene carriers(6). The polymorphism was localised to chromosome 4(6). The identity of the responsible gene was settled in 1993 by the Huntington's disease collaborative research group. Using samples from a Venezuelan kindred, they localised the gene to chromosome 4p16.3. The HD gene (*HTT*) is 180kb long and has 67 exons, a CAG repeat expansion in exon 1 is responsible for the disease process. It was noted in this work that larger repeat lengths led to earlier onset disease. Further studies in cases with repeat lengths between 30 and 40 clarified that repeats between 36 and 39 were associated with reduced prevalence, whilst repeat lengths of 40 or more inevitably led to disease onset within the normal lifespan(7–9). Extending this observation, very high repeat lengths were associated with earlier onset(10, 11). Juvenile onset HD (symptoms before the age of 21) is associated with repeat lengths of over 50(12, 13). The repeat expansion is unstable(12): leading to two important observations: firstly, the repeat length is dependent on the tissue of origin, with longer repeat lengths found in neural tissue, particularly from the striatum, these hyper-expanded *HTT* repeat lengths are predictive of cell-type vulnerability(14, 15); and secondly, that HD displays anticipation(5, 16). The increases in repeat expansion length occurs at meiosis in the father, hence patients who inherit mutant *HTT* from the male line, often have an earlier age of onset(10, 17, 18).

1.4.2 Function of Huntingtin in Health

HTT codes for a 350 kDa protein (HTT). HTT is expressed throughout the human body, but the levels are highest in brain and testes(19–21). The repeat expansion codes for a polyglutamine repeat at the n-terminal end of *HTT*(22). This may mediate membrane association(23). HTT is involved in many cellular processes. Early evidence demonstrated that HTT is necessary for embryogenesis, as homozygotic gene knockout is embryonically lethal(24, 25). There is some disagreement about the effects of reduction of function, as some groups have reported

that heterozygotic inactivation of *HTT* did not result in any ill effects in a murine model(24, 26), but other workers have found subtle cognitive and behavioural changes, in addition to damage to the subthalamic nucleus(27). HTT in healthy subjects has a role in vesicle movement, particularly in axonal transport(28, 29). It is involved in mitochondrial transport(30) and prevents apoptosis(31). HTT also plays a critical role in gene regulation: a number of groups have demonstrated knock-down or alteration of gene expression by mutant HTT(32, 33). HTT binds to transcriptional regulators, and is associated with BDNF reduction following a reduction in transcription(34).

1.4.3 Disease Mechanisms of Mutant Huntingtin

The mechanism or mechanisms by which the repeat expansion leads to disease are not entirely elucidated, and are an ongoing subject of considerable complexity beyond the scope of this review. The earliest work attempted to clarify whether the damage associated with mutant HTT relates to loss of function, gain of toxic function or a combination of the two: the paper by O'Kusky et al, describing behavioural deficits and basal ganglia damage associated with heterozygotic knock-down in a murine model is suggestive of some effects related to loss of function(27). Intracellular aggregates of HTT and intracellular inclusions are well described(35–37) in HD, possibly analogous to those found of beta amyloid and alpha synuclein in Alzheimer's and Parkinson's disease respectively. A paper in 2000 by Yamamoto et al(38), lends strong support to toxic gain of function. They showed that in a murine model with a conditional knock-in mutant HTT, gene expression resulted in HD neuronal inclusions, neurodegeneration and the HD motor phenotype, but silencing of mutant HTT led to reversal of the behaviour and the neuronal damage. The cellular aggregates of mutant HTT (inclusion bodies) are also the subject of considerable debate, regarding whether the inclusion bodies are incidental to cellular toxicity, prevent toxic effects of mutant HTT, or if the inclusion bodies themselves are toxic to neurons(39, 40). Mutant HTT has been shown to disrupt mitochondrial function, leading to reductions in ATP production and altered calcium homeostasis, which can activate the p53 pathway(41–46). Wild-type HTT has also been shown to interact with HIP-1, whereas the mutant HTT does not: release of this protein triggers apoptosis by a caspase pathway(47).

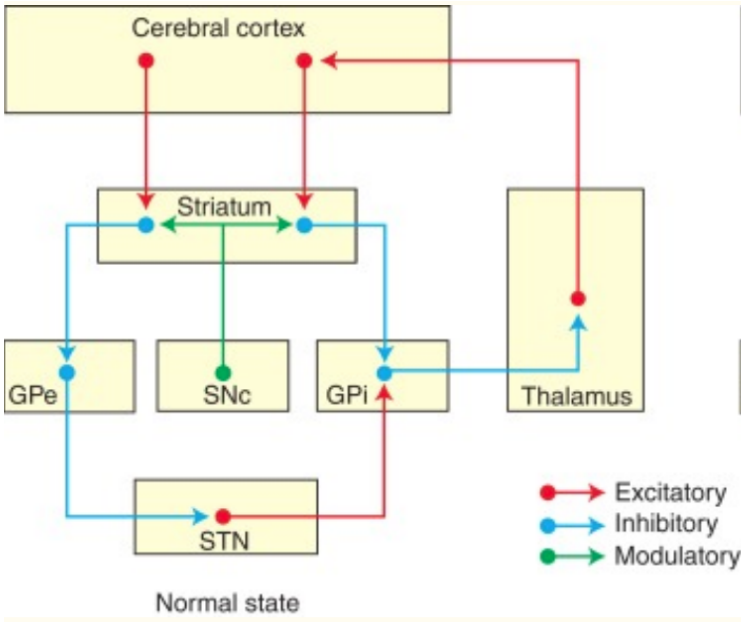
1.5 Neuropathology of Huntington's disease

Much of the formal neuropathology undertaken in any disease, is of necessity focussed on end stage cases who have died as consequence of the illness. Therefore, results of pathological analysis regarding the most significantly affected structures does not imply that these are affected earliest in the disease course, without comparator samples of brains from cases with earlier stage disease. Neuroimaging offers an alternative method of determining the earliest affected structures, however, many modern imaging techniques have not been verified with definite pathological or physiological data, and the methods are reliant on multiple significance tests to infer changes in brain structure or function: hence have a very high vulnerability to type II error. Thus where possible, this review includes both imaging and pathological evidence for the structures and networks affected by HD. Furthermore, one unresolved issue regarding the neuropathology of HD, (particularly in the latter stages of the disease) is the extent to which atrophy in any structure is due to retrograde degeneration when the structure loses its target neurons – it is unclear how much of the later stage degeneration is secondary rather than primary.

1.5.1 Striatum and Basal Ganglia Structures

The striatum is comprised of the caudate and putamen nucleii, which are divided by the internal capsule. It forms part of a network responsible for the refinement of motor patterns generated in the cortex: modulatory input from the cortex activates the striatum (and substantia nigra), leading to disinhibition of the thalamus by deactivation of the internal segment of the globus pallidus (GPi); the thalamus then provides excitatory input back to the cortex(48–51). The striatum also receives excitatory input from the substantia nigra (dopaminergic) and dorsal raphe nucleus (serotonergic)(52, 53). The striatum has two major efferent pathways, mediated by GABAergic medium spiny neurons (MSNs): the direct pathway which is modulated by D1 receptor stimulation on medium spiny neuron cell bodies – these cells reduce activity of the GPi, leading to the afore-mentioned disinhibition of the thalamus. MSNs innervating the direct pathway carry enkephalin. The indirect pathway, modulated by D2 receptor stimulation on MSNs, leads to increased Gpi inhibition via a pathway involving the external segment of the globus pallidus and subthalamic nucleus(54–56). MSNs in the indirect pathway carry substance P. It is hypothesised that the direct and indirect pathways act together to inhibit motor activity in some muscle groups and facilitate it in other, so movement can occur in a co-ordinated fashion(57). An overview of this network is shown in Figure 1.1

Figure 1.1: Functional Organisation of the Basal Ganglia



GPi-Globus Pallidus Interna, GPe-Globus Pallidus Externa, STN-Subthalamic Nucleus, SNc-Substantia Nigra Pars Compacta. Adapted from Lanciego et al(57).

In HD, it is well recognised that the striatum is one of the earliest structures affected, with damage occurring in a characteristic directional pattern: dorsal to ventral, medial to lateral and caudo-rostral (18, 58–62). Vonsattel developed the grading system for striatal damage in HD(58). Grade 0 represents absent macro or microscopic damage to the striatum. Grade 1 shows no macroscopic damage, but microscopic neuronal loss in the head of the caudate, whilst grades 2, 3 and 4 reflect moderate, severe and very severe striatal damage. The major cell type affected is the medium spiny neuron, and the indirect pathway is affected prior to the direct pathway(58, 63–67). The striatum is divided into matrix and striosomes: generally speaking it is thought that degeneration of medium spiny neurons in the matrix leads to motor symptoms, whilst striosomal loss leads to affective symptoms(68, 69). However, the strongest symptom associations with striatal damage in HD relate to cognitive and motor changes(70–72).
Other basal ganglia structures are also affected by HD: some groups have found the substantia nigra to be abnormal in HD, particularly the pars reticulata(18, 73). The globus pallidus atrophies as a consequence of HD, and in keeping with the involvement of the indirect prior to the direct pathway, the external segment atrophies prior to the internal segment(74). The subthalamic nucleus is also affected by this atrophy(62, 70, 74).

1.5.2 Cortex

The cortex is also affected by HD pathology; much of the early neuropathological work focussed on the striatal damage, however some studies recognised cortical degeneration. De la Monte(62) and co-workers demonstrated early involvement of the cortex (21-29% atrophy in HD cases compared with controls), albeit this atrophy was smaller than that affecting the striatum (caudate 57%, putamen 64%). Cortical atrophy had also been demonstrated by Lange et al(74). The cortical atrophy preferentially affects specific layers: namely layers III, V and VI, which are predominantly composed of cortical pyramidal neurons. These layers are involved in communication between cortical layers, but the main efferent pathway terminates on medium spiny neurons in the striatum(48, 75–78). Cortical atrophy occurs in concert with striatal damage, having been found even at Vonsattel stage 1(62). Later imaging work has confirmed the earlier pathological studies. Rosas(79), demonstrated cortical thinning in HD, (importantly from a methodological perspective, they confirmed the reliability of their imaging technique in post-mortem HD brains). Although the sample size was small (11 HD cases, 13 controls), they were able to show that cortical thinning progressed from posterior to anterior regions, and the sensori-motor cortex was the most affected region in manifest disease. Later work in a much larger sample confirmed these findings in a presymptomatic cohort: showing a posterior- ante-

rior progression, with relative sparing of the ventro-medial frontal cortex(80). Further work by this group(81), demonstrated heterogeneity of cortical thickness in early HD, with most marked thinning affecting sensori-motor cortex, precuneus, parahippocampal gyrus, superior regions of parietal, temporal and superior and middle frontal cortex. Thinning in these regions was shown to correlate with cognitive measures (for example verbal fluency performance correlated with frontal regions: pre-central gyrus, posterior superior frontal cortex, but also parietal, temporal and occipital regions: superior temporal, lingual gyrus, precuneus and cuneus.)

These observations have been extended by other groups. The anterior cingulate cortex is involved in the functions of cognitive control and conflict monitoring, with connections to the limbic system and prefrontal cortex, modulating activity within these structures(82–85). Pathological studies have demonstrated that atrophy in anterior cingulate cortex is associated with affect scores of HD patients in life(68), and this observation is supported by imaging work(86); smaller cingulate volume has been found to correlate with depression scores and impaired recognition of negative emotion(87). Insular cortex plays a role in recognition of aversive stimuli(88), such as pain, but also in social behaviour and negative emotion recognition (89–91). Pathology studies in HD have demonstrated insular atrophy(92), whilst neuroimaging studies have also shown insular damage(93, 94), several groups have proceeded to show insular changes mediate impairments in disgust recognition(95, 96). The orbito-frontal cortex has functions in predicting rewarding outcomes and decision making; lesions of this structure are associated with impaired learning under conditions of ambiguity(97, 98, 98, 99). The orbito-frontal cortex has strong connections with the ventral striatum, and in keeping with the relative sparing of medial and ventral frontal regions seen in the structural neuroimaging studies(79, 80), there are fewer studies demonstrating involvement in HD. Ille et al(100), found that orbito-frontal cortical atrophy in HD correlated with poorer performance on a negative emotion recognition task, whilst Holtbernd(101) and co-workers showed altered functional activity during motor sequence learning. Dorso-lateral prefrontal cortex mediates classical executive functions: set shifting, planning motor actions, working memory(102–104). Early pathology studies have shown HD related damage to this region(77, 105), whilst later functional neuro-imaging studies have shown altered activity during executive function (working memory and Simon) tasks(106–109). Intriguingly one of the studies in premanifest patients showed increased activity rather than the decreases seen in the other studies: this may reflect neural compensation, prior to performance decrement(109).

1.5.3 Thalamus and Subthalamic Nucleus

The thalamus forms one of the major nodes in the cortico striatal network(49, 51), in addition to relaying sensory information from the body to the cortex, and motor patterns to the body by cortico-spinal tracts. The medial aspects of the thalamus carry fibres from the reticular formation involved in arousal and attention(110, 111). The subthalamic nucleus forms part of the indirect pathway, along with the external segment of the globus pallidus(51). Thalamic atrophy has been found in the brains of patients affected by HD: predominantly in stages 3 and 4(18, 62). Atrophy of the subthalamic nucleus has also been noted(74), again occurring later in the disease process(58), although a more recent study suggests that the degree of subthalamic nuclear damage correlates with that of damage to the striatum(70). Imaging work using a voxel-based morphometry (VBM) protocol in HD patients, has shown that thalamic atrophy predicts poorer cognitive performance(112), and is associated with impairments in fear recognition: a combined fMRI protocol and VBM study showed thalamic atrophy and hypoactivation during a facial emotion recognition task predicted poorer fear recognition(87).

1.5.4 Hypothalamus

The hypothalamus regulates homeostatic functions such as sleep, and appetite(113–116). Post-mortem studies demonstrated atrophy of the lateral hypothalamus in HD (117, 118), demonstrating that the degree of cell loss predicted age at onset of disease and age at death. This region of the hypothalamus produces orexin, which has roles in arousal and appetite, and has been shown to be abnormal in a mouse model of HD(119). Alterations of somatostatin levels (which has roles in regulating insulin and glucagon) have been found in HD(120). Structural neuroimaging studies have shown atrophy of the hypothalamus even in pre-symptomatic individuals(93, 121, 122), however this has not been replicated by all groups(123).

1.5.5 Amygdala

The amygdala, which forms part of the limbic system plays a central role in the experience of emotion, and mediates the foundation of stimulus-reward and stimulus-punishment relationships(124, 125). The amygdala is atrophied in HD, both in pathological studies and on neuroimaging(81, 93, 95, 126, 127). The atrophy is not as severe as that affecting the caudate and putamen, with one study finding a reduction in amygdalic volume of 24% compared with controls, whilst the putamen was reduced by 53%(128). A PET study found reduced dopaminergic binding in the amygdala of HD patients(129), whilst functional imaging studies have suggested

changes in amygdalic connectivity related to irritability(130), impairment on a social cognition task ('reading the mind in the eyes')(131) and the experience of sadness(87).

1.5.6 Hippocampus

The hippocampus is a central structure in episodic memory: it is critical to sequence learning, and both spatial and temporal learning processes. Pathology studies in HD have shown macroscopic atrophy of the hippocampus, whilst microscopy of the region has shown preferential cell loss in the CA1 region(18, 62, 132). This region has been shown to mediate the context-dependent aspect of autobiographical memory formation (133, 134) in animal models, whilst in a cohort of patients with selective CA1 lesions, extensive autobiographical memory was lost(135). In neuro-imaging studies, hippocampal atrophy has been seen in HD, although it was comparatively spared (9% reduction in volume compared with controls) when set against the atrophy in putamen(53%) and caudate (37%). Pavese and co-workers also demonstrated a reduction in hippocampal dopamine receptor binding in subjects with HD. Whilst cognitive psychology studies have shown a range of deficits in HD patients on tasks that specifically target mnemonic function(136, 137).

1.5.7 White Matter

White matter forms connections between brain regions, governing network integrity and hence is necessary for normal network function throughout the central nervous system. De la Monte and co-workers demonstrated macroscopic atrophy of white matter at all stages of HD, almost as severe as that affecting the striatum(62), whilst neuroimaging studies have shown white matter damage prior to motor onset (particularly in the occipital region: in keeping with work showing posterior-anterior progression of cortical damage(79, 138)), furthermore statistical modelling techniques predicting onset showed that adding white matter loss improved predictive power over the predictive model with striatal atrophy in isolation(128, 139, 140). White matter loss has been correlated with both motor and cognitive impairment in HD; particularly corpus callosal atrophy and frontal white matter loss(141, 142). What remains unclear is whether this is related to primary damage from HD leading to axonal or myelin loss, or whether the white matter loss is secondary to cell body damage in grey matter structures.

1.5.8 Cerebellum

The cerebellum plays a central role in balance and movement sequencing and co-ordination. Early work did not find significant cerebellar involvement in HD; however, later studies have shown atrophy in the latter stages of the disease(18, 58, 128, 138).

1.6 Clinical symptoms of Huntington's disease

1.6.1 Motor Deficits in Huntington's disease

The motor symptoms of HD are the most obvious, even to a lay observer, and consequently have received much of the research attention and clinical focus. For much of the 20th century, the condition was referred to as Huntington's chorea, with the change in terminology to Huntington's disease arising as a result of the increased recognition of cognitive and behavioural changes. HD causes choreiform movements – flitting, writhing movements of the limbs, trunk and facial muscles, which can appear semi-purposeful. Later in the disease, patients often become more bradykinetic, with increasing dystonia (co-contraction of agonist and antagonist muscles) and rigid. Oculomotor deficits (impaired saccadic and pursuit movements) and dysphagia (perhaps as a consequence of impaired motor sequencing) are all well-described(143–145). The appearance of hyperkinetic abnormalities prior to the onset of akinetic-rigid features, may reflect the relatively earlier damage to the indirect pathway(22, 145).

The earliest motor features, seen even in some pre-manifest individuals are dysarthria, impairments on the Luria tri-step test, and chorea; the oculomotor, dystonic and dysphagic changes tending to occur later in the disease. Unsurprisingly the development of chorea is the most likely herald of a diagnosis of motor onset(146, 147).

1.6.2 Cognitive Changes in Huntington's disease

Limitations of Testing for Cognitive Decline

Measuring cognitive changes in any disease can be problematic because of the inherent confounding in the testing process. Longitudinal testing is vulnerable to memory deficits in the patient population- visuo-spatial task performance (for example) may improve in healthy controls because of practice effects, but memory deficits in affected subjects may lead to less prominent practice effects; thereby demonstrating an apparent visuo-spatial deterioration over time in affected cases compared with controls. The tasks may be confounded by differing pre-morbid

ability of subjects (which may in part be driven by socio-economic status – a particular problem for families with inherited disease). Finally, the tests themselves are often dependent on multiple cognitive processes (a minimum level of executive function is needed to follow instructions for example), and may have ceiling and floor effects.

Early Descriptions of Cognitive Decline in HD

George Huntington described cognitive impairment in his initial monograph: "As the disease progresses the mind becomes more or less impaired", despite this, recognition of the dementing process in HD was relatively limited until the latter 20th century. Early reports of cognitive dysfunction were purely descriptive: alluding to the cognitive changes seen in HD sufferers in state asylums, authors used unpalatable terms such as 'unemployable', 'mentally weak'(148). Formal diagnosis of cognitive change in HD, was first found using the mini-mental state examination(149, 150) Cognitive testing in HD patients, using the MMSE in addition to the symbol digit modalities test was found to correlate with structural changes in the caudate using computed tomography imaging(151).

Formal Diagnosis of Dementia in HD

A formal diagnosis of dementia was made in 66% of a manifest HD cohort, using a criterion of performance 2 standard deviations below the mean values of control performance(152), whilst Leroi and colleagues found 80% of manifest HD patients had a diagnosis of dementia or cognitive disorder by DSM IV criteria(153). DSM(154) criteria originally made specific reference to memory decline, which is not the earliest, or most severely affected cognitive domain(136, 147, 155, 156) in HD. Peavy and co-workers (155), proposed alternative criteria: significant decline in two major cognitive domains leading to functional impairment that is progressive, based on the major cognitive contributors to functional decline in HD (attention, psychomotor speed, initiation). These changes have been adopted into the criteria for dementia diagnosis in the most recent update of the DSM(154).

Progression of Cognitive Changes in HD

It has become generally accepted that cognitive decline is one of the earliest features of HD. Work in a large at-risk cohort (family history of HD in first degree relatives, manifest individuals were excluded from the cohort) blind to their own genetic status has shown differences on

performance of the symbol digit modalities task (SDMT)(147) in gene positive compared with gene negative patients. The PREDICT-HD study found declines on a range of tasks in presymptomatic HD patients: the earliest deficits were found on facial emotion recognition, psychomotor slowing (speeded tapping) and a smell recognition test; these findings have also been seen by earlier groups in smaller cohorts(136, 157–160). Further work in the PREDICT-HD cohort has found that declines in the SDMT, Trails A & B, smell identification and Stroop interference test occurred prior to any motor deficits(156). The impairments in recognition of facial emotion have been found by other groups, and negative emotion (anger, fear, disgust) seems disproportionately affected, a finding which has been linked to insula dysfunction(96, 161, 162). Deterioration in performance on tasks of executive function is apparent at a later phase of the pre-manifest period with worse performance in pre-symptomatic patients on tasks of set-shifting, verbal fluency and planning(136, 163–167). Memory impairment, with recall disproportionately affected over recognition memory occurs in late presymptomatic and early symptomatic periods(136, 168–170). Visuo-spatial and attentional impairments have also been found in presymptomatic cohorts(136, 164, 171).

Social Cognition in HD

Impaired recognition of facial emotion is part of a wider pattern of deficits of deficits in social cognition (interacting with other people and interpreting human behaviour) found in HD. Snowden et al(172), found impaired interpretations of social cues in HD patients when asked to describe the motivations of characters in humorous cartoons, which has been replicated on a similar test of social inference(173). A number of tasks of social cognition have been developed such as the faux-pas test (vignettes are read to the subject, they are then asked if anyone in the scenario did something inappropriate)(174), 'reading the mind in the eyes' test(175), and theory of mind tests(176). A number of these tests have been used in HD subjects(177–179). A recent meta-analysis showed deficits in social cognitive tasks both in manifest and pre-symptomatic patients(180).

1.6.3 Psychopathology in Huntington's Disease

Prevalence in Manifest HD

Early accounts of HD, including the original description, by George Huntington, comment on psychopathology, describing 'insanity' and allude to an increased frequency of suicide(148, 181–185). Most studies were pedigree descriptions and gave brief descriptive accounts of be-

havioural changes seen in the disease. Nonetheless, these early workers were often very perceptive in describing some the features that have since been more systematically described; alluding to 'poverty of thought' 'carelessness' and also describing violent and aggressive behaviour. Later accounts relate more disinhibited or impulsive behaviour, such as addiction and hypersexuality(186–189), whilst affective disorders were also recognised(190, 191). Caine and co-workers(192), systematically documented the psychopathology using formal note review and diagnostic assessment using the mental state examination. They found psychiatric symptoms in 14/18 cases; predominantly apathy and irritability. Studies using formal diagnostic instruments(193–195), confirmed the central nature of the triad of apathy, irritability and depression.

This work all predates the advent of genetic testing programmes for HD. A systematic review(196), included 7 papers describing the prevalence of psychiatric symptoms in manifest HD patients with a confirmed genetic test. This study found the highest rates for apathy (34-76%), and irritability (38-73%), lower rates for depression(33-69%), anxiety (34-61%) and obsessive compulsive symptoms(10-52%), with a minority of patients developing psychotic symptoms (3-11%). Obsessive compulsive symptoms can be nosologically difficult in HD, as whilst some HD patients undoubtedly do develop obsessive compulsive disorder(197), some of the symptoms overlap with perseveration: reflecting the executive dysfunction seen in the disease. Most researchers from a psychiatric background would distinguish between ego-dystonic obsessive-compulsive symptoms and ego-neutral perseveration, although concrete neuropsychological or neurobiological evidence to support this distinction is limited. The UHDRS behaviour score which was used for some of the studies in the review, does not distinguish between perseveration and obsessive-compulsive symptoms(198). Later studies in large data sets from the REGISTRY study, confirmed the central nature of apathy (28%), irritability (13.9%) and depression (12.7%).

Pre-Symptomatic Psychopathology

Some controversy existed over the appearance of psychiatric features prior to motor onset; with some studies not finding evidence of psychopathology in pre-symptomatic carriers(199). However, 'mental onset' was described by a number of groups, even prior to genetic testing programmes(186, 189, 200). Large cohorts in the PREDICT-HD study have found higher levels of obsessive compulsive symptoms using the Schedule of Compulsions, Obsessions, and Pathological Impulses (SCOPI)(201, 202). Whilst assessment of general psychopathology in large cohorts using the symptoms checklist – revised(203), and the frontal systems behavioural scale (measuring apathy, disinhibition and executive dysfunction) (204), has found increased rates of psychiatric symptoms across most domains for carriers versus non-carriers(205–208), although the domains

covering psychotic and anxiety symptoms did not show consistent differences between gene carriers and controls.

Psycho-social versus Neurobiological Nature of Psychopathology

Prior to genetic testing, significant controversy existed over whether the increased rates of psychopathology in HD related to the consequences of having a neurodegenerative disease (or being at risk of developing HD), or whether the neurodegenerative cerebral damage led directly to neuropsychiatric symptoms. Several studies have addressed this: Julien(209) and colleagues measured psychopathology immediately prior to gene testing in a cohort of people undergoing predictive testing: they found higher rates of depression and irritability among gene positive individuals compared with those testing negative. The PHAROS study found higher rates of psychopathology, particularly apathy and irritability in a cohort 'at-risk' for HD, but blinded to their own genetic status(147, 210).

Longitudinal Progression of Psychopathology in Huntington's Disease

The studies in presymptomatic cohorts outlined above show higher prevalence of neuropsychiatric symptoms in presymptomatic subjects, however, they do not address changes in prevalence of these symptoms as HD progresses. Craufurd et al(211), showed increasing prevalence of apathy in later disease stages of HD, whilst irritability was present from the earliest stages, peaked then decreased, and depressive symptoms were not clearly linked to any disease stage. This work was replicated in a longitudinal study by the same group(212). The TRACK-HD study(165, 166), found that the only psychiatric variable to reliably distinguish between cases and controls, and progress even from the pre-symptomatic stages was apathy. Reedeker et al(213), also found that apathy progressed with disease, whilst, a further study by this group(197) using a formal psychiatric diagnostic instrument the composite international diagnostic interview (which does not include symptoms such as apathy and perseveration) in 106 presymptomatic HD subjects, found incident psychiatric disorders in 13.2%, but remitted psychiatric disorders in 7.5%. The commonest psychiatric symptom was depression. A study by Hubers et al(214), found incident suicidality in 7% of presymptomatic HD subjects over a 2 year follow-up, although they excluded any subjects who had suicidal ideation at baseline.

1.7 Neuropsychiatric Symptoms in Other Disorders

1.7.1 Apathy

Measurement and Cognitive Processes Leading to Apathy

Apathy is a reduction in goal-directed behaviour(215), it is a feature of many neurological and psychiatric disorders(216–218). It is measured using a variety of different scales, such as the apathy evaluation scale(215), apathy scale(219), Lille apathy rating scale(220) and subsections of the problem behaviours assessment for HD(221) and the neuropsychiatric inventory(222). A number of different tasks have been used in apathetic populations; in particular deficits in executive function have been linked to apathy in a number of different disorders including Parkinson's disease(223–225), Alzheimer's disease(226–228), fronto-temporal dementia(229, 230), vascular dementia(231) and schizophrenia(232, 233). In keeping with this, planning and changing response are important components of goal-directed behaviour and are themselves heavily dependent on executive function. However, there is also extensive literature on tasks of reward and motivation in apathetic behaviour: with evidence for reduced reward sensitivity(234, 235), impaired facial emotion recognition and reduced effort for equivalent reward(235–237).

Neuroanatomy

Apathy has been reported following following focal lesions to a number of sites; these have predominantly been located in the the frontal lobes, limbic system and basal ganglia. A meta-analysis of the clinical consequences of basal ganglia damage (primarily secondary to ischaemia, haemorrhage and hypoxia) demonstrated that a reduction in goal-directed behaviour was seen in 13%, with the vast majority involving the caudate(238), this has been confirmed by further reports(239, 240). Globus pallidus lesions can also cause apathy(234, 241, 242). Cortical lesions are also frequently reported to cause apathy: lesions of the ventromedial prefrontal cortex are well-recognised to result in apathetic behaviour(243–246), as are anterior cingulate cortex lesions(247). Damage to the thalamus and subthalamic nucleus has also been shown to result apathetic behavioural syndromes(248–250). A number of groups have looked for neuroanatomical correlates of impaired goal-directed behaviour in diseases associated with apathy; this work has to a large extent been in keeping with the studies involving focal lesions. The regions involved are again localised to cortico-striatal networks. The anterior cingulate cortex is atrophied or hypofunctional in apathetic patients with Alzheimer's disease(251–253), fronto-temporal dementia (251, 254), and Parkinson's disease(255). The orbito-frontal cortex is also heavily linked to apathetic behaviour: demonstrating atrophy or hypoperfusion in associations with apathy

in Alzheimer's disease(256–258), fronto-temporal dementia(251, 259), Parkinson's disease(260, 261) and progressive supranuclear palsy(251) whilst the caudate has been implicated in apathy in a number of disease states including both 'cortical' and 'subcortical' dementias (260–264). Insular changes are widely reported in association with apathy (in Parkinson's disease (265, 266), Alzheimer's disease (251), and fronto-temporal dementia (259)). Finally, changes in both dorsolateral prefrontal cortex (atrophy and hypoperfusion) (in Alzheimer's disease (257, 267); fronto-temporal dementia (254, 268), and Parkinson's disease (260)) and thalamus (Parkinson's disease (260); and fronto-temporal dementia (259)) have been linked with apathy.

1.7.2 Impulsivity and Disinhibition

Measurement and Cognitive Processes

Impulsivity (or disinhibition(269)) is acting rashly or without forethought, and covers a wide variety of actions that are "poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes"(270). Although it often leads to adverse outcomes, on occasion it can be advantageous (for example acting quickly to seize an opportunity), high impulsivity is also associated with improved performance on some neuropsychological tasks (271). It is a feature of many neuropsychiatric disorders including most addictions, attention deficit hyperactivity disorder (ADHD), borderline personality disorder and bipolar(272, 272, 273); it also occurs in relation to dopaminergic treatment in Parkinson's disease(274). Impulsivity is now widely recognised to be a heterogenous construct, with separate cognitive processes leading to impulsive behaviour(270, 275, 276). Furthermore, there are a number of questionnaires and also task measures of impulsivity behaviour, which have minimal overlap(277, 278). The processes known to be involved are inter-temporal (delay) discounting (valuing an immediate reward over a larger delayed reward), motor inhibition (the ability to inhibit a pre-potent response), risk-taking, reflection impulsivity or cognitive impulsivity (deciding before all information is known)(270, 275, 276, 279).

Neuroanatomy

Impulsive behaviour following brain injury is well described, the case of Phineas Gage, has been discussed extensively, and recent work showed probable involvement of the ventromedial prefrontal cortex(280), whilst many further studies have reported impulsive behaviour following lesions to this region and the adjacent orbito-frontal cortex, particularly in association with increased delay discounting(281–283). Lesions in this region have also been associated with impaired future perspective on the iowa gambling task(98), and cognitive impulsivity – acting

too quickly on the matching familiar figures test(284). Furthermore, lesions to this region has shown altered reward value and risk taking, but no change in inhibition(285, 286). Lesions of the inferior frontal gyrus have been shown to cause motor impulsivity with impaired performance on tasks such as the Go Nogo and stop signal reaction task(287, 288). Impulsive behaviour and reduced motor inhibition have been demonstrated following subthalamic nucleus lesions(289, 289, 290). Insular involvement has been demonstrated in impulsive behaviour(281, 291), with no alteration of betting with increasing risk, on a gambling task(281), but intriguingly, reduced delay discounting(283). Dorsolateral prefrontal cortex, caudate and putamen lesions have also been reported to cause impulsive behaviour(238, 291–293). This is replicated in imaging studies in disease populations, with reduced fMRI signal during rewarded trials in striatum and cingulate cortex seen in addiction and adhd populations (294–297). Studies of inhibitory tasks in fMRI show reduced signal during inhibition focally in the striatum, ventral and ventro-lateral prefrontal cortex, and in a distributed fronto-parietal network (298–302), in bipolar disorder, addiction and ADHD, although other groups have found the converse(303). Inter-temporal choice tasks in an addicted population has shown increased signal in the cingulate and ventro-lateral prefrontal cortex(304).

1.7.3 Irritability and Aggressive Behaviour

Measurement and Cognitive Processes

Snaith(339) defines irritability as a "state characterised by reduced control over temper which usually results in irascible verbal or behavioural outbursts, although the mood may be present without observed manifestation. It may be experienced as brief episodes, in particular circumstances, or it may be prolonged and generalised. The experience of irritability is always unpleasant for the individual and overt manifestation lacks the cathartic effect of justified outbursts of anger." Aggression is the outward expression of this anger, and can be either verbal, directed at inanimate objects, or directed at other people. There are a number of questionnaires to assess aggression and irritability; such as the Snaith irritability scale(340), Buss-Durkee hostility inventory(341) and the life history of aggression questionnaire(342). Task-based assessments of irritability and aggression have either been based on those developed for impulsivity, and reference the concept of impulsive aggression(343), or are based on measuring aggressive behavioural responses to provocation(344, 345). These responses can either be 'stealing' points from an opponent in game play, or administering mild shocks or auditory aversive stimuli to an unseen (fictional opponent). Motor inhibition (measured by the stop signal task or go nogo task) is

impaired in psychopaths, and deficits have also been found on delay discounting tasks, the Iowa gambling task, set-shifting tasks and facial emotion recognition tasks in aggressive and irritable populations(343, 346–350).

Neuroanatomy

The experience of anger in healthy controls has been localised to a number of regions: the amygdala, ventromedial prefrontal cortex, orbito-frontal cortex, anterior cingulate cortex, insula and temporal poles(351–356), whilst imminent threat activates the peri-aqueductal grey(357). Lesions of the hypothalamus, orbito-frontal cortex, frontal poles and ventro-medial prefrontal cortex have been associated with violent or aggressive behaviour(284, 347, 348, 358–362). Whilst basal ganglia lesions appear to lead to aggressive behaviour on rare occasions(238): in the largest case series, none were reported. Reduced volume, hypoperfusion or reduced activation has been noted of the antero-medial temporal regions, amygdala and hippocampus in patient populations with irritable or aggressive behaviour(363–370), although other groups have found increased amygdala signal during threat or aversive stimuli(371, 372). Atrophy or hypoperfusion of the ventromedial prefrontal cortex, orbito-frontal cortex and cingulate cortex has also been linked with aggressive behaviour(371, 373–376), in populations with high levels of aggression.

1.7.4 Depressed Mood and Major Depressive Disorder

Measurement and Cognitive Processes

Theoretical work regarding depression, has most recently been influenced by the ideas of Beck(295, 305), who describes the concepts of negative schemata: sufferers re-interpret events in a negative light and ignore any positive interpretations of stimuli or actions. This is supported by the major endophenotypes underlying major depressive disorder: reduced reward value (anhedonia), negative salience (sadness and guilt), altered motor activity (psychomotor retardation or agitation), in addition to the 'neurovegetative' domains of altered sleep and appetite(306). Formal psychiatric diagnosis according to DSM criteria(154) is the gold standard measure of depression, and can be aided by using instruments such as the mini international neuropsychiatric interview(307), but a range of other scales are available to score depressive symptomatology such as the hospital anxiety and depression score(308). Cognitive assessment of patients with major depressive disorder has demonstrated impairment on executive function tasks(309, 310). However, tasks to specifically assess depressive symptomatology have also been developed, showing deficits in disengaging from negative stimuli and a cognitive bias towards negative stimuli(311, 312), reward deficit(313, 314), altered reward and effort processing using novel(315, 315) and

established tasks, such as the progressive ratio(316).

Neuroanatomy

Case reports of depression following focal brain injury are comparatively less common than those relating to impulsive, aggressive or apathetic behaviour, but the lack of publications may reflect the common assumption that depression following brain injury is an expected consequence, either of illness in general, or the social or cognitive consequences of brain injury. However depression has been reported following injuries to the frontal pole(317, 318), left prefrontal cortex(319) and caudate(238); whilst deep brain stimulation to the anterior cingulate cortex and lateral habernula has been reported to alleviate depression(320, 321). The default mode network (DMN), is active at rest, where it is thought to be associated with 'inwardly directed' thought and subserves the medial prefrontal cortex, cingulate cortex, insula, thalamus, amygdala and hippocampus(322). The DMN is recognised to be overactive in major depressive disorder (323, 324)and is thought to reflect rumination: excessive rumination scores have been shown to correlate with increased activity of the DMN in major depression (322, 324, 325). Functional imaging studies of major depressive disorder using a regional analysis during emotional stimuli have shown reduced activity in a number of regions during reward (cingulate, orbitofrontal cortex, ventral striatum(326–330)) and increased activity during loss, or in response to sad stimuli (anterior cingulate, medial prefrontal cortex, amygdala(329, 331–333)). Volumetric and resting state perfusion studies have shown atrophy and reduced perfusion in limbic and frontal regions (orbito-frontal cortex, prefrontal cortex, amygdala, thalamus and hippocampi(334–338)).

1.8 Synthesis and Aims of this Work

Huntington's disease affects many of the brain regions involved in neuropsychiatric disturbance outlined in this review. However, the cognitive psychology and imaging studies of neuropsychiatric symptoms in HD to date have been largely negative or inconsistent. This may reflect methodological differences, but it also may reflect a heterogeneity of cognitive processes contributing to the expression of these symptoms. This body of work maps the different neuropsychological processes that may contribute to the generation of depressed mood, apathy, impulsive behaviour and irritability in HD using a battery of tasks that probe separable cognitive processes.

Chapter 2

Materials and Methods

2.1 Introduction

This chapter describes patient recruitment, inclusion criteria, and an overview of neuropsychiatric assessments and protocols that are common to all chapters; specific methodological issues for each chapter will be described in those chapters and not duplicated here.

2.2 Recruitment Strategy, Ethics and Consent

The vast majority of genetically confirmed HD patients are already enrolled in the multi-centre, Europe-wide observational study REGISTRY (MREC number 10/WSE04/7), which became the worldwide study ENROLL (MREC number 13/WA/0192) in 2014. Those able to attend clinic are reviewed on a regular basis (at least yearly) to address any new or current problems associated with HD. As such, they are regularly offered the opportunity to participate in different studies (consent is specifically sought about being contacted for other studies when being entered into REGISTRY and ENROLL). In the course of normal clinical attendances, patients were offered the opportunity to participate in the study. Additionally, patients (identified as eligible by clinicians working at these sites) who previously expressed an interest in participating in further research were approached directly by letter and telephone follow-up. Patients not already part of ENROLL or REGISTRY, but who were identified by the clinical team as being interested in research, were approached in person at a routine clinical appointment by the clinical team, and informed about the study. We recruited from the Cardiff HD clinic, which has between 250 and 300 patients at any one time. The study was approved by the Research Ethics Committee for Wales (13/WA/0300) and all subjects gave informed consent before participating.

If patients expressed an interest, then they were given the patient information sheet and allowed as much time as they required to consider if they would like to enter the study (in practice, participants were given at least 24 hours before being contacted by a member of the study team). Control participants were recruited from family members of subjects (gene negative siblings/parents or spouses), approached at the same consultation or asked directly by the participating patient (if approached outside of the direct clinical contact situation) and offered a flyer for the study. Again if they expressed an interest they were given a patient information sheet and as much time as they require, to consider participation more fully before being contacted again by one of the research team (by letter, telephone or in person). Family members were specifically sought as controls in this situation as they have the same social milieu and are exposed to similar stresses as patients, but do not have the disease. We also recruited from word of mouth and poster advertising within Cardiff University and University Hospital Wales, in order to increase our control cohort.

Consent for participation (patients and volunteer controls) was taken when the participant arrived for the first day of assessments. Participants were given the opportunity to clarify outstanding areas of uncertainty or ask any further questions regarding the study if they so wished before consent was taken. The consent form specified that a mix of situational, observational and computer based tasks were to be used. As much detail as possible was given, but participants were informed that some parts of the tests required their initial ignorance of the purpose of the test and the reasons behind it, although this was explained to them after completing the battery of assessments.

2.3 Inclusion and Exclusion Criteria

We recruited patients aged 18 or over at study commencement, with a positive genetic test for the HD repeat expansion (CAG repeat length 36 or greater) confirmed either through formal review of laboratory results, or through correspondence with a previous treating clinician, we did not include anyone diagnosed on family history and symptoms alone, owing to the existence in South Wales of a known population of patients with DRPLA (Dentato-rubro-pallido-luysian Atrophy), and another cohort of patients carrying the c9orf72 mutation, which is also recognised as a HD phenocopy. We recruited patients who were felt able to perform the tasks, namely at any stage of the disease from pre-symptomatic to moderate stages; we did not exclude any

individuals based solely on UHDRS (Unified HD rating scale) and TFC (Total Functional Capacity). As we planned to image our cohort, we excluded anyone with severe chorea (chorea score in UHDRS >20), pregnant women, patients with severe claustrophobia, any patient with non-MRI compatible implants, and finally any participant with a neurological disease or brain injury other than HD. Control participants had to satisfy the inclusion/exclusion criteria, apart from the genetic testing for HD. Control participants either had no family history of HD or other movement disorders, or (if the control participant was genetically related to one of the patients) a confirmatory negative genetic test for HD.

2.4 Duration of Subjects Participation

Study participants were consented to participate for a total of 3 years maximum, in order to take part in a subsequent imaging study. The initial testing battery could be performed in one visit and took approximately 4 hours to complete in total, but subjects were offered the opportunity to take separate sessions on different days, completed over the course of 1 week if participants preferred.

2.5 Demographic Variables and Testing Process

All patients had an up to date medication history and motor examination (medication history was taken on the day, a motor examination using the UHDRS protocol was performed, if one had not been performed within the last 3 months). Full scale IQ was calculated accordingly to the formula derived by Crawford(377) using age, social class and years of education. This approach was chosen, as previous work has shown that reading tests are vulnerable to the cognitive decline in HD when the disease becomes motor-symptomatic (378). Dopaminergic and Serotonergic drugs were converted to Olanzapine and Fluoxetine equivalents using figures from meta-analyses (379, 380) and the WHO recommended daily dose (in the case of Tetrabenazine) in order to standardise and correct for these variables. Demographic variables, motor examination and questionnaires were performed before the tasks, to avoid task performance prejudicing motor and conventional psychiatric assessment. Prior to all of the neuropsychological tasks, subjects were asked to do a timed-tapping experiment and response time to a visual stimulus, in order to control to gain a baseline assessment and control for the motor features of the disease

during statistical analysis. Subjects were tested in a quiet room free from external distractions. Task order was randomised in order to avoid order effects. Breaks were encouraged ad libitum throughout the testing process. Subjects were asked to place themselves at a comfortable distance from the laptop screen before starting the computer-based tasks. All tasks were coded and run using the E-prime 2.0 software package (except where indicated), and performed on a Lenovo thinkpad laptop computer.

2.6 Recruitment and Demographics Analysis

We recruited 53 patients, there were 26 females among the patients. 26 controls were recruited: 13 from word of mouth advertising and 13 from gene-negative family members, 17 in this group were female. The patient group were slightly older (53.92 compared with 46.85 years of age), but this was not statistically significant. The patients had a slightly lower premorbid IQ (calculated using Crawford's method: as outlined above), as well as being on higher levels of Olanzapine and Fluoxetine equivalents. The total motor score was unsurprisingly markedly higher in the HD group (mean 36.58 compared with 1.48).

2.7 Data Analysis

Group comparisons comparing HD patients and controls were performed using t-tests if the groups were normally distributed (Histogram appraisal, and test of skew <0.5) or Wilcoxon rank sum tests if they were not. Linear regression was used to look at which particular tasks predicted psychiatric symptoms, with a forced entry approach, adding potential confounding variables to the model as independent variables. Post-hoc tests for assumptions underlying multiple linear regression were performed – Shapiro test on residuals for normality, Goldfeld-Quandt test and Durbin-Watson test to ensure the results were reliable. For any regression analyses not satisfying these tests, the dependent variable was appraised using histograms and an appropriate distribution chosen (Poisson for non-negative, positively skewed integer data: evidence of overdispersion was corrected for using negative binomial models) or logistic regression for binary variables. Psychometric characteristics of the novel tasks were assessed using Cronbach's alpha and Kuder Richardson 20 tests for internal consistency, and correlation with established measures in our whole cohort (HD cases and controls) for construct validity. Any data sets with missing variables were excluded in a pair wise fashion from any analyses. Further details of specific analyses are included in the results chapters.

2.8 Tasks, Questionnaires and Cognitive Assessments

Participants undertook a series of objective computerised tasks using a laptop computer. To avoid order effects, although the clinical examination, demographic variables and questionnaires were completed before the task battery, task sequence was randomised. Before starting the battery of assessments, all subjects completed a simple reaction time game and a timed tapping assessment, firstly as baseline measures of motor ability (as this was relevant on some tasks) and secondly to ensure that they could complete at least some of the task battery before commencing.

This is an overview of the task battery: in depth accounts of the methods of individual tasks and relevant outcome measures are described in the individual results chapters. Psychometric data is included for novel assessments.

2.8.1 Balloon Analogue Risk Task

Subjects are instructed that the goal of the task is to win as much money as possible by pumping up some balloons. They are told that the larger they pump a balloon, then the more points they will win, but at some point the balloon will 'pop'. If the balloon 'pops', they lose the points from that trial (381). This task was designed to measure impulsive behaviour, but measures of punishment, reward and risk-taking have been derived for the apathy and impulsivity chapters.

2.8.2 Extra-dimensional Set Shift Task

This is a standard task of ability to change response set: a measure of executive function, known to be impaired in motor-manifest HD, that changes with disease progression (164, 382). It is used in the apathy, impulsivity and depression chapters.

2.8.3 Frustrative Non-Reward

This task is based on an animal task(383), where animals expect to receive a reward and are then denied one: which has been shown to lead to behavioural aggression in animals. This task is used in the irritability chapter.

2.8.4 Iowa Gambling Task

Subjects are told the goal of the task is to win as much money as possible. They are told that they can select from 4 different decks of cards. Every time they choose a card the subject will win money, however, sometimes they will be told they have lost money too. They are told the aim of the game is to win as much money as possible by learning which decks perform more poorly over time (more money is lost than won), and avoiding these decks (99). This task is used in the apathy, impulsivity and irritability chapters.

2.8.5 Klőppel task

This task is a variant of that developed by Klőppel (130), designed to evoke frustration. It is used in the impulsivity chapter.

2.8.6 Maze Task

This is a novel task, designed by the author. Subjects are told they will be placed in a series of situations – 15 in total. They are told they must decide what they want to do next in that particular situation. It is designed to be a measure of option generation and selection. Cronbach's alpha was 0.7 (95% Confidence Intervals 0.64-0.76) and the correlation with phonemic verbal fluency (as a measure of novel concept generation) was strong: correlation coefficient -0.60 p=3.89x10-6. Longer response times on Maze, correlated with lower phonemic verbal fluency scores. It is used in the apathy chapter.

2.8.7 Monetary Choice Questionnaire

This is a 27 item questionnaire, which assesses subjects willingness to accept a delay in receiving money, in return for a larger sum of money over an immediate, lower reward (384).

2.8.8 Optimistic Influence Test

This task was designed for this study by the author, as an assessment of depressive cognition. Subjects are shown a race and asked whether they feel they can influence the result by boosting the speed of the slower runner. Cronbach's alpha was 0.59 (95% Confidence Intervals 0.41-0.77), whilst there was a trend level negative correlation with the negative urgency score, and trend level positive correlation with the positive urgency score from the UPPS P (correlation coefficients -0.21 and 0.22 p=0.078, 0.070 respectively). This suggests that more optimistic responses were associated with more optimistic behaviour under conditions inducing positive affect, and less pessimistic behaviour under conditions inducing negative affect. This task is used in the depression chapter.

2.8.9 Persistence Task

This task was developed for this study by the author. It measures sensitivity to punishment. Subjects are told that they must race against another car. The other car is always faster. The outcome measure is latency to terminating the task by the participant. Cronbach's alpha was 0.81 (95% Confidence Intervals 0.74-0.88), whilst a logistic mixed model of inaccuracy following punishment on the BART showed there was a significant interaction between Persistence score and stimulus value consistent with impaired response to large punishment (Pseudo R^2 0.053, interaction estimate 1.24×10^{-3}, p=0.00079). It is employed in the apathy chapter.

2.8.10 Phonemic Verbal Fluency

This task is a standard test of executive function, known to be sensitive to cognitive decline in HD(385). It is used in the apathy, impulsivity and depression chapters.

2.8.11 Probabilistic Selection Learning Task

This is a visual association learning task (386). It is used in the apathy chapter.

2.8.12 Progressive Ratio

This task is based on the animal protocol (387): subjects are asked to increase effort on successive trials to gain a fixed value reward. It is used in the apathy and depression chapters.

2.8.13 Reward Ratio

This task measures whether subjects modify their reaction time in a situation where they receive a reward compared with no reward, and whether they will work harder for higher rewards. It was based on the cued reward reaction time task developed by Roshan Cools(388). Cronbach's alpha was 0.65 (95% Confidence Intervals 0.50-0.81), whilst there was a non-significant correlation with the Progressive Ratio breakpoint (an established measure of reward value and effort) correlation coefficient -0.06, p=0.12. It is employed in the apathy and depression chapters.

2.8.14 Tower Task

This task was based on the point subtraction aggression paradigm(344). Subjects can steal points from an opponent in response to provocation. It is used in the irritability chapter.

2.8.15 Stop-Signal Response Task

This is a test of behavioural inhibition (motor impulsivity: the ability to inhibit a prepotent response) (389).

2.8.16 Ultimatum Game

This is an economic decision making game. Subjects are told that there is a sum of money to be divided between two people and are asked about what offer they would make, and what is the value of the lowest offer they would accept. The outcome is influenced by notions of fairness, social cognition and rational choice(390, 391). It is used in the impulsivity and irritability chapters.

2.9 Questionnaires

In order to validate the assessments we used previously well-validated measures of the behavioural symptoms in HD as our current gold standard assessments. In order to ensure maximum reliability and reproducibility, we used at least 2 assessments of every domain of behavioural change that we tested. We specifically used a range of instruments that included self and carer-ratings as well as clinician judgement, and employed symptom-specific scales as well as instruments that rate behavioural change over a number of different symptom complexes.

Formal psychiatric diagnoses (present and past) were assessed using the MINI. This is a well-validated, structured interview for non-psychiatrists, that scores participants according to DSM-IV criteria for psychiatric illness(307).

We used the short form problem behaviours assessment for HD(165, 211, 221). The best validated symptoms scale in HD. This clinician administered, semi-structured interview rates a particular behavioural change or psychiatric symptom over the last month based on patient and carer report, and scores each symptom for frequency and severity, each on a 4 point scale. The final score for any particular symptom is the combined severity x frequency. Thus the maximum score is 16 for any particular symptom, and the minimum, 0. The symptoms assessed are – depressed mood, suicidal ideation, anxiety, irritability, aggression, apathy, perseveration, obsessive-compulsive behaviours, delusions, hallucinations, and disorientation.

The apathy evaluation scale (clinician)(215) was used as a specific apathy measure – subjects are asked a series of questions about their motivation, lifestyle, work and behaviour – they are then scored by the clinician from 1-4 on each question, based on their responses and carer/next of kin responses. The minimum score is 18, the maximum is 76.

The Snaith irritability scale (340)was used to assess irritable behaviour – this is a self report questionnaire, comprising 18 questions, each response is scored from 0-3 based on frequency or perceived severity of the behaviour. The range is 0-54.

The Barrett impulsivity Scale (BIS-11)(392) was used for impulsive behaviour, this self-report measure asked 30 questions, each rated from 1-4 (from 'rarely/never' to 'almost always') and uses the responses to generate an overall score out of 120, along with sub-scores for attention, non-planning and motor impulsivity.

The UPPS-P (393) comprises 56 self-rated questions each scored from 1-4. Scores are then generated for 5 different areas associated with impulsive behaviour: negative urgency, positive urgency, lack of premeditation, lack of perseverance and sensation seeking.

The behavioural inhibition scale behavioural activation scale (394), is a 24 question self-report measure that generates sub-scores for behavioural inhibition (range 6-24), drive (range 4-16), fun-seeking (range 4-16), and reward responsiveness (range 4-20).

Chapter 3

Apathy

3.1 Introduction

Apathy is defined by Levy and Czernecki(395) as "a quantifiable reduction in goal-directed behaviour" and occurs commonly in many diseases affecting different parts of the brain: cortex (Fronto-temporal dementia (FTD) and Alzheimer's disease(217, 229, 268, 396)), white matter (subcortical vascular disease(397, 398)) and basal ganglia (Parkinson's disease(218, 399, 400), Huntington's disease(196, 211, 401). Imaging and lesion studies have shown apathetic behaviour as a consequence of damage to each of these structures, albeit with a focus on the basal ganglia and medial frontal structures(238, 252, 263, 402–406)

Huntington's disease (HD), is caused by a CAG repeat expansion in the Huntingtin gene on chromosome 4. It leads to progressive neuro-degeneration, primarily of medium spiny neurons, although also cortical regions and white matter(37, 58, 166). It leads to progressive motor, cognitive and psychiatric dysfunction over a 20-30 year period. Apathy is a core symptom of HD, affecting up to 80% of patients(196, 211), and has significant, deleterious effects on quality of life and everyday functioning(407–409). Apathy is evident in HD patients before the motor onset of symptoms(210), and progresses with advancing disease(166). The PHAROS study found higher rates among gene-carriers versus non-carriers blinded to their genetic status(210), demonstrating that apathy is not simply a psychological reaction to a genetic diagnosis of HD, developing symptoms or being at risk of HD. However, the neurobiology of apathy in HD remains obscure: human structural imaging studies have not found consistent correlations with apathy: some studies have proved negative(410–412); Delmaire et al(402), found an association between apathy score and reduced fractional anisotropy in the rectus gyrus; Martinez-Horta (628) demonstrated a correlation of apathy with both amygdala atrophy, and reduced amygdala

perfusion; whilst Baake et al(413), showed a correlation of apathy with reduced thalamic volume. Task-based functional MRI studies have not found associations between apathy and functional activation changes using reward-based, working memory or set shifting tasks(414–416). One resting state functional imaging study found higher apathy was associated with increased functional connectivity in a network involving the caudate, parahippocampal gyrus, orbitofrontal cortex and cingulate cortex, although the precise mechanism by which this leads to apathetic behaviour remains obscure(417). A trial of a dopaminergic agent did not improve apathy in HD(418), suggesting it is not primarily mediated through reward-based, or dopaminergic mechanisms. None of these studies demonstrate significant overlap between the neural structures found to correlate with apathetic behaviour. This may reflect methodological differences, a diffuse network dysfunction (dysfunction of different nodes within a single network that governs goal-directed behaviour), or alternatively the processes that contribute to apathetic behaviour may be heterogenous, and subserved by disparate neural structures and networks.

Theoretical work by Le Heron et al, Ernst and Paulus, and Levy, Dubois and Czernecki(216, 395, 419, 420) concerning goal-directed behaviour and decision-making, emphasise the parallel and sequential contributory processes (option generation and selection, planning, evaluation, learning and updating, willingness to exert and maintain effort) underlying these processes. Despite this, the focus of most work in apathy has been on reward value, motivation and executive function. Several groups have attempted to map deficits in goal-directed behaviour in FTD and PD, more comprehensively(230, 254, 421). However, these studies either used a case-control approach, (comparing performance between patients and healthy controls, without using task performance to predict apathetic behaviour), selected a more limited group of tasks, or omitted a gold-standard assessment of apathy, thus limiting conclusions regarding the neuropsychology of apathy. There has been no comprehensive evaluation of the precise cognitive mechanisms underlying apathy in HD. We developed a battery of novel and established tasks to comprehensively probe specific aspects of goal-directed behaviour, hypothesising that apathy in HD will show a distinctive profile of deficits.

3.2 Materials and Methods

3.2.1 Participants

As outlined in materials and methods, fifty-three HD gene positive (>36 CAG repeats) patients were recruited from the Cardiff University HD clinic. Disease severity ranged from presymptomatic to moderately symptomatic based on their total motor scores (TMS) on the unified HD rating scale (UHDRS)(422). Twenty-six age-matched controls were recruited from family members not at risk for HD and healthy volunteers recruited through advertising.

3.2.2 General Procedures and Questionnaires

Gold standard apathy assessments were the Apathy Evaluation Scale (AES) and the apathy subscore of the short form Problem Behaviours Assessment for HD (PBA apathy), which are well-verified, robust assessments for apathy in HD and other diseases(166, 211, 215). We used the Behavioural Inhibition Scale Behavioural Activation Scale (BISBAS)(394) as a measure of reward and impulsivity. All general procedures and questionnaires were completed prior to starting the tasks.

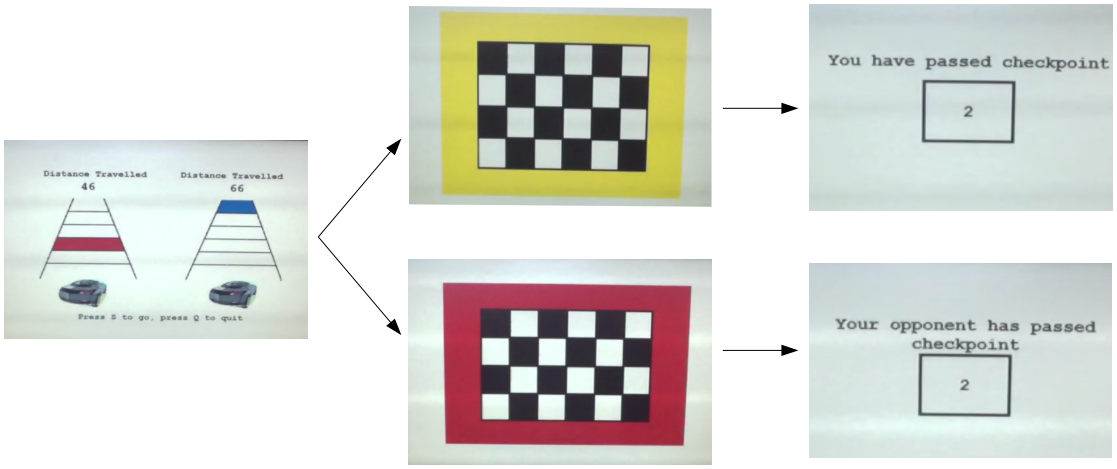
3.2.3 Computer tasks

The battery comprised pre-existing and novel(*) tasks covered processes hypothesised to contribute to goal-directed behaviour: option generation, option selection, planning, evaluation, effort and learning.

Persistence* (Outcome Evaluation to social aversive stimuli):
Participants saw two cars on the screen. They operated one by tapping the 'S' key (faster tapping increased the speed) and were told that they would race against their opponent in the other car other over two races. They were told to press 'Q' at any point if they wished to quit the game. The distances travelled were displayed above the respective cars and every time either car passed a checkpoint, a chequered flag was displayed (yellow for the subject, red for their opponent) followed by the checkpoint number. The game was programmed so that the "opponent" was consistently faster. Each race ended when the opponent finished: the first after forty checkpoints, and the second after eighty checkpoints. If subjects asked "does this race have an

end?" they were told "yes it does end". Other queries received the response: "all I can tell you, is keep tapping on the spacebar to go, or press Q if you wish to quit". The outcome measure was the time spent in the task (maximum 10 minutes).

Figure 3.1: Persistence Task



As outlined, participants tapped 'S' on the keyboard repeatedly to increase the 'distance travelled' shown above each car. Every time either car passed a checkpoint (every 100 units travelled) a checkered flag (on a red background if the opponent passed the checkpoint, or a yellow background for the participant) would be displayed followed by the relevant update screen. As can be seen in the first image the instruction 'press S to go, press Q to quit is permanently displayed' throughout the task. The on-screen S was changed to Spacebar for the task used in the experiment.

Maze* (Option Generation and Selection):

Subjects were presented with fifteen different scenarios (for example "you are alone next to a red house") and asked to verbalise "what you would do next" as quickly as possible. The investigator read each scenario to the participant and responded for the participant, as soon as they started to give an answer. The outcome measure was the mean verbal response time. The scenarios are described in Appendix B.

Phonemic Verbal Fluency (PVF) (423) (Executive Function)

Subjects were told they had a minute to think of as many words beginning with one letter as they could, there were three trials (for words beginning with F, A and S respectively). The outcome variable was the total number of novel words generated across all trial

Iowa Gambling Task (IGT)(99) (Outcome Evaluation)

This task was coded in Pebl(424). Subjects were asked to draw cards from four packs: they were informed that every card would win money, but sometimes they would lose money too. The aim of the task was to work out which packs lost more money, than they earned ("bad packs") and avoid these packs. The outcome variable was the avoidance of a high-win, higher-loss pack in the final twenty-five selections (the most reliable outcome metric(425)).

Extra-dimensional Set-Shift Task (EDSST) (Executive Function)

This task was a modified version of a reversal learning task(426). Subjects were asked to choose between two houses, to find gold coins. They were told the rule for which house was correct would change after a certain number of correct selections. The dimensions were 'orange' versus 'blue' house and 'cat' or 'no cat'. The rule changed after seven correct answers in a row and cycled from 'orange house' to 'cat' to 'blue house' to 'no cat'. When twenty switches were completed, the game ended. Failure to learn the rule after twenty trials terminated the task. The number of set shifts was the outcome measure.

Probabilistic Selection Learning Task (PSLT) (386) (Learning and Updating).

Subjects were asked to learn which stimulus from a pair was correct most often. Three pairs were shown, each with different probabilistic contingencies (Pair AB: A is correct on 80% of trials, B is correct on 20% of trials; Pair CD: C is correct on 70% of trials, B is correct on 30% of trials; Pair EF: E is correct on 60% of trials, B is correct on 40% of trials). The original task separated the outcome into positive and negative learning scores, we totalled the scores to give a general measure of visual associative learning.

Reward Ratio (Outcome evaluation of reward value and effort).

This was a simplified cued reaction time (RT) task(388). Participants were instructed "press spacebar as quickly as possible when you see 'PPPP". They were told there was a practice level of thirty trials, followed by a rewarded task to win points and that faster tapping scored higher. RT $<$ 0.7 x baseline RT scored 10; RT 0.7-1.0 x baseline RT scored 5; RTs slower than baseline scored zero. The task ended when three-hundred points were scored. The outcome measure was a ratio of RT in the rewarded versus unrewarded conditions.

Progressive Ratio (Outcome evaluation of reward value and effort).

This task measured effort for a fixed reward(387). Participants were instructed to compete for a prize by opening boxes; winning meant they could move to the next level. They were told that as the game progressed, the prize would arrive later, requiring them to search for longer to win and move to the next level, and that although the game did end, they would not be informed about the total number of levels. There were eighteen levels in total, for the first nine levels, the winning box arrived within the first five boxes opened, whilst on the second half of the game the winning box was discovered in the last five boxes opened (there were 18 levels). Pressing "Q" allowed them to advance to the next level without winning. The outcome measure was levels reached without pressing "Q" (breakpoint).

Balloon Analogue Risk Task (BART) (381) (Generalised Linear Mixed Model (GLMM) Task)

Subjects were instructed to inflate a series of balloons to earn money, which they could bank at will, but that over-inflation could pop the balloon resulting in loss of any money not banked. Subjects encountered three different coloured balloons, each with a different minimum and maximum value for number of pumps before it popped (two and eight, two and thirty two and two and one hundred and twenty eight in the first thirty trials; two and sixteen, eight and thirty-two and sixteen and sixty-four in the final sixty trials). Each pump gained the subject 5 cents ('trial points'), but also increased the risk of loss. The actual number of pumps before a 'pop' randomly varied on each trial between the minimum and maximum value.

3.2.4 Statistical Analysis and Modelling

All statistical analyses were completed in R(427). Dopaminergic and serotonergic drugs were converted to olanzapine and fluoxetine equivalents derived from meta-analyses(379, 380) or WHO

standard daily dose calculations (for tetrabenazine(428)- taken by one participant only). Premorbid IQ was calculated using Crawford's method(377); we used a demographic method rather than a reading test such as the NART, as prior evidence in the HD population(378, 429, 430) showed that whilst reading ability was preserved prior to motor onset, this declined in association with cognitive deterioration and disease progression thereafter, whilst demographic methods were much less affected by disease progression(378, 429, 430). Variables were analysed for normality: group comparisons employed t-test, or the Wilcoxon signed rank test as appropriate. Linear regression was used to look for task predictors of apathy, initially alone, and subsequently including potential confounding variables (age, premorbid IQ, drug doses, depression and motor impairments) in the HD group. The Bonferroni correction was set at 0.00555 for the task battery, which contained nine tests. The PSLT, Maze, letter fluency and set shifting tasks were performed on a sub-cohort of HD participants (final thirty-seven recruited for the probabilistic selection learning task and final twenty-four recruited for the others) as the tasks were developed later in the testing process; all controls completed the full battery.

Extraction of Behavioural Parameters from the BART

Exploitation of Reward

We created a parameter for exploitation of reward: VE = VG/VO (value-gained/maximum value on offer for each trial – i.e. the randomly generated 'pop' point for that trial) and compared models, with fixed effects of PBA Apathy, PBA Depression, BISBAS subscores, case status (HD versus control), medication (Olanzapine and Fluoxetine) and IQ. As an a priori plan, any relevant variables were included as fixed effects in subsequent models.

Inaccuracy, Excess and Deficient Performance

Each balloon had an optimum number of pumps, which participants learnt by experimentation throughout the task. Making pumps beyond the optimum, led to expected loss (risk of loss x value of loss) exceeding expected gain (chance of gain x value of gain). We calculated the number of pumps above or below this value and expressed these as a proportion of the optimum, to create a parameter for excessive responses (expected loss exceeds expected reward), and deficient responses (optimum value is not maximised). Finally we calculated total variation from the optimum (pumps above or below optimum divided by optimum) to calculate overall inaccuracy.

Task Performance

The outcome of the task is based on total money accrued. We created a parameter - 'reactivity' to compare post-loss (following a popped balloon – lost money) trials with post-reward trials to explore the effect of loss on performance. Final models were compared with and without the addition of potential confounding variables (PBA depression, Olanzapine and Fluoxetine doses, age, gender and TMS).

As participants were not explicitly told the maximum value or risk of 'pop' on the BART, we expected performance to improve over time: the "trial" variable acted as a measure of learning.

GLMM Modelling of Behaviour: BART data

We created random effects generalised linear mixed models using the glmmTMB(431) function in R(427), to explore the effect of relevant variables on performance within the task. The models used binomial distributions for logistic data, and Poisson distributions for count or count-derived data. The random effect term specified by-subject variation, and a zero-inflation correction was included. We added relevant clinical variables (case status, PBA apathy score, and trial) to models initially in isolation, then subsequently added them as separate fixed effects, before looking at models of interactions between variables. Models were compared by weighted Akaike information criterion (AIC) values using bbmle(432), to see which model best fit the data, and provided the most parsimonious explanation as described by Burnham and Anderson, and Bolker et al(433, 434). Briefly, the closer the weight of each model's AIC to 1, the better it explains variation in the data. Models using the AES score failed to converge (AES was essentially completely non-orthogonal with case status), thus PBA apathy score was used.

3.3 Results

There were no significant differences of age or gender between the HD group and controls. The HD group had higher scores on the PBA Apathy, AES, TMS, and drug doses, and lower premorbid IQ. Persistence, Maze and PVF demonstrated the strongest predictive relationships with apathy, and best discriminated between groups (Tables 3.1 & 3.2).

Tests for the assumptions underlying multiple linear regression were all met (Shapiro's test of normality on the residuals was non-significant, as was the Durbin-Watson test for autocorrelation and Goldfeld-Quandt test for heteroscedasticity).

Table 3.1: Demographics

	HD	Controls	
Age	53.92 (33-82)	46.85 (20-75)	
IQ	103.53 (88.75-125.27)	109.73 (89.79-128.51)	*
Gender	26/53 female	17/26 female	
PBA Apathy	5.04 (0-16)	0.5 (0-4)	***
Apathy Evaluation Scale	38.48 (18-72)	18.85 (18-26)	***
PBA Depression	3.08 (0-12)	1.81 (0-9)	
Olanzapine dose (mg)	1.98 (0-41.25)	0	***
Fluoxetine dose (mg)	21.85 (0-146.5)	2.4 (0-22.2)	***
CAG Repeat Length	42.5 (38-50)	-	
Total Motor Score	36.58 (0-89)	1.48 (0-6)	***

* 0.05 ** 0.01 *** 0.001

Table 3.2: Task Comparisons

Task	Cohens d	PBA Apathy R^2	AES R^2
Maze	1.42	0.41	0.32
PVF	1.22	0.26	0.24
Persistence	0.72	0.33	0.25
PSLT	0.73	0.12	0.14
IGT	0.55	0.022	0.077
EDSST	0.38	0.25	0.26
BAS Reward	0.34	0.0063	-0.018
Progressive Ratio	0.31	-0.0020	0.0082
Reward Ratio	0.09	-0.0019	-0.024

Adjusted R^2 from simple regression analysis, Cohen's d from group comparisons

3.3.1 Individual Task Performance

Persistence Task

Higher scores indicate decreased sensitivity to aversive stimuli (failure on the race) . The HD group showed significantly higher scores on this task compared to controls (means HD=1621s, Control=1049s; p=0.0051), and higher scores significantly predicted apathy on the AES (adjusted R^2=0.25, p=0.00021) and PBA apathy (adjusted R^2=0.33, p=0.000018). When confounders were included in the model, this effect remained and the significance survived the Bonferroni correction on both the AES (p=0.0029) and the PBA Apathy (p=0.00032) (Table 3.1, Figures 3.2 & 3.3). In HD, decreased sensitivity to aversive stimulus predicts apathy.

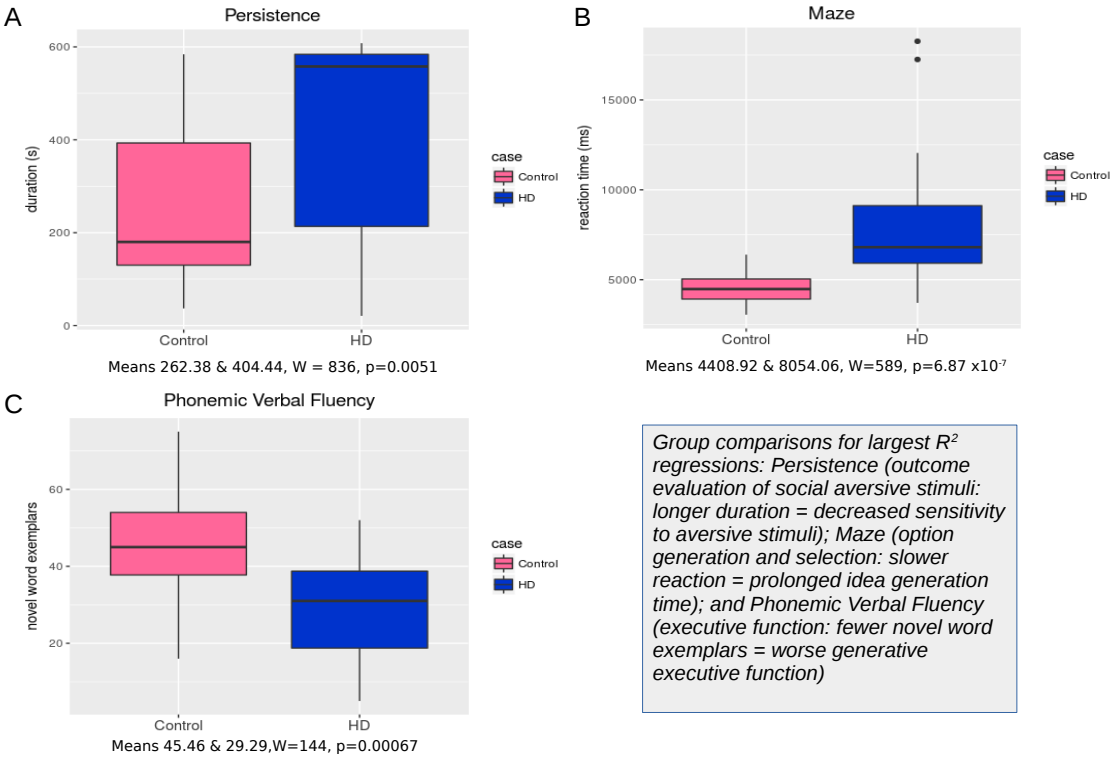
Maze Task

Faster reaction times demonstrate better task-performance (faster idea generation). HD reaction times were almost twice those of controls (means 7792, 4408 ms, p=6.87 x10-7). Slower reaction times had a highly significant predictive relationship with apathy measured by the AES (adjusted R^2=0.35, p=0.0019) and PBA apathy (adjusted R^2=0.43, p=0.00036) (Table 3.2, Figures 3.2 & 3.3). However, the addition of confounders meant the relationship was no longer significant.

PVF

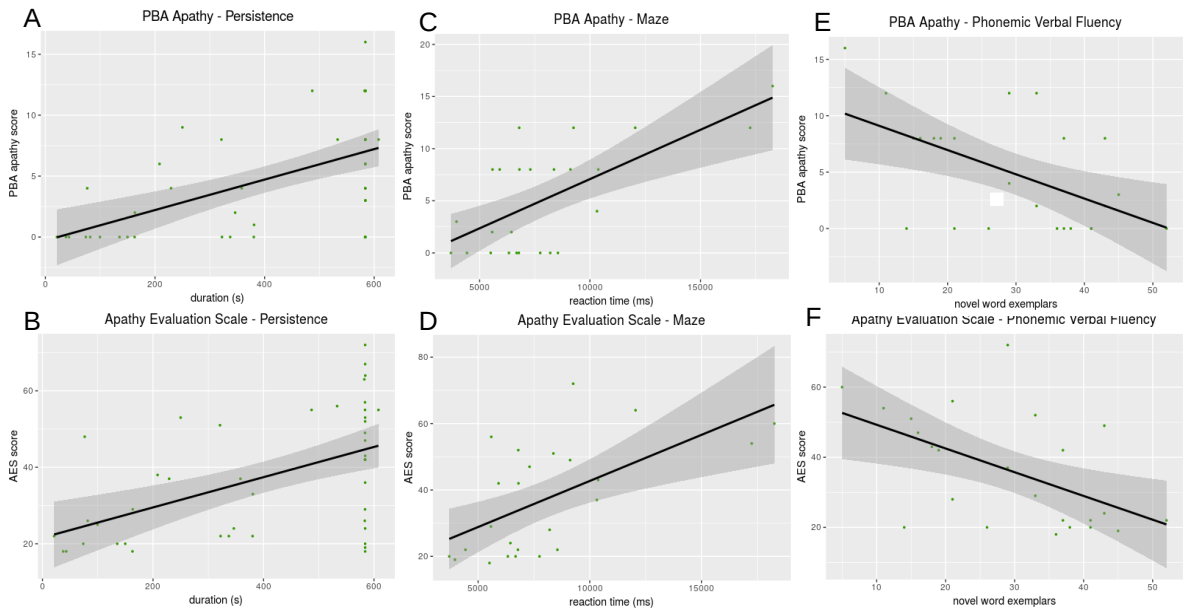
The HD group was markedly impaired compared with controls, generating markedly lower scores (means 33.24 & 45.46; p=0.00017). Regression showed lower scores predicted increasing apathy (AES: adjusted R^2=0.24, p=0.0083; PBA apathy: adjusted R^2=0.26)(Table 3.3, Figures 3.2 & 3.3). However, when the potential confounders were included, significance was lost.

Figure 3.2: Group Comparisons



Group comparisons for largest R^2 regressions: Persistence (outcome evaluation of social aversive stimuli: longer duration = decreased sensitivity to aversive stimuli); Maze (option generation and selection: slower reaction = prolonged idea generation time); and Phonemic Verbal Fluency (executive function: fewer novel word exemplars = worse generative executive function)

Figure 3.3: Prediction of Apathy by Task Performance



Increasing apathy is predicted by increasing insensitivity to social loss (A&B), slower idea generation (C&D), and poorer executive function (E&F).

Table 3.3: Persistence

	Dependent variable:			
	PBA Apathy		**AES**	
	Estimate	P Value	Estimate	P Value
(Intercept)	−0.29	0.81	21.59	0.000016
Persistence	0.013	0.000018	0.040	0.00021
R^2	0.34		0.27	
Adjusted R^2	0.33		0.25	
F Statistic (df = 1; 44)	23.07***		16.37***	

	Estimate	P Value	Estimate	P Value
(Intercept)	−3.67	0.55	31.10	0.16
Persistence	0.011	0.00032	0.033	0.0029
Age	0.077	0.17	0.25	0.21
IQ	−0.020	0.68	−0.27	0.12
TMS	0.031	0.30	0.20	0.07
Olanzapine Equivalent	0.10	0.38	0.34	0.41
Fluoxetine Equivalent	0.0034	0.88	0.027	0.74
PBA Depression	0.11	0.47	−0.073	0.90
R^2	0.49		0.51	
Adjusted R^2	0.39		0.42	
F Statistic (df = 7; 36)	4.98***		5.42***	

Note: Regression Significance $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.005$

Table 3.4: Maze

	Dependent variable:			
	PBA Apathy		**AES**	
	Estimate	P Value	Estimate	P Value
(Intercept)	−2.37	0.24	14.97	0.042
Maze	0.00094	0.00036	0.0028	0.0019
R^2	0.43		0.35	
Adjusted R^2	0.41		0.32	
F Statistic (df = 1; 23)	17.50***		12.27***	

	Estimate	P Value	Estimate	P Value
(Intercept)	−0.31	0.97	49.29	0.08
Maze	0.001	0.055	0.001	0.39
Age	−0.055	0.49	−0.19	0.49
IQ	−0.0031	0.97	−0.23	0.33
TMS	0.084	0.029	0.38	0.0049
Olanzapine Equivalent	0.90	0.047	3.83	0.015
Fluoxetine Equivalent	−0.0051	0.86	0.041	0.66
PBA Depression	−0.0068	0.98	−0.53	0.52
R^2	0.696		0.702	
Adjusted R^2	0.563		0.572	
F Statistic (df = 7; 16)	5.235***		5.392***	

Note: Regression Significance *p<0.05; **p<0.01; ***p<0.005

Table 3.5: Phonemic Verbal Fluency

	Dependent variable:			
	PBA Apathy		**AES**	
	Estimate	P Value	Estimate	P Value
(Intercept)	11.26	0.000065	56.04	0.00000015
PVF	−0.22	0.0069	−0.68	0.0083
R^2	0.29		0.28	
Adjusted R^2	0.26		0.24	
F Statistic (df = 1; 22)	8.89**		8.40**	

	Estimate	P Value	Estimate	P Value
(Intercept)	3.24	0.66	50.57	0.037
PVF	−0.14	0.095	−0.24	0.32
Age	0.014	0.84	−0.16	0.47
IQ	0.018	0.81	−0.12	0.60
TMS	0.073	0.093	0.37	0.010
Olanzapine Equivalent	1.045	0.019	3.94	0.0055
Fluoxetine Equivalent	−0.010	0.74	−0.014	0.88
PBA Depression	−0.096	0.71	−0.45	0.56
R^2	0.69		0.73	
Adjusted R^2	0.55		0.61	
F Statistic (df = 7; 15)	4.80**		5.92***	

Note: Regression Significance *p<0.05; **p<0.01; ***p<0.005
PVF - Phonemic Verbal Fluency

IGT

Higher scores are associated with impaired outcome evaluation. HD participants performed significantly worse than controls (means 3.73 and 5.78 respectively, p=0.037). Impaired performance was only predictive of AES score, and this effect was not maintained with the inclusion of confounding variables (Table 3.6, Figures 3.4 & 3.5)

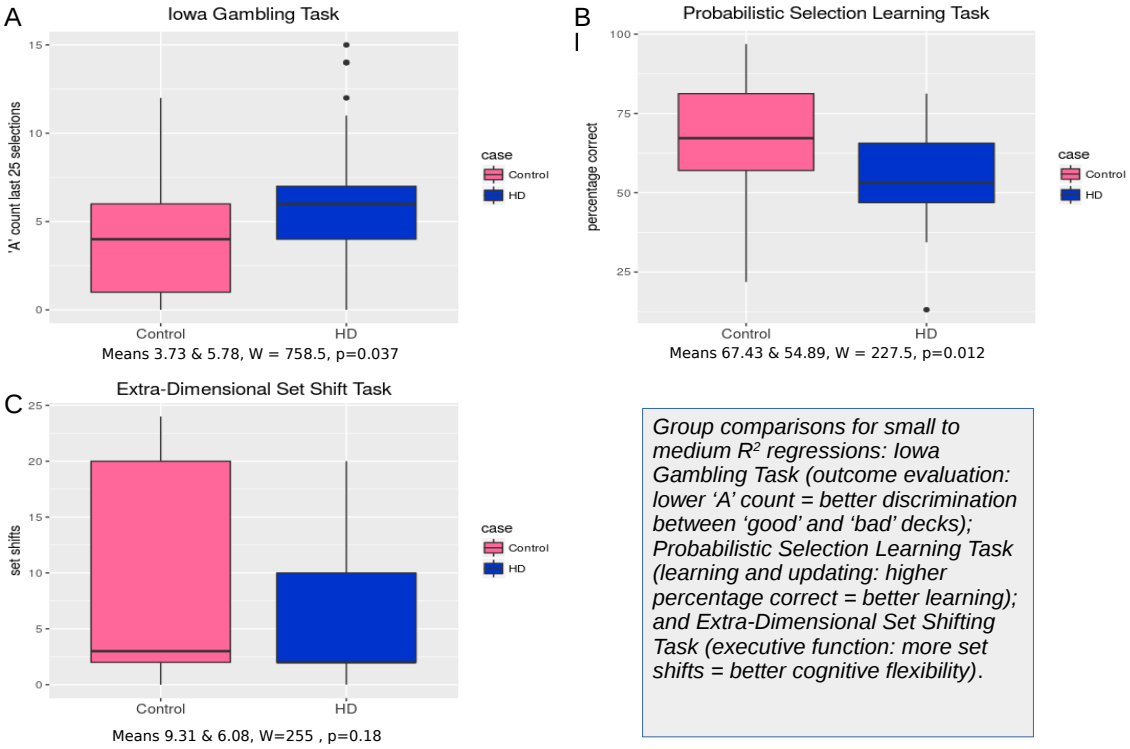
PSLT

The outcome variable was percentage-correct: higher scores demonstrated better learning. The HD group had a smaller mean than the control group (54.89% versus 67.43%, p = 0.012). Simple linear regression analyses demonstrated an initial association with both apathy measures, but this difference did not surpass the Bonferroni correction and did not survive when confounding variables were included (Table 3.7, Figures 3.4 & 3.5).

EDSST

Higher scores indicate more set-switches achieved and hence better executive function. HD patients made fewer set switches compared with controls, (6.08 vs 9.31) but this finding was not significant (p = 0.18). Within the HD group, lower completed set shifts was associated with higher apathy scores, but this relationship failed to maintain significance after inclusion of the confounders in the regression(Table 3.8, Figures 3.4 & 3.5).

Figure 3.4: Group Comparisons



Group comparisons for small to medium R^2 regressions: Iowa Gambling Task (outcome evaluation: lower 'A' count = better discrimination between 'good' and 'bad' decks); Probabilistic Selection Learning Task (learning and updating: higher percentage correct = better learning); and Extra-Dimensional Set Shifting Task (executive function: more set shifts = better cognitive flexibility).

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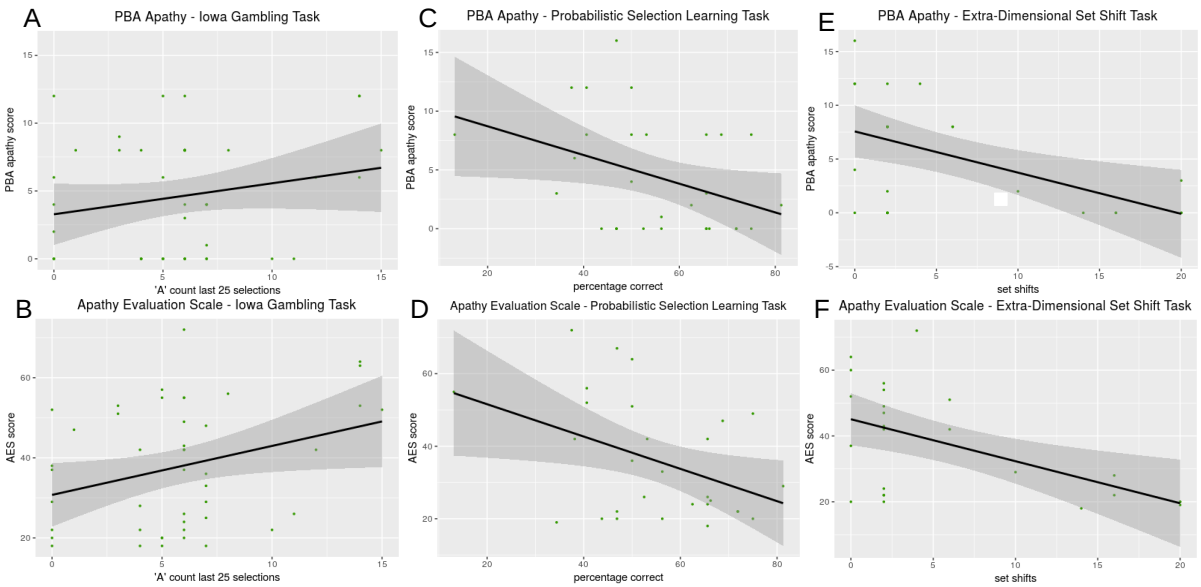
Figure 3.5: Prediction of Apathy by Task Performance



Increasing apathy is predicted by increasing insensitivity to outcome (A&B), poorer learning (C&D), and worse executive function (E&F).

Table 3.6: Iowa Gambling Task

	Dependent variable:			
	PBA Apathy		**AES**	
	Estimate	P Value	Estimate	P Value
(Intercept)	3.28	0.0056	30.73	0.00000000089
IGT	0.23	0.16	1.22	0.036
R^2	0.044		0.098	
Adjusted R^2	0.022		0.077	
F Statistic (df = 1; 43)	2.0031		4.68*	

	Estimate	P Value	Estimate	P Value
(Intercept)	−1.34	0.85	36.98	0.14
IGT	0.20	0.27	0.78	0.21
Age	0.030	0.61	0.099	0.62
IQ	0.0045	0.94	−0.19	0.36
TMS	0.054	0.12	0.25	0.040
Olanzapine Equivalent	0.17	0.17	0.59	0.18
Fluoxetine Equivalent	−0.012	0.63	−0.022	0.81
PBA Depression	0.16	0.41	0.17	0.81
R^2	0.28		0.36	
Adjusted R^2	0.13		0.23	
F Statistic (df = 7; 35)	1.91		2.84*	

Note: Regression Significance $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.005$
IGT - Iowa Gambling Task

Table 3.7: Probabilistic Selection Learning Task

	Dependent variable:			
	PBA Apathy		**AES**	
	Estimate	P Value	Estimate	P Value
(Intercept)	11.15	0.0016	60.50	0.0000060
PSLT	−0.12	0.037	−0.45	0.026
R^2	0.15		0.17	
Adjusted R^2	0.12		0.14	
F Statistic (df = 1; 27)	4.79*		5.53*	

	Estimate	P Value	Estimate	P Value
(Intercept)	4.75	0.49	56.61	0.021
PSLT	−0.014	0.78	−0.11	0.54
Age	0.0036	0.95	0.036	0.86
IQ	−0.039	0.52	−0.30	0.13
TMS	0.080	0.033	0.35	0.0069
Olanzapine Equivalent	1.059	0.0019	2.90	0.0077
Fluoxetine Equivalent	0.0098	0.97	0.037	0.69
PBA Depression	0.14	0.55	−0.052	0.95
R^2	0.58		0.64	
Adjusted R^2	0.44		0.51	
F Statistic (df = 7; 20)	4.019**		4.97***	

Note: Regression Significance *p<0.05; **p<0.01; ***p<0.005
PSLT - Probabilistic Selection Learning Task

Table 3.8: Extra-dimensional Set Shift Task

	Dependent variable:			
	PBA Apathy		**AES**	
	Estimate	P Value	Estimate	P Value
(Intercept)	7.57	0.0000014	45.080	0.000000000029
EDSST	−0.38	0.0061	−1.28	0.0051
R^2	0.28		0.29	
Adjusted R^2	0.25		0.26	
F Statistic (df = 1; 23)	9.13**		9.58**	

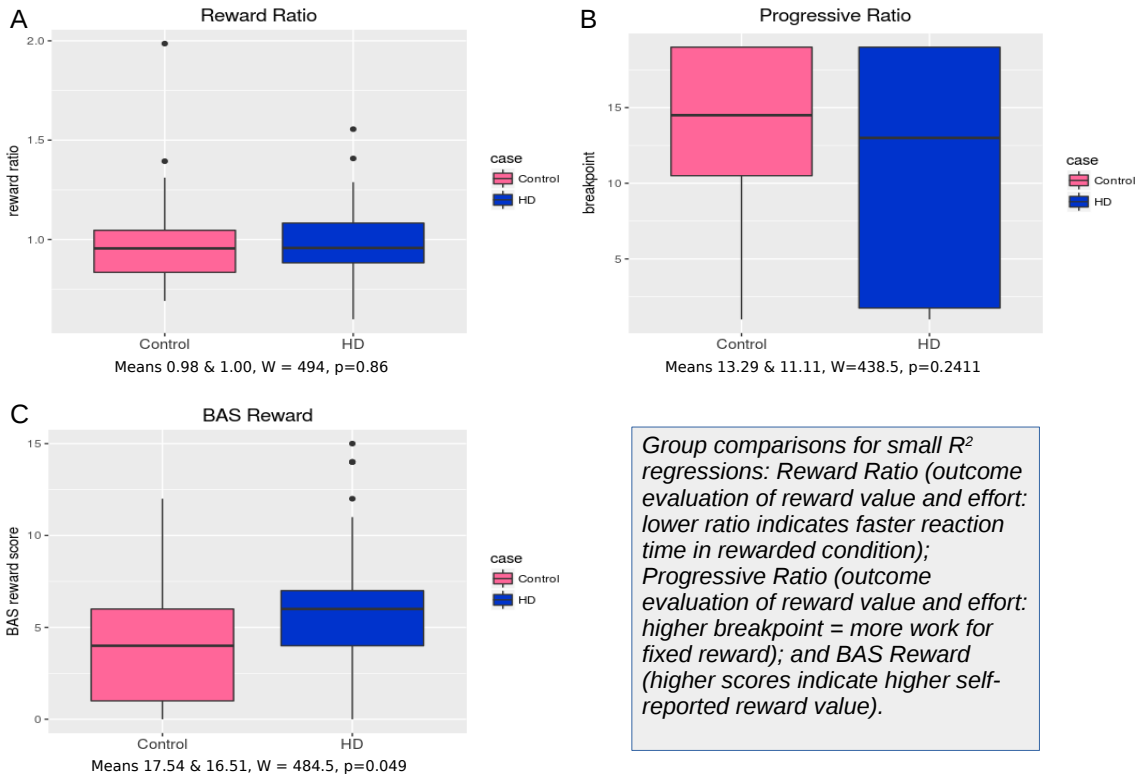
	Estimate	P Value	Estimate	P Value
(Intercept)	5.84	0.48	56.59	0.034
EDSST	−0.074	0.63	−0.25	0.59
Age	0.014	0.86	−0.11	0.65
IQ	−0.051	0.53	−0.26	0.28
TMS	0.10	0.022	0.39	0.0049
Olanzapine Equivalent	1.19	0.017	4.15	0.0066
Fluoxetine Equivalent	0.010	0.74	0.065	0.48
PBA Depression	−0.081	0.77	−0.58	0.49
R^2	0.62		0.69	
Adjusted R^2	0.45		0.56	
F Statistic (df = 7; 16)	3.73*		5.17***	

Note: Regression Significance *p<0.05; **p<0.01; ***p<0.005
EDSST -
Extra-dimensional Set Shift Task

Measures of Reward and Effort: BAS Reward, Progressive Ratio, Reward Ratio task

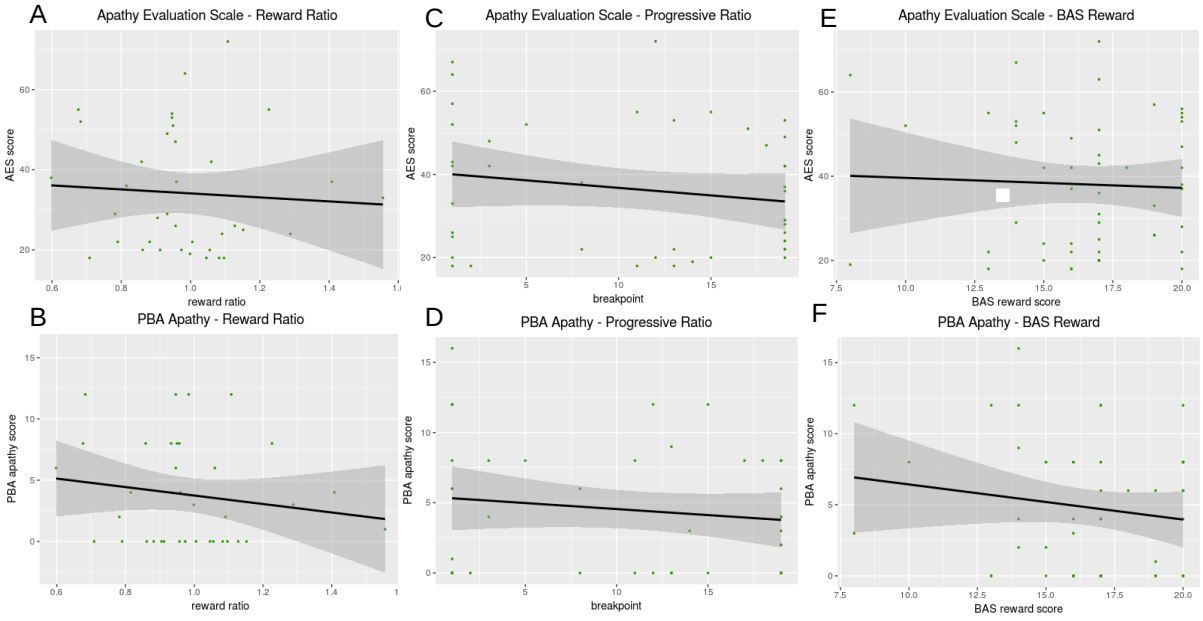
The BAS Reward score was slightly lower (showing reduced sensitivity to reward) in HD compared with controls (17.5, 16.5, p= 0.049), but this did not surpass Bonferroni, and was not predictive of apathy in the models. Neither of the other measures (Progressive Ratio, Reward Ratio) showed group differences or predicted apathy in the Poisson GLMs (Tables 3.9, 3.10, 3.11, Figures 3.6 & 3.7). Negative Binomial GLMs were used when the assumptions underlying linear regression were not met, as stated in the tables.

Figure 3.6: Group Comparisons



Group comparisons for small R^2 regressions: Reward Ratio (outcome evaluation of reward value and effort: lower ratio indicates faster reaction time in rewarded condition); Progressive Ratio (outcome evaluation of reward value and effort: higher breakpoint = more work for fixed reward); and BAS Reward (higher scores indicate higher self-reported reward value).

Figure 3.7: Prediction of Apathy by Task Performance



Regressions all non-significant. Graphs suggest increasing apathy is predicted by slowing reaction time in rewarded conditions(A&B), reduced effort for a fixed reward (C&D), and lower self-reported reward value (E&F).

Table 3.9: BAS Reward

	Dependent variable:			
	PBA Apathy		**AES**	
	negative binomial		*OLS*	
	Estimate	P Value	Estimate	P Value
(Intercept)	2.28	0.026	41.99	0.0017
BAS Reward	−0.043	0.41	−0.24	0.75
R^2			0.0020	
Adjusted R^2			−0.018	
F Statistic			0.10 (df = 1; 49)	
Log Likelihood	−136.026			
Akaike Inf. Crit.	276.051			
Pseudo R^2	0.0097			

	Estimate	P Value	Estimate	P Value
(Intercept)	3.22	0.20	80.51	0.0077
BAS Reward	−0.081	0.17	−0.89	0.20
Age	0.0047	0.77	0.0082	0.97
IQ	−0.018	0.29	−0.40	0.041
TMS	0.031	).00037	0.357	0.00094
Olanzapine Equivalent	0.055	0.097	0.60	0.12
Fluoxetine Equivalent	−0.0072	0.33	−0.01670.84	
PBA Depression	−0.0048	0.92	−0.28	0.61
R^2			0.41	
Adjusted R^2			0.31	
F Statistic			4.14^{***} (df = 7; 41)	
Log Likelihood	−121.36			
Akaike Inf. Crit.	258.71			
Pseudo R^2	0.23			

Note: *p<0.05; **p<0.01; ***p<0.005

Table 3.10: Reward Ratio

	Dependent variable:			
	PBA Apathy		**AES**	
	OLS		*negative binomial*	
	Estimate	P Value	Estimate	P Value
(Intercept)	7.20	0.052	3.67	$<2\text{x}10^{-16}$
Reward Ratio	−3.46	0.34	−0.14	0.70
R^2	0.026			
Adjusted R^2	−0.0019			
F Statistic	0.93 (df = 1; 35)			
Log Likelihood			−149.83	
Akaike Inf. Crit.			303.65	
Pseudo R^2			0.0042	

	Estimate	P Value	Estimate	P Value
(Intercept)	4.4	0.63	4.078	$1.12\text{x}10^{-7}$
Reward Ratio	−0.37	0.92	0.098	0.75
Age	0.061	0.42	0.0060	0.33
IQ	−0.051	0.42	−0.012	0.024
TMS	0.050	0.21	0.0081	0.014
Olanzapine Equivalent	0.14	0.32	0.013	0.21
Fluoxetine Equivalent	0.0023	0.93	0.00063	0.77
PBA Depression	−0.047	0.82	−0.0085	0.62
R^2	0.27			
Adjusted R^2	0.087			
F Statistic	1.48 (df = 7; 28)			
Log Likelihood			−134.62	
Akaike Inf. Crit.			285.24	
Pseudo R^2			0.45	

Note: *p<0.05; **p<0.01; ***p<0.005

Table 3.11: Progressive Ratio

	Dependent variable:			
	PBA Apathy		**AES**	
	negative binomial		*OLS*	
	Estimate	P Value	Estimate	P Value
(Intercept)	1.70	$3.44\text{x}10^{-16}$	40.39	$2.78\text{x}10^{-12}$
Progressive Ratio	−0.019	0.48	−0.36	0.25
R^2			0.031	
Adjusted R^2			0.0082	
F Statistic			1.36 (df = 1; 42)	
Log Likelihood	−113.61			
Akaike Inf. Crit.	231.21			
Pseudo R^2	0.0097			

	Estimate	P Value	Estimate	P Value
(Intercept)	1.32	0.54	59.025	0.014
Progressive Ratio	0.0027	0.93	−0.15	0.62
Age	−0.00069	0.97	−0.067	0.77
IQ	−0.011	0.57	−0.29	0.15
TMS	0.031	0.0083	0.33	0.013
Olanzapine Equivalent	0.065	0.093	0.71	0.098
Fluoxetine Equivalent	−0.0077	0.39	−0.027	0.77
PBA Depression	0.024	0.69	0.075	0.91
R^2			0.38	
Adjusted R^2			0.25	
F Statistic			2.99* (df = 7; 34)	
Log Likelihood	−100.93			
Akaike Inf. Crit.	217.85			
Pseudo R^2	0.20			

Note: *p<0.05; **p<0.01; ***p<0.005

3.3.2 Generalised Linear Mixed Models of Behaviour – Balloon Analogue Risk Task

Exploitation of Reward

We compared models with fixed effects of case status, PBA depression, PBA apathy, IQ, medication, and BISBAS subscores. The best model (weight 0.559), showed a positive effect of IQ (p=0.011) on reward exploitation. Notably, IQ was lower in the HD group compared with controls: IQ was included as a fixed effect in all subsequent models. The model of case status demonstrated a trend-level effect of reduced exploitation of reward(AIC 8357.8, Estimate -0.29, Standard Error 0.15, Z Score -1.94, p=0.052), none of the other models approached a significant effect (Tables 3.12 & 3.13, Figure 3.8).

Excessive Responding

Model comparison yielded 2 models with almost equivalent weights – PBA apathy score, case and IQ as fixed effects (weight 0.305), and a second model that also included a fixed effect of trial (weight 0.223). Both models showed a negative effect of case (HD subjects had less excessive responding than controls: p= 0.038 in both models), but higher apathy scores resulted in more excessive responding (p= 0.012 in both models), there was no significant effect of trial. Including the BISBAS sub scores (reward, drive, fun-seeking, and inhibition) as fixed effects did not improve the Apathy/Case/IQ model. Repeating the modelling comparison without the random effects term, showed the best model (weight 0.971) now included the behavioural inhibition score, which had a negative association with excessive responses ($p=9.02 \times 10^{-5}$), but the effect of apathy ($p=3.85 \times 10^{-9}$) and case ($p=1.85 \times 10^{-7}$) on excessive responding was unchanged: the random effects term accounts for individual variation in risk-taking (Tables 3.14 - 3.19, Figure 3.8).

Deficient Responding and Inaccuracy

Model comparisons demonstrated that both deficient responding and inaccuracy were best explained by models including trial as a fixed effect in isolation. Deficient and inaccurate responding reduced with increasing trial ($p=9.9 \times 10^{-10}$, and 4.88×10^{-8} respectively) and increasing IQ (p=0.0090 and 0.0051 respectively)(Tables 3.20 - 3.23, Figure 3.8). Apathy did not have a significant effect in any of the models that included it as a variable.

Figure 3.8: Generalised Linear Mixed Models - Initial Parameters

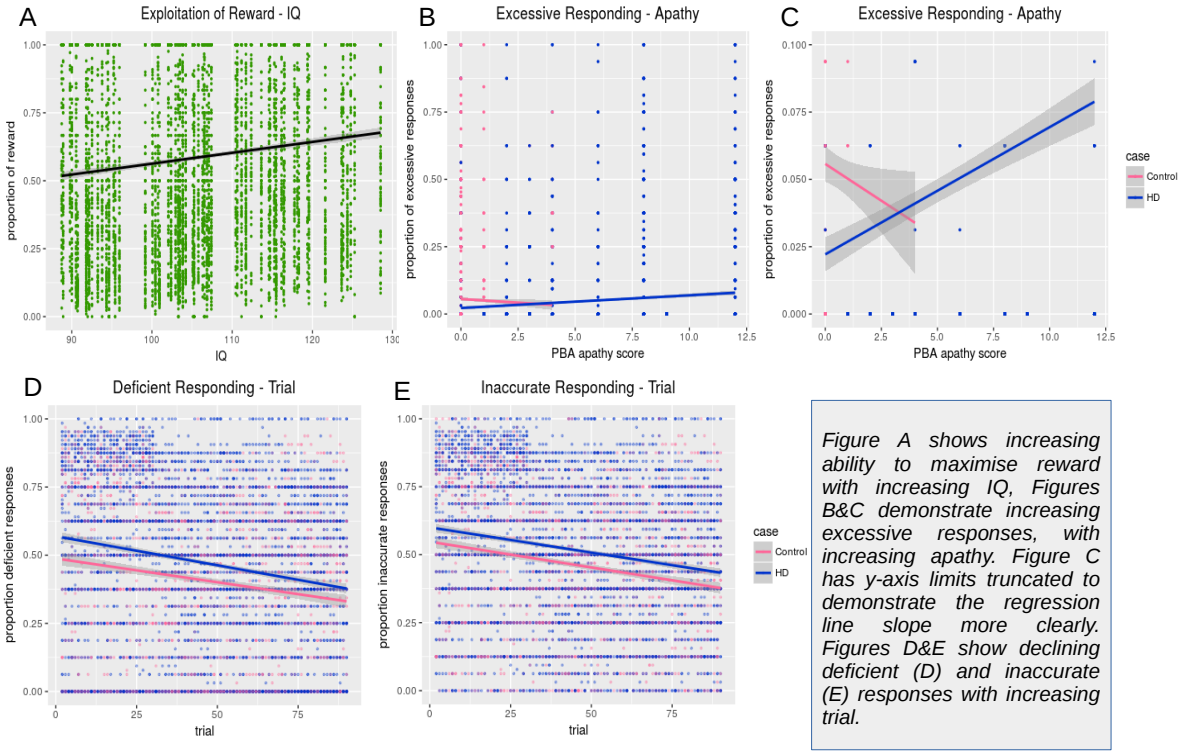


Figure A shows increasing ability to maximise reward with increasing IQ, Figures B&C demonstrate increasing excessive responses, with increasing apathy. Figure C has y-axis limits truncated to demonstrate the regression line slope more clearly. Figures D&E show declining deficient (D) and inaccurate (E) responses with increasing trial.

Table 3.12: Exploitation of Reward: Model Selection

	dAIC	df	weight
Model Exploit IQ	0.0	4	0.559
Model Exploit Case	2.5	4	0.162
Model Exploit Depression	4.7	4	0.054
Model Exploit Olanzapine	5.0	4	0.046
Model Exploit BAS Reward	5.1	4	0.044
Model Exploit BAS Funseeking	6.0	4	0.029
Model Exploit BIS	6.0	4	0.028
Model Exploit Fluoxetine	6.1	4	0.027
Model Exploit Apathy	6.1	4	0.026
Model Exploit BAS Drive	6.1	4	0.026

'BAS Reward' - Behavioural Activation Scale- Reward Subscale,
'BAS Funseeking' - Behavioural Activation Scale- Funseeking Subscale,
'BAS Drive' - Behavioural Activation Scale- Drive Subscale,
'BIS' - Behavioural Inhibition Scale

Table 3.13: Model Exploit IQ

Random Effects:		Variance:	0.31	Std.Dev:	0.56	
	Estimate	Std. Error	Z Value	P Value	CI Lower	CI Upper
(Intercept)	-1.43	0.72	-1.99	0.046	-2.83	-0.024
IQ	0.017	0.0067	2.54	0.011	0.0039	0.030

Table 3.14: Excessive Responding: Model Selection

	dAIC	df	weight
Model Excess Case+Apathy	0.0	6	0.305
Model Excess Case+Apathy+Trial	0.6	7	0.223
Model Excess Case:Apathy	0.9	7	0.196
Model Excess Apathy	2.2	5	0.099
Model Excess Case:Apathy:Trial	2.6	11	0.082
Model Excess Trial	3.5	5	0.053
Model Excess Case	4.0	5	0.041

'+' denotes additional fixed effect, ' : ' denotes interaction

Table 3.15: Model Excess Pump Case+Apathy

Random Effects:		Variance:	0.77	Std.Dev:	0.89	
	Estimate	Std. Error	Z Value	P Value	CI Lower	CI Upper
(Intercept)	-3.37	0.22	-15.53	$<2x10^{-16}$	-3.79	-2.94
Case	-0.66	0.32	-2.078	0.038	-1.28	-0.037
PBA Apathy	0.093	0.037	2.51	0.012	0.020	0.17
IQ	0.22	0.13	1.62	0.10	-0.045	0.48

Table 3.16: Model Excess Pump Case+Apathy+Trial

Random Effects:		Variance:	0.77	Std.Dev:	0.89	
	Estimate	Std. Error	Z Value	P Value	CI Lower	CI Upper
(Intercept)	-3.49	0.24	-14.43	$<2x10^{-16}$	-3.97	-3.019
Case	-0.66	0.32	-2.078	0.038	-1.28	-0.037
PBA Apathy	0.093	0.037	2.51	0.012	0.020	0.17
Trial	0.0026	0.0022	1.17	0.24	-0.0018	0.0070
IQ	0.22	0.13	1.62	0.10	-0.044	0.48

Table 3.17: Excessive Responding BISBAS: Model Selection

	dAIC	df	weight
Model Excess Case+Apathy	0.0	6	0.620
Model Excess Case+Apathy+BIS	3.3	6	0.116
Model Excess Case+Apathy+BAS Reward	3.5	6	0.109
Model Excess Case+Apathy+BAS Drive	4.1	6	0.079
Model Excess Case+Apathy+BAS Funseeking	4.2	6	0.076

'BAS Reward' - Behavioural Activation Scale- Reward Subscale,
'BAS Funseeking' - Behavioural Activation Scale- Funseeking Subscale,
'BAS Drive' - Behavioural Activation Scale- Drive Subscale,
'BIS' - Behavioural Inhibition Scale
'+' denotes additional fixed effect, ' : ' denotes interaction

Table 3.18: Excessive Responding BISBAS: Model Selection: No Random Effect Term

	dAIC	df	weight
Model NoRandom Case+Apathy+BIS	0.0	4	0.971
Model NoRandom Case+Apathy+BAS Reward	5.1	4	0.0710
Model NoRandom Case+Apathy	12.7	3	0.0016
Model NoRandom Case+Apathy+BAS Drive	14.6	4	<0.001
Model NoRandom Case+Apathy+BAS Funseeking	14.8	4	<0.001

'BAS Reward' - Behavioural Activation Scale- Reward Subscale,

'BAS Funseeking' - Behavioural Activation Scale- Funseeking Subscale,

'BAS Drive' - Behavioural Activation Scale- Drive Subscale,

'BIS' - Behavioural Inhibition Scale

'+' denotes additional fixed effect, ' : ' denotes interaction

Table 3.19: Model NoRandom Case+Apathy+BIS

	Estimate	Std. Error	Z Value	P Value	CI Lower	CI Upper
(Intercept)	-1.25	0.11	-11.64	$<2\text{x}10^{-16}$	-1.46	-1.039
PBA Apathy	0.046	0.0079	5.89	$3.85\text{x}10^{-9}$	0.031	0.062
Case	-0.37	0.071	-5.21	$1.85\text{x}10^{-7}$	-0.51	-0.23
BIS	-0.018	0.0045	-3.92	$9.02\text{x}10^{-5}$	-0.027	-0.0088

'BIS' - Behavioural Inhibition Scale

Table 3.20: Deficient Responding: Model Selection

	dAIC	df	weight
Model Deficient Trial	0.0	5	0.639
Model Deficient Apathy+Case+Trial	1.2	7	0.350
Model Deficient Apathy:Case:Trial	8.2	11	0.011
Model Deficient Case	36.1	5	<0.001
Model Deficient Apathy+Case	36.7	6	<0.001
Model Deficient Apathy	37.2	5	<0.001
Model Deficient Apathy:Case	38.6	7	<0.001

'+' denotes additional fixed effect, ' : ' denotes interaction

Table 3.21: Model Deficient Trial

Random Effects:		Variance:	0.065	Std.Dev:	0.26	
	Estimate	Std. Error	Z Value	P Value	CI Lower	CI Upper
(Intercept)	-0.64	0.048	-13.43	$<2\text{x}10^{-16}$	-0.73	-0.55
Trial	-0.0045	0.00073	-6.11	$9.9\text{x}10^{-10}$	-0.0059	-0.0030
IQ	-0.093	0.036	-2.61	0.0090	-0.16	-0.023

Table 3.22: Inaccuracy: Model Selection

	dAIC	df	weight
Model Inaccuracy Trial	0.0	5	0.6889
Model Inaccuracy Apathy+Case+Trial	1.7	7	0.3017
Model Inaccuracy Apathy:Case:Trial	8.6	11	0.0095
Model Inaccuracy Case	27.5	5	<0.001
Model Inaccuracy Apathy+Case	29.5	6	<0.001
Model Inaccuracy Apathy	29.5	5	<0.001
Model Inaccuracy Apathy:Case	31.4	7	<0.001

'+' denotes additional fixed effect, ' : ' denotes interaction

Table 3.23: Model Inaccuracy Trial

Random Effects:		Variance:	0.01675	Std.Dev:	0.1294	
	Estimate	Std. Error	Z Value	P Value	CI Lower	CI Upper
(Intercept)	-0.54	0.038	-14.20	$<2x10^{-16}$	-0.62	-0.47
Trial	-0.0038	0.00069	-5.46	$4.88x10^{-8}$	-0.0051	-0.0024
IQ	-0.066	0.024	-2.80	0.0051	-0.11	-0.020

Task Performance

We compared models looking at the effects of apathy, post-reward/post-loss and trial on task performance (trial points scored) in HD subjects and controls. Comparing case models with individual fixed effects, multiple fixed effects, and interactions, demonstrated the best model to be the most complex interaction model (apathy:reactivity:trial - weight 1.0). This model showed a positive effect of apathy on trial points (apathetic individuals scored more points, p=0.021), a positive interaction of post-loss trial and apathy (apathetic individuals scored more points on post-punishment trials, $p<2x10^{-16}$), a negative interaction of apathy and trial (increased apathy resulted in deteriorating performance over time, $p= 3.72x10^{-14}$) and a negative interaction between apathy, reactivity and trial (increasing apathy resulted in deteriorating performance over time on post-punishment trials, $p=1.56\ x10^{-13}$).

To explore this deterioration in performance, we looked at models of pop probability: the best model (weight 0.5003) had fixed effects of reactivity, apathy and IQ. The probability of pop increased with apathy (p= 0.016) and on post-loss trials (p= 0.0007).

There were only low levels of apathy in the control group, nevertheless, including apathy improved the model (weight 1.0). However, the apathy in the control group was clearly different to that in HD: on post loss trials, performance improved over time in the control group with increased apathy (Tables 3.24 - 3.29, Figure 3.9).

Comparing models using likelihood ratio tests, none of the Task Performance models were improved by adding age, drug doses, TMS or PBA depression scores.

Figure 3.9: Generalised Linear Mixed Models – Task Performance and Pop Probability

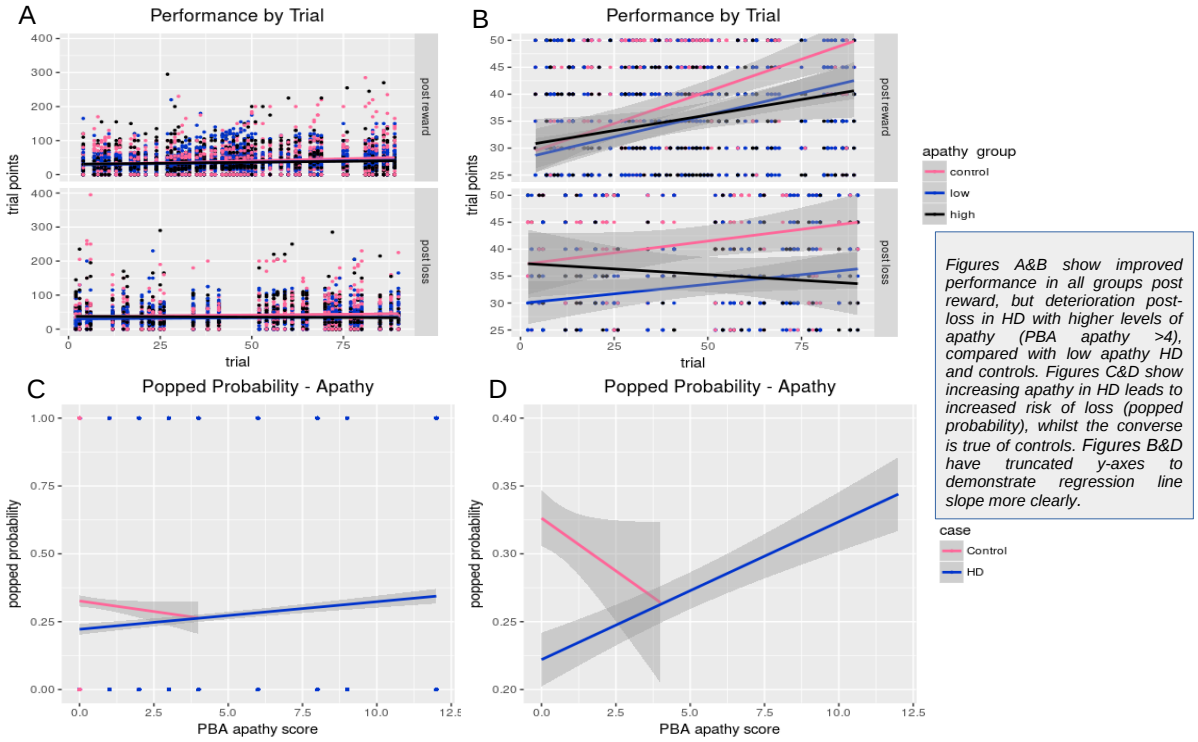


Table 3.24: Task Performance: Model Selection

	dAIC	df	weight
Model Performance Apathy:Reactivity:Trial	0.0	11	1
Model Performance Apathy+Reactivity+Trial	340.3	7	<0.001
Model Performance Trial	347.9	5	<0.001
Model Performance Apathy:Reactivity	1289.2	7	<0.001
Model Performance Apathy:Reactivity	1293.2	6	<0.001
Model Performance Reactivity	1294.8	5	<0.001
Model Performance Apathy	1311.1	5	<0.001

'+' denotes additional fixed effect, ' : ' denotes interaction

Table 3.25: Model Performance Apathy:Reactivity:Trial

Random Effects:		Variance:	0.21	Std.Dev:	0.46	
	Estimate	Std. Error	Z Value	P Value	CI Lower	CI Upper
(Intercept)	1.36	$7.024\text{x}10^{-1}$	1.93	0.053	-0.019	2.73
PBA Apathy	$3.72\text{x}10^{-2}$	$1.61\text{x}10^{-2}$	2.31	0.021	0.0056	0.069
Reactivity	$-8.71\text{x}10^{-3}$	$1.72\text{x}10^{-2}$	-0.51	0.61	-0.042	0.025
Trial	$5.22\text{x}10^{-3}$	$2.053\text{x}10^{-4}$	25.40	$< 2\text{x}10^{-16}$	0.0048	0.0056
IQ	$1.99\text{x}10^{-2}$	$6.62\text{x}10^{-3}$	3.005	0.0027	0.0069	0.033
PBA Apathy:Reactivity	$2.24\text{x}10^{-2}$	$2.67\text{x}10^{-3}$	8.39	$< 2\text{x}10^{-16}$	0.017	0.028
PBA Apathy:Trial	$-2.52\text{x}10^{-4}$	$3.33\text{x}10^{-5}$	-7.58	$3.72\text{x}10^{-14}$	-0.00032	-0.00019
Reactivity:Trial	$5.59\text{x}10^{-6}$	$3.098\text{x}10^{-4}$	0.018	0.99	-0.00060	0.00061
PBA Apathy:Reactivity:Trial	$-3.64\text{x}10^{-4}$	$4.93\text{x}10^{-5}$	-7.38	$1.56\text{x}10^{-13}$	-0.00046	-0.00027

'+' denotes additional fixed effect, ' : ' denotes interaction

Table 3.26: Popped: Model Selection

	dAIC	df	weight
Model Popped Apathy+Reactivity	0.0	6	0.5003
Model Popped Apathy+Reactivity+Trial	1.9	7	0.1971
Model Popped Apathy:Reactivity	1.9	7	0.1906
Model Popped Reactivity	3.4	5	0.0897
Model Popped Apathy:Reactivity:Trial	6.7	11	0.0175
Model Popped Apathy	9.4	5	0.0045
Model Popped Trial	14.9	5	<0.001

'+' denotes additional fixed effect, ' : ' denotes interaction

Table 3.27: Model Popped Apathy+Reactivity

Random Effects:		Variance:	0.39	Std.Dev:	0.62	
	Estimate	Std. Error	Z Value	P Value	CI Lower	CI Upper
(Intercept)	-3.53	1.0027	-3.53	0.00042	-5.50	-1.57
PBA Apathy	0.056	0.023	2.40	0.016	0.010	0.10
Reactivity	0.25	0.075	3.39	0.00070	0.11	0.40
IQ	0.020	0.0095	2.11	0.035	0.0015	0.039

Table 3.28: Task Performance Controls: Model Selection

	dAIC	df	weight
Model PerformanceControl Apathy:Reactivity:Trial	0.0	11	1
Model PerformanceControl Reactivity:Trial	46.4	7	<0.001
Model PerformanceControl Reactivity+Trial	278.3	6	<0.001
Model PerformanceControl Apathy+Reactivity+Trial	280.2	7	<0.001
Model PerformanceControl Trial	341.8	5	<0.001
Model PerformanceControl Apathy:Reactivity	915.3	7	<0.001
Model PerformanceControl Reactivity	936.7	5	<0.001
Model PerformanceControl Apathy+Reactivity	938.6	6	<0.001
Model PerformanceControl Apathy	1040.3	5	<0.001

'+' denotes additional fixed effect, ' : ' denotes interaction

Table 3.29: Task Performance Controls, No PBA Apathy: Model Selection

	dAIC	df	weight
Model PerformanceControl Reactivity:Trial	0.0	7	1
Model PerformanceControl Reactivity+Trial	231.9	6	<0.001
Model PerformanceControl Trial	295.4	5	<0.001
Model PerformanceControl Reactivity	890.3	5	<0.001

'+' denotes additional fixed effect, ' : ' denotes interaction

Table 3.30: Model PerformanceControl Apathy:Reactivity:Trial

Random Effects:		Variance:	0.13	Std.Dev:	0.36	
	Estimate	Std. Error	Z Value	P Value	CI Lower	CI Upper
(Intercept)	2.98	0.833.59	0.00033	1.36	4.61	
PBA Apathy	0.025	0.060	0.41	0.68	-0.094	0.14
Reactivity	0.29	0.016	18.38	$< 2\text{x}10^{-16}$	0.26	0.32
Trial	0.0055	0.00019	28.84	$< 2\text{x}10^{-16}$	0.0051	0.0059
IQ	0.0073	0.0075	0.98	0.33	-0.0074	0.022
PBA Apathy:Reactivity	-0.066	0.012	-5.45	$5.13\text{x}10^{-8}$	-0.090	-0.042
PBA Apathy:Trial	-0.00063	0.00015	-4.095	$4.22\text{x}10^{-5}$	-0.00093	-0.00033
Reactivity:Trial	-0.0044	0.00029	-15.70	$< 2\text{x}10^{-16}$	-0.0049	-0.0038
PBA Apathy:Reactivity:Trial	0.00071	0.00023	3.025	0.0025	0.00025	0.0012

'+' denotes additional fixed effect, ' : ' denotes interaction

3.3.3 Exploratory Analyses

Performance on the Maze task predicted PVF and EDSST performance, and Persistence performance predicted IGT performance.

To assess validity of the reward based measures, we compared scores on the BAS reward, Progressive Ratio and Reward Ratio tasks using GLMs (assumptions underlying linear regression were not met) in the control group. Higher breakpoint on progressive ratio and faster reaction time on the reward ratio task were significantly associated (AIC 183.54, estimate -0.88, p = 0.012), higher breakpoint was also associated with higher scores on the BAS reward (AIC 185.73, estimate 0.038, p = 0.0438), but there was no association between the Reward Ratio and BAS reward score (AIC 141.71, estimate -0.068, p = 0.72).

Table 3.31: Maze and Executive Function

	Dependent variable:			
	EDSST *negative binomial*		PVF *negative binomial*	
	Estimate	P Value	Estimate	P Value
(Intercept)	3.54	$9.03\text{x}10^{-9}$	4.14	$<2\text{x}10^{-16}$
Maze	−0.00025	0.0015	−0.00010	$1.38\text{x}10^{-5}$
Log Likelihood	−67.33		−89.42	
Akaike Inf. Crit.	138.67		182.85	
Pseudo R^2	0.32		0.42	

PVF=Phonemic Verbal Fluency, EDSST = Extra Dimensional Set Shift Task

Table 3.32: Generalised Linear Models - Persistence and Task Battery

	Dependent variable:									
	PVF		EDSST		PSLT Negative		BAS Reward		Progressive Ratio	
	Estimate *negative binomial*	P Value	Estimate *negative binomial*	P Value	Estimate *negative binomial*	P Value	Estimate *negative binomial*	P Value	Estimate *negative binomial*	P Value)
(Intercept)	3.60	$<2\text{x}10^{-16}$	2.35	$3.38\text{x}10^{-5}$	4.16	$<2\text{x}10^{-16}$	5.86	$<2\text{x}10^{-16}$	2.18	$2.24\text{x}10^{-13}$
Persistence	−0.00037	0.33	−0.0014	0.26	−0.00040	0.24	0.0086	0.81	0.00055	0.40
Log Likelihood	−80.88		−63.55		−127.71		−317.13		−144.65	
Akaike Inf. Crit.	165.77		131.10		259.43		638.25		293.29	
Pseudo R^2	0.043		0.048		0.039		0.0014		0.013	

PVF=Phonemic Verbal Fluency, EDSST = Extra Dimensional Set Shift Task, PSLT Negative = Probabilistic Selection Learning Task - learning from negative feedback,
PSLT Negative = Probabilistic Selection Learning Task - learning from negative feedback, BAS Reward - Behavioural Activation Scale, Reward subscore

Table 3.33: Multiple Linear Regressions - Persistence and Task Battery

	Dependent variable:					
	Maze		PSLT		Reward Ratio	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	6,720.93	$3.98\text{x}10^{-6}$	64.086	$1.29\text{x}10^{-10}$	0.95	$1.69\text{x}10^{-14}$
Persistence	1.079	0.65	−0.022	0.12	$7.79\text{x}10^{-5}$	0.64
R^2	0.010		0.086		0.0067	
Adjusted R^2	−0.039		0.052		−0.023	
F Statistic	0.21 (df = 1; 20)		2.55 (df = 1; 27)		0.22 (df = 1; 33)	

PSLT = Probabilistic Selection Learning Task - learning from feedback

3.4 Discussion

Our main finding was that decreased sensitivity to aversive stimuli was associated with apathy in HD. Furthermore, deficits in reward sensitivity or altered reward-effort calculations were not predictive of apathy in HD. To our knowledge, this is the first conclusive demonstration that apathy is associated with impaired responses to aversive stimuli in any disease. This deficit was seen on tasks of competitive failure (Persistence), and monetary loss (BART): increasing apathy was associated with more popped balloons, increased excessive responding and poorer performance on BART over time, post-loss. The Persistence deficit is unlikely to be explained by impaired memory for instructions, or executive function (such as attention) as the instructions are displayed on screen at all times, and no association with executive function tasks was seen. Furthermore adding IQ to the regression models and GLMMs did not change the effects of apathy. Risk-taking in the BART was accounted for by the random effects: the altered performance of apathetic individuals with HD was not related to impulsivity. Confounding variables (age, medication, TMS and depression score) did not improve the GLMMs.

Altered response to aversive stimuli has been found in other neurological diseases(254, 421, 435, 436) and also HD(88, 437). However, the prior work in HD did not investigate the association of altered responses to aversive stimuli with apathy. Ersche and co-workers(629) showed insensitivity in learning from punishment, but not reward in cocaine addiction. In FTD, Perry et al(435) showed an association between impaired responses to aversive stimuli and atrophy in the insula and amygdala, and also an association between disinhibited behaviour and ventral putamen atrophy; disinhibition also correlated with apathy scores. However, they did not link apathy with changes in response to aversive stimuli(435, 436). A comparison of FTD(254), and PD(421) on a multi-component task of initiation, planning and motivation: found differences between the FTD group and controls, but did not look for predictors of apathy within the FTD group, whilst the study in PD did not find group differences or consistent associations between their task and gold-standard apathy measures. Lansdall et al(230) used a battery of tasks assessing reward, risk-taking and impulsivity in patients with various fronto-temporal degenerations, but did not include gold standard assessments of apathy, or look for altered responses to aversive stimuli. Thus our study is the first to show deficits in response to aversive stimuli leading to apathy.

Several neuropsychological processes might contribute to the deficit found in aversive stimulus response: impaired recognition of aversive stimuli, differential learning from loss and reward, reduced loss aversion, or inability to change behaviour following the stimulus. HD patients

show impaired recognition of negative emotions(96, 166, 438, 439), which is associated with changes in the insula(96), as do patients with FTD(440–442). This deficit in FTD is part of a more widespread deficit in aversive stimulus sensitivity(435). Frank(386) showed that differences in learning from loss and reward in PD are driven by dopamine, a process mediated by the intra-basal ganglia indirect (inhibitory - NoGo) and direct (excitatory – Go) pathways respectively(443). However, the direct and indirect pathways in HD are both impaired: deficits in excitatory and inhibitory processing in HD are best explained by impaired co-ordination of bilaterally damaged pathways, consistent with medium spiny neuron injury(444). Furthermore a randomised controlled trial of a dopaminergic agent in HD did not improve apathy(418). Loss aversion(445), (where potential loss is a more significant behavioural influence than an equivalent potential reward(446)) has been shown to be mediated by the amygdala (where apathy correlates with grey matter atrophy in HD(447)), striatum, thalamus and insula(281, 448–451). Furthermore in HD, dorsal striatal damage has been shown to mediate a deficit in learning from loss(88). Set shifting is impaired in HD, even from very early stages(164, 382, 452), however scores on the EDSST did not correlate with performance on the Persistence task, nor did our other measure of executive function: phonemic verbal fluency. This evidence suggests the aversive-stimulus deficit is mediated either by impaired recognition of loss (insular dysfunction), impaired learning from loss (dorsal striatal damage) or altered loss aversion (amygdala, insula or striatum). The previous imaging studies of apathy in HD have demonstrated associations between apathy and amygdala atrophy, thalamic atrophy and altered connectivity in a distributed network involving the caudate; all these regions are potential loci where dysfunction in learning from, or responding to, aversive stimuli could be mediated.

The lack of contribution of reward related processes to apathy in HD is likely to be robust: we used three different assessments – self-report of reward value, and two tasks mediating reward and effort, both shown to correlate with apathy in other disease states (453, 454). None showed significant differences on group (after Bonferroni) comparison, or correlation with apathy scores. This disparity (relatively preserved reward and impaired sensitivity to aversive stimuli) has been seen in other diseases such as FTD(435). There are some suggestions that reward-related processing in HD is impaired: Palminteri found deficits on the reward aspect of their task in symptomatic HD participants(88); one conference abstract reported a deficit on a progressive ratio task(455); and there is fMRI evidence of ventral striatum hypoactivity in HD during reward (but no behavioural deficit)(437). We were concerned that our tasks did not sufficiently test reward and effort related processes, however the exploratory comparisons in the control group showed predictive ability of one measure from another, for all but the BAS reward

score and reward ratio task. Furthermore, our GLMMs demonstrated a trend level effect for reduced levels of exploitation of reward, and less excessive responding in the HD group compared with controls.

In keeping with previous work(456, 457), we found executive function measures predicted apathy in HD, however correction for multiple confounding variables meant this effect was lost; which may reflect lack of power in our study on these measures. The Maze task demonstrated slower RT was associated with increasing apathy in HD. However, this association was not maintained in the multiple linear regression models. As with our executive function findings, this may be a function of sample size, or the contribution to apathetic behaviour in HD may not be as major as that relating to aversive stimuli. We considered whether this task might be merely testing executive function: lower PVF scores and EDSST scores strongly correlated with slower RT on the Maze task. PVF and Maze are both concerned with idea generation, and may share a common mechanism, whilst shifting response set contributes to PVF(458, 459).

In interpreting the results of this study, it is important to consider the strengths and limitations of the work. We demonstrated an association between reduced sensitivity to aversive stimuli and apathy, both on performance in a single task measuring response to social stimuli, and across a range of outcomes (popped balloons, trial points, excessive responses) using different statistical technique on a second task of monetary reward and loss. Inclusion of potential confounding variables in the models in both tasks did not change the results. Our results demonstrating minimal deficits in response to rewarding stimuli, are likely to be robust; we used three different measures, and demonstrated significant relationships between the reward/effort measures in the control cohort. A smaller sample of our cohort completed the PSLT and option-selection/executive function battery (Maze Task, PVF, EDSST). This lack of power may explain the lack of association between executive function and apathy found by other groups(456), however, the earlier work did not correct for all the confounders we included in our model, so may represent a type II error. The lack of clear effect of executive function processes on apathy does not invalidate our main finding of a disparity between reward and aversive stimuli underlying apathy in HD, nor the confirmation of the hypothesis that goal-directed behaviour is separable into different component processes. We chose to use a demographic method rather than a reading test such as the NART to assess premorbid IQ, as prior evidence in the HD population(378, 429, 430) showed that whilst reading ability was preserved prior to motor onset, this declined in association with cognitive deterioration and disease progression thereafter, whilst demographic methods were much less affected by disease progression. Akinesia can mimic ap-

athy, but our analyses specifically included a measure of motor score related to disease (TMS from the UHDRS). Finally, our study included three clinical trial patients randomised into a placebo-controlled drug trial of Pridopidine, a dopamine stabilising agent. Exclusion of their data did not affect the findings.

In summary, we have demonstrated that goal-directed behaviour, is potentially separable into component processes, which opens up new avenues for the neurobiological investigation of deficits in this cognitive domain. Specifically, we have shown an association between apathy and impaired sensitivity to aversive stimuli in HD. Our computerised battery performed well in relation to standard clinical tests and has considerable translational potential for animal models and as a surrogate marker for treatment trials.

Chapter 4

Impulsivity

4.1 Introduction

Impulsivity encompasses "actions that are poorly conceived, prematurely expressed, unduly risky, or inappropriate to the situation and that often result in undesirable outcomes"(460). It is a behaviour that is seen in many different neurological and psychiatric disorders: Parkinson's disease(274), Huntington's disease(461), fronto-temporal dementia(230, 436), obsessive compulsive disorder(462), attention deficit hyperactivity disorder(463) and addiction(272, 464). These disorders all share a pathological focus on cortico-striatal circuits, the frontal lobes, or basal ganglia. Here we focus on Huntington's disease (HD) which is a progressive neurodegenerative disorder caused by a repeat expansion of the Huntington gene carried on chromosome 4). HD affects the dorsal striatum in its earliest stages(37, 58, 59, 61), but progresses to involve wider areas of cortex and white matter with advancing disease. Patients with HD exhibit a wide range of behavioural abnormalities(206, 211, 465), including behaviours classically associated with impulsivity such as impulsive aggression, addiction and hypersexual behaviour(181, 186, 187, 206, 466–468).

Research on impulsivity initially treated it as a unitary concept, however it has become apparent that in fact, multiple neuropsychological processes and neurobiological changes contribute to produce this behaviour(270, 275, 276). There is ongoing debate about exactly which processes contribute to impulsive behaviour, and what the best assessment to measure impulsivity is, both in humans and in animal models. There are a number of different questionnaires, which aim to cover different dimensions of impulsivity; the Barrett Impulsivity Scale (BIS-11), Behavioural Inhibition Scale Behavioural Activation Scale (BISBAS), and the Urgency, Perseverance Premeditation Sensation Seeking Scale (UPPSP) (392–394). The majority of this type of assessment

have been compiled by creating large banks of questions, trialling them in large cohorts from the general population, and then using factor analysis to divide the question bank into different sub-dimensions of impulsivity, and exclude non-contributory questions(392–394). The questionnaires are then further validated by comparison with other impulsivity scales(394) or between control populations and groups with high levels of impulsive behaviour(392). The BIS-11 has subscales of attention, motor and non-planning. It has been widely used in clinical populations and shown significant discriminatory ability and reliability(392, 469). The UPPSP was originally compiled by Whiteside and Lynam, with an additional component added by Cyders in 2007. It assesses 5 domains "Negative Urgency", "Positive Urgency", "Lack of Premeditation", "Lack of Perseverance" and "Sensation Seeking"(393, 470). The BISBAS is based on a theoretical model of approach-avoidance behaviour, and has one inhibitory subscale and three activation subscales: "Fun-Seeking", "Reward Responsiveness" and "Drive"(394). There are other questionnaires more focussed on personality-traits such as the Eysenck Venturesomeness-Impulsiveness(471), in addition to questionnaires which focus on one aspect of impulsivity such as the Sensation Seeking Scale(472).

Questionnaire assessments of impulsivity are reliant on self-report, thus are vulnerable to subjects lack of insight, social desirability bias (answering in a way, that subjects perceive to be more socially desirable) and finally, if there has been a measurable change in impulsivity (for example secondary to a brain injury), then it is not clear if subjects modify their responses to account for the change, or answer based on their prior, long-standing preferences/behaviour. Furthermore, compilation of the questionnaires is vulnerable to compiler's biases about what constitutes impulsive behaviour, potentially over-valuing some components, whilst undervaluing or excluding others. However,the questionnaires have high test-retest reliability, suggesting that they measure a personality trait, rather than a transient mood state(473, 474), and have been shown to reliably discriminate between groups with high and low impulsivity(469, 475).

In addition to questionnaires, a number of different tasks have been developed, which measure impulsivity and can be used in both humans and animal models. These are based on distinct neuropsychological mechanisms: delay discounting (valuing immediate rewards over larger, delayed ones), measured by the Kirby monetary choice questionnaire(384) or delay discounting task(476); motor disinhibition (acting prematurely, not inhibiting a response correctly), measured by the continuous performance task(477), stop signal task(389) or go nogo task(478); risk-taking (making higher risk choices) assessed by the Cambridge gambling task(291) or balloon analogue risk task(381); and a less well-defined spectrum of decision-making impairments, such as acting before

all information is known (measured by the 'Beads' task(479) or information-sampling task(480)), or failing to recognise future outcomes – assessed using the Iowa gambling task(481). The tasks circumvent the problems of insight and social desirability seen in the questionnaires. These also allow direct translational assessments between animal models of disease (including lesion or pharmacological manipulations) and humans suffering from the disease. However, they may reflect a 'state' rather than 'trait' assessment, and hence have lower test-retest reliability over time than questionnaire assessments(474).

Furthermore, the individual tasks show little correlation with each other, as they measure separable neuropsychological processes, and none of the tasks to date in different populations have shown strong associations with the questionniares, making it difficult to definitively measure impulsive behaviour(277, 278).

In HD, a number of these measures have been employed, to assess levels of impulsivity in HD compared to controls. Impairments on the Iowa gambling task have been found in HD patients compared with controls(482, 483), although the impairment did not correlate with disinhibition measured by the Frontal Systems Behavioural Scale. A larger, recent study found deficits in manifest, but not premanifest individuals with HD(484). Whilst other studies of the Iowa gambling task in HD have been negative, albeit these studies had comparatively small patient cohorts(485). Deficits on the Stroop and go nogo tasks have also been seen widely in HD(136, 166, 171, 478), although both of these tasks involve an element of task switching/response selection known to be impaired in HD(164, 382)), rather than measuring pure motor inhibition or 'stopping'. The only study to date of the stop signal reaction task in HD (496) did not find a difference between cases and controls, albeit the sample was premanifest. There are no published papers studying delay discounting in HD, a conference abstract suggested no evidence of difference in a small sample(486). A study of the Cambridge gambling task suggests intact decision making under risk, but impaired response inhibition(487). To our knowledge, there are no studies using the balloon analogue risk task in HD. One study used the BISBAS and BIS in HD, finding higher levels of impulsivity on the BIS, but not the BISBAS.

Further to this, HD patients take a wide variety of medication known to influence impulsive behaviour, and none of the above works corrected for this.

A number of unanswered questions arise from this work:

1) Is there a specific inhibitory deficit, or have the previous studies mis-identified a problem with

task switching?

2) Is there evidence of risk-taking behaviour?

3) Which task provides the most sensitive measure of impulsivity in HD, and hence which brain regions are most likely to be involved in leading to this behaviour?

4) What is the best questionnaire measure of impulsive behaviour in HD, and are deficits on self-report measures limited by insight?

4.2 Materials and Methods

4.2.1 Participants

As described in methods, we recruited 53 patients with a genetic diagnosis of HD (CAG repeat length >36) from the Cardiff University HD clinic, ranging in severity from the premanifest to moderately-symptomatic in the manifest stage. Patients were classified as premanifest based on a total motor score (TMS)<11(166) and diagnostic confidence <4, from the Unified Huntington's disease Rating Scale(422) (UHDRS). 26 control participants were recruited from family members not at risk of HD, local advertising.

Participants completed questionnaires and tasks as outlined below.

4.2.2 Questionnaires

Urgency Premeditation Perseverance Sensation Positive Scale (UPPS-P)(393, 470)

This 59 item questionnaire was developed from a factor analysis of previous impulsivity scales. Each item is scored, from 1-4 on a Likert scale (1 = "Agree Strongly", 4 = "Disagree Strongly"). The final totals for each sub-score indicate higher levels of the particular quality, hence some of the items are reverse-scored. An initial 4 factor scale was developed, before additional work(393), suggested an additional 5th factor. This is a self-report measure and hence is reliant on participant insight. The 5 factors covered are 'Negative urgency': acting rashly under conditions of negative affect- "I have trouble controlling my impulses", 'Lack of premeditation': acting without forethought - "I am a cautious person", 'Lack of perseverance': stopping before a task is completed- "I generally like to see things through to the end", 'Sensation Seeking': valuing

novel experience and risk- "I quite enjoy taking risks"; and 'Positive urgency': acting rashly under conditions of positive affect- "When I am very happy, I can't seem to stop myself from doing things that can have bad consequences". It has been widely used and subject to extensive validation(488).

Behavioural Inhibition Scale Behavioural Activation Scale (BISBAS)(394)

This questionnaire was originally developed to test Gray's theories(489, 490) underlying motivated or goal-directed behaviour, namely that personality types have a behavioural activating system (BAS, which drives movement or activity towards rewards) and a behavioural inhibitory system (BIS, drives behaviours that avoid loss or punishment), and that human behaviour is governed by a balance between the two. Gray proposed that individuals have different personalities, and different activity levels of each of the competing systems, and relative activity would change depending on the circumstances. Impulsive behaviour could hence occur as a consequence of a lack of inhibitory activity, or BAS overactivity. The questionnaire is a 24 item instrument, which generates sub-scores for 'Behavioural Inhibition' (BInS): sensitivity to punishment/aversive outcomes - "I worry about making mistakes"); 'Drive' (BAS Drive): a measure of motivation - "I go out of my way to get things I want"; 'Fun Seeking' (BAS Fun Seeking): valuing novelty- "I crave excitement and new sensations"; and Reward Responsiveness (BAS Reward): value of reward - "It would excite me to win a contest") Each item is Likert scored from 1(strong agreement) to 4(strong disagreement). The authors performed a factor analysis to validate the original questionnaire, which has been replicated in a number of other populations(491, 492).

Barratt Impulsivity Scale (BIS-11)

This questionnaire has 30 items, scored using Likert scores from 1 (rarely/never) to 4 (almost always). It has been in use for 50 years, and is now on its eleventh version. An exploratory and confirmatory factor analysis in 3 different populations(392) has validated 3 subscales: Attention (BIS Att) which measures reduced attention ("I don't pay attention"), Motor (BIS Motor) which measures impaired self-control ("I am self-controlled" - reverse scored item) and Non-Planning (BIS Non Plan) which measures lack of planning or forethought ("I plan trips well ahead of time"). Higher sub-scores indicate higher levels of the behaviour.

Monetary Choice Questionnaire(384)

This is a measure of delay discounting: temporally distant rewards being viewed less favourably than immediate ones. It consists of 27 items, each offering a choice between an immediate, smaller reward, and a delayed larger one. The outcome measure is kD – a measure of the slope of the hyperbolic discounting curve. KD was calculated using an automated scoring system(493, 494).

4.2.3 Tasks

Stop Signal Reaction Task (SSRT)(389)

The stop signal reaction task assesses motor inhibition. Subjects were given the following instructions "Press the left keyboard button (Z)when you see a square and press the right button when you see a circle. React as quickly as you can. Sometimes shortly after you see a circle or square you will hear a 'beep'. If you hear the 'beep' do not respond. There will be an initial practice level followed by 3 test levels". The outcome measure was the stop signal response time: a measure of the reaction time for inhibitory responses measured in milliseconds. Longer reaction times are indicative of slower inhibitory neural circuits and hence higher motor impulsivity.

Balloon Analogue Risk Task(381)

Subjects were told "You will now play a game, where you pump up balloons to earn money. The larger the balloon gets the more money you will earn. If the balloon gets too big it will pop and you will lose the money. If you feel the balloon is as large as you want it to be, press the 'bank' button and your money will be added to your bank." There were three different colours of balloon, which could pop at any point between a maximum and minimum value (2-8, 2-32 and 2-128 in the first thirty trials, 2-16, 8-32 and 16-64 in the final sixty trials). Subjects did not know which was the higher value balloon, but learned this information by trial and error as the task progressed. Every pump gained the subject 5 cents, but increased the risk of popping the balloon and losing all money from that trial. There were 90 trials in total. The outcome measure was the average pump (as described by the original authors), as a measure of risk-taking.

Iowa Gambling Task

This task was originally designed to measure learning from implicit aversive stimuli, in a cohort of patients with ventro-medial prefrontal cortex lesions(99)but has been shown to be impaired in patients with focal lesions in other sites(495). Subjects were told "You will see 4 decks of cards when you start the game. You must choose cards from each deck. Every time you pick a card you will win money. Some times after you have chosen a card and won money, you will then lose money too. You must keep playing until the game stops. The most important thing to note is this: some decks are 'bad' decks where over time, you will win more than you lose. The object of the game is to win as much money as possible by avoiding the 'bad' decks". Subjects made 100 selections. Decks 'A' and 'B' were high win ($100) but very high loss, whilst 'C' and 'D' were low win ($50) but even smaller losses. Over time 'C' and 'D' were the good decks. A meta analysis identified the number of cards chosen from deck 'A' as being the most reliable outcome measure of the task(425). We used the version from the online Pebl software package(424).

Executive Function Measures

We used two measures of executive function known to be abnormal in HD(136, 164, 382): the phonemic verbal fluency (PVF)(in which subjects were asked to generate as many novel word exemplars beginning with a specific letter as they could in 1 minute, this was performed for the letters F, A and S(423)), and an extra-dimensional set-shifting task modified from a reversal learning task, which necessitated extra-dimensional set shifts between colour and location of a stimulus(426). These tasks were employed to assess the effect of executive function on impulsivity task performance.

Statistical Analysis

All analyses were conducted in R, a widely available online statistical software package(427). Before deciding on our analysis technique, we reviewed the distributions of our data, which conformed to a Poisson distribution, on all variables except SSRT, which had a Gamma distribution, and the executive function measures which were Gaussian. We compared performance

between controls, pre-manifest and manifest individuals (symptomatic onset was delineated as a score of '4' on the UHDRS diagnostic confidence score or a TMS >10, based on the TRACK-HD data(166). Dopaminergic and serotonergic drug doses were converted to olanzapine and fluoxetine equivalents based on meta-analyses(379, 380). IQ was calculated using Crawford's method(377), as reading test estimates of IQ deteriorate in the symptomatic HD population(378, 429, 430). We used generalised linear models (GLMs), as the assumptions underlying ANOVAs were not met (Goldfeld-Quandt test was significant, demonstrating heterogeneity of variance). For each variable, we initially created a GLM looking at the effect of disease group in isolation, then added potential confounding variables to each model (age, IQ, gender, Olanzapine dose, Fluoxetine dose). For all analyses, we treated disease status as an ordered variable with 3 ascending levels of effect (control subjects (lowest), premanifest HD subjects (middle) and manifest HD subjects (highest)). We did not add TMS to the models, as disease status was calculated in part from the TMS value. We corrected for the family wise error rate (using the Bonferroni correction) of disease status on tasks and the questionnaire subscales in the GLMs. We used Tukey post-hoc tests to study the relationships between levels of disease status in the GLMs.

4.3 Results

4.3.1 Demographics

The premanifest group was smaller than both the control and manifest group. The manifest group was older than both the premanifest and control groups: the Tukey test of the GLM showed significant differences between the manifest group and controls ($p < 0.001$) and premanifest group ($p < 0.001$). IQ was lower in both HD groups, but there were no significant group differences on post-hoc testing. No significant differences were found for gender balance or Olanzapine dose equivalent across disease categories, although there was a significant difference between manifest and premanifest groups for Olanzapine dose equivalent on Tukey post-hoc testing ($p=0.00081$), but Fluoxetine dose equivalent was higher in both manifest and premanifest groups compared with controls ($p < 0.001$ in both groups), the manifest group had slightly lower Fluoxetine dose equivalents than the premanifest group ($p=0.0237$). As expected TMS scores were higher in both HD groups than controls ($p < 0.001$ for both comparisons), and the premanifest group also had higher scores than controls ($p < 0.001$).

Table 4.1: Demographics

	Controls	Premanifest	Manifest	
N	26	12	41	
Age	46.85 (20-75)	41.92 (34-51)	57.44 (33-82)	***
IQ	109.73 (89.79-128.51)	103.11 (88.75-119.57)	103.66 (90.73-125.27)	*
Gender	17/26 female	8/12 female	18/41 female	
Olanzapine dose (mg)	0	0.62 (0-7.5)	2.39 (0-41.25)	
Fluoxetine dose (mg)	2.4 (0-22.2)	24.92 (0-95.4)	20.93 (0-146.5)	***
CAG Repeat Length	-	41.33 (38-46)	42.85 (40-50)	
Total Motor Score	1.48 (0-6)	4 (0-9)	46.12 (12-89)	***

$*p < 0.05$ $**p < 0.01$ $***p < 0.005$

4.3.2 Tasks

Iowa Gambling Task

The Iowa Gambling Task (IGT) is a measure of decision making under ambiguity, subjects select cards from 4 different decks labelled A, B, C and D which have different rewards and losses over time. A recent meta-analysis showed that the most reliable outcome measure was the number of cards selected from deck A in the last 25 trials(425). Comparison of cases and controls using a Wilcoxon test showed higher mean selections in the cases (5.78 & 3.73), a difference which was significant (p = 0.037). The GLM showed a highly significant, positive effect of disease status on task performance (p = $1.87\text{x}10^{-5}$). Post-hoc testing showed significantly higher scores for manifest compared with premanifest (p = 0.0224) and control (p <0.001). Adding confounders to the model did not change the direction of the relationship or the significance(Table 4.2, Figure 4.1).

Stop Signal Reaction Task

The stop signal reaction task (SSRT) is a measure of motor inhibition. The outcome variable is stop signal reaction time: slower (i.e. longer) reaction times indicate slower cognitive 'stop' processes and hence poorer motor inhibition. Group comparisons between cases and controls showed much slower stop reaction times in HD participants compared with controls (means 496.25 & 304.42, p = 0.0004537). Disease status in the GLM had a highly significant, positive effect on SSRT (p = $4.63\text{x}10^{-5}$). Post-hoc testing showed slower SSRT in the manifest group compared with premanifest subjects(p < 0.001), and premanifest subjects were slower than controls at trend level (p = 0.068). Addition of confounders to the GLM did not change the direction or significance of the relationship; given the strong motor element of the task we also added 'Go' stimulus reaction time to the model, and the significant effect of disease status on SSRT was still retained(Table 4.3, Figure 4.1).

Delay Discounting

The Monetary Choice Questionnaire was used to measure delay discounting (a preference for smaller, immediate rewards over larger, delayed ones). The outcome variable was the kD – the slope of the hyperbolic discounting curve(493, 494). Higher kD values indicate a stronger preference for immediate reward. Group comparisons using the Wilcoxon test showed no differences between kD values in cases compared with controls (means 0.08 and 0.06 respectively, p =

0.9622). The GLM looking at disease status in isolation, did not find a significant relationship between disease status and kD. Adding confounding variables to the model did not change this relationship(Table 4.4, Figure 4.1).

Balloon Analogue Risk Task

The Balloon Analogue Risk Task was used as a measure of risk taking behaviour, the originators of the task used the average pump on unexploded balloons and showed an association of this measure with existing measures of sensation seeking and impulsive behaviour(381). Group comparisons between cases and controls showed lower average pump values (means 10.61 and 12.55 respectively, p = 0.039). The effect of disease status on BART average pump was significant (p = 0.018): post-hoc testing (Tukey) showed that this was significant for the comparison of manifest group and controls: more affected subjects had lower BART average pump scores. Adding confounders to the GLM meant that the significance was lost of the effect of disease status on task performance(p=0.06)(Table 4.5, Figure 4.1).

Executive Function Measures: Effect on Impulsivity Task Performance

Phonemic verbal fluency task performance differed between groups: HD cases had lower scores than controls (p= 7.05×10^{-5}). A GLM demonstrated a significant effect of disease status on PVF score: increasing disease stage was associated with lower PVF score (Pseudo R^2 0.30, Estimate -13.05, p=5.61×10^{-5}). Adding confounders to this model did not alter the direction or significance of this relationship (Pseudo R^2 0.49, Estimate -1.13, p=0.0025). GLMs predicting SSRT and IGT task performance from PVF scores did not show any significant relationships. Adding PVF scores to the confounders in GLMS of disease status on IGT and SSRT performance did not alter the direction or significance of the relationships.

Extra-dimensional set shift task (EDSST) performance did not differ between groups (p=0.17). However a GLM showed a significant effect of disease status on task performance: fewer set shifts were completed with increasing disease stage (Pseudo R^2 0.10, Estimate -3.75, p=0.041). Adding confounders to this model meant the significance was lost. GLMs showed EDSST performance predicted both IGT performance (Pseudo R^2 0.19 Estimate -0.059, p=0.0026) and SSRT (Pseudo R^2 0.22 Estimate 7.31×10^{-5}, p=0.028). Adding EDSST scores as an additional confounding variable in models of disease status did not affect the direction or significance of the relationship between disease status and SSRT (Pseudo R^2 0.45 Estimate 73.50, p=0.023), but did affect the

significance of the relationship between disease status and IGT performance (Pseudo R^2 0.22 Estimate -0.018, p=0.90).

Figure 4.1: Tasks

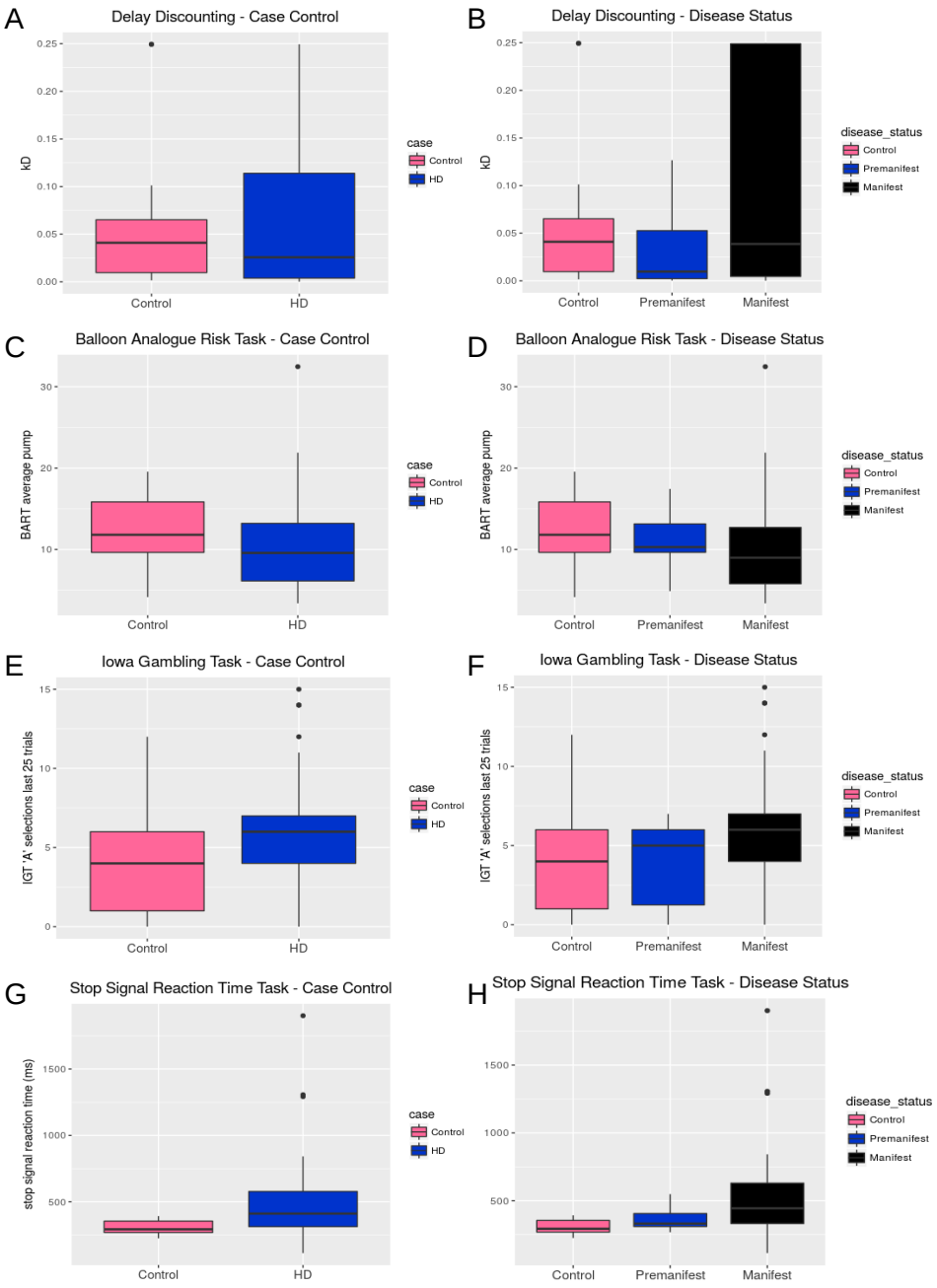


Table 4.2: Iowa Gambling Task

	Dependent variable:	
	IGT 'A' Count	
	Estimate	P Value
(Intercept)	1.51	$<2x10^{-16}$
Disease Status	0.37	0.000019
Observations	71	
Log Likelihood	−212.43	
Akaike Inf. Crit.	430.85	

	Dependent variable:	
	IGT 'A' Count	
	Estimate	P Value
(Intercept)	2.012	0.00089
Disease Status	0.28	0.0043
Age	0.012	0.0036
Gender (Male)	0.23	0.040
Olanzapine Equivalent	0.023	0.051
Fluoxetine Equivalent	−0.0032	0.28
IQ	−0.011	0.036
Observations	67	
Log Likelihood	−187.76	
Akaike Inf. Crit.	391.51	

Bonferroni corrected alpha level: 0.0125

Tukey Test - Manifest>Premanifest p=0.022, Manifest>Control p<0.001

Table 4.3: Stop Signal Reaction Task

	Dependent variable:	
	SSRT	
	Estimate	P Value
(Intercept)	5.97	$<2\text{x}10^{-16}$
Disease Status	0.41	$4.63\text{x}10^{-5}$
Observations	68	
Log Likelihood	−445.33	
Akaike Inf. Crit.	896.66	

	Dependent variable:	
	SSRT	
	Estimate	P Value
(Intercept)	5.46	$1.76\text{x}10^{-14}$
Disease Status	0.26	0.0038
Age	0.00047	0.90
Gender (Male)	0.019	0.85
Olanzapine Equivalent	0.020	0.095
Fluoxetine Equivalent	−0.0028	0.25
'Go' Reaction Time	0.00092	$6.47\text{x}10^{-5}$
IQ	−0.0017	0.72
Observations	64	
Log Likelihood	−405.49	
Akaike Inf. Crit.	829.00	

Bonferroni corrected alpha level: 0.0125

Tukey Test - Manifest>Control p<0.001

Table 4.4: Delay Discounting

	Dependent variable:	
	kD	
	Estimate	P Value
(Intercept)	−1.57	$6.64\text{x}10^{-8}$
Disease Status	0.19	0.59
Observations	72	
Log Likelihood	−5.38	
Akaike Inf. Crit.	16.76	

	Dependent variable:	
	kD	
	Estimate	P Value
(Intercept)	−0.39	0.89
Disease Status	0.015	0.97
Age	0.0095	0.60
Gender (Male)	0.33	0.50
Olanzapine Equivalent	0.021	0.70
Fluoxetine Equivalent	−0.0029	0.83
IQ	−0.017	0.48
Observations	68	
Log Likelihood	−5.18	
Akaike Inf. Crit.	26.35	

Bonferroni corrected alpha level: 0.0125

Table 4.5: Balloon Analogue Risk Task

	Dependent variable:	
	BART Average Pump Estimate	P Value
(Intercept)	2.43	$<2x10^{-16}$
Disease Status	−0.13	0.0183
Observations	72	
Log Likelihood	−Inf.00	
Akaike Inf. Crit.	Inf.00	

	Dependent variable:	
	BART Average Pump Estimate	P Value
(Intercept)	1.10	0.0073
Disease Status	−0.12	0.060
Age	−0.00021	0.94
Gender (Male)	0.18	0.018
Olanzapine Equivalent	−0.015	0.12
Fluoxetine Equivalent	0.0046	0.011
IQ	0.011	0.0012
Observations	68	
Log Likelihood	−Inf.00	
Akaike Inf. Crit.	Inf.00	

Bonferroni corrected alpha level: 0.0125

Tukey Test - Manifest>Control p=0.046

4.3.3 Questionnaires

UPPS P

Negative Urgency

Negative urgency is the tendency to act rashly under conditions of negative affect. Higher scores indicate a higher propensity to this behaviour. Case control comparison showed a significantly higher score among cases using the Wilcoxon test (means 30.37, 24.19, $p = 0.018$). Disease status in the GLM strongly predicted higher levels of negative urgency ($p = 6.4x10^{-6}$). Post-hoc tests showed significantly higher scores for both the premanifest and manifest groups compared with controls ($p < 0.001$ for both comparisons), but no difference between premanifest and manifest groups. Addition of confounders to the model did not result in the relationship becoming non-significant(Table 4.6, Figure 4.2).

Lack of Premeditation

Lack of premeditation is to act without forethought. Higher scores indicate higher propensity to display this behaviour. Comparison of cases and controls using the Wilcoxon test showed higher scores among HD subjects (means 21.25, 19.46, $p = 0.045$). However, disease status in the GLM did not show a significant relationship with Lack of Premeditation(Table 4.7, Figure 4.2).

Lack of Perseverance

Lack of perseverance is an inability to remain focussed on a task. Higher scores demonstrate a higher propensity for this behaviour. Comparison of cases and controls using the Wilcoxon test showed significantly higher scores in the HD group (means 21.55 17.85, $p = 0.035$). There was a significant positive effect of disease status on Lack of Perseverance score ($p = 8.01\ x10^{-5}$). Post-hoc testing demonstrated a significant difference for manifest and controls only ($p <0.001$). Addition of confounders to the model did not result in the relationship becoming non-significant(Table 4.8, Figure 4.2).

Sensation Seeking

Sensation seeking is the tendency to search out new and exciting experiences. Higher scores on the questionnaire reflect a higher tendency to display this behaviour. There were no differences between cases and controls, and no significant effect of disease status in the GLM on sensation-seeking scores(Table 4.9, Figure 4.2).

Positive Urgency

Positive urgency is the propensity to act rashly under conditions of positive affect: higher scores on the questionnaire reflect a stronger tendency to exhibit this behaviour. Cases had much lower scores than controls (means 38.88, 49.08, $p = 0.00035$). Disease status in the GLM had a highly significant, negative effect on positive urgency score ($p = 2.11\text{x}10^{-11}$). Post-hoc testing demonstrated lower scores of both premanifest ($p = 0.0058$) and manifest groups ($p < 0.001$) compared with controls, but no significant difference between the manifest and premanifest groups. Addition of confounders to the GLM did not change the significance or direction of this relationship(Table 4.10, Figure 4.2).

Figure 4.2: UPPS P

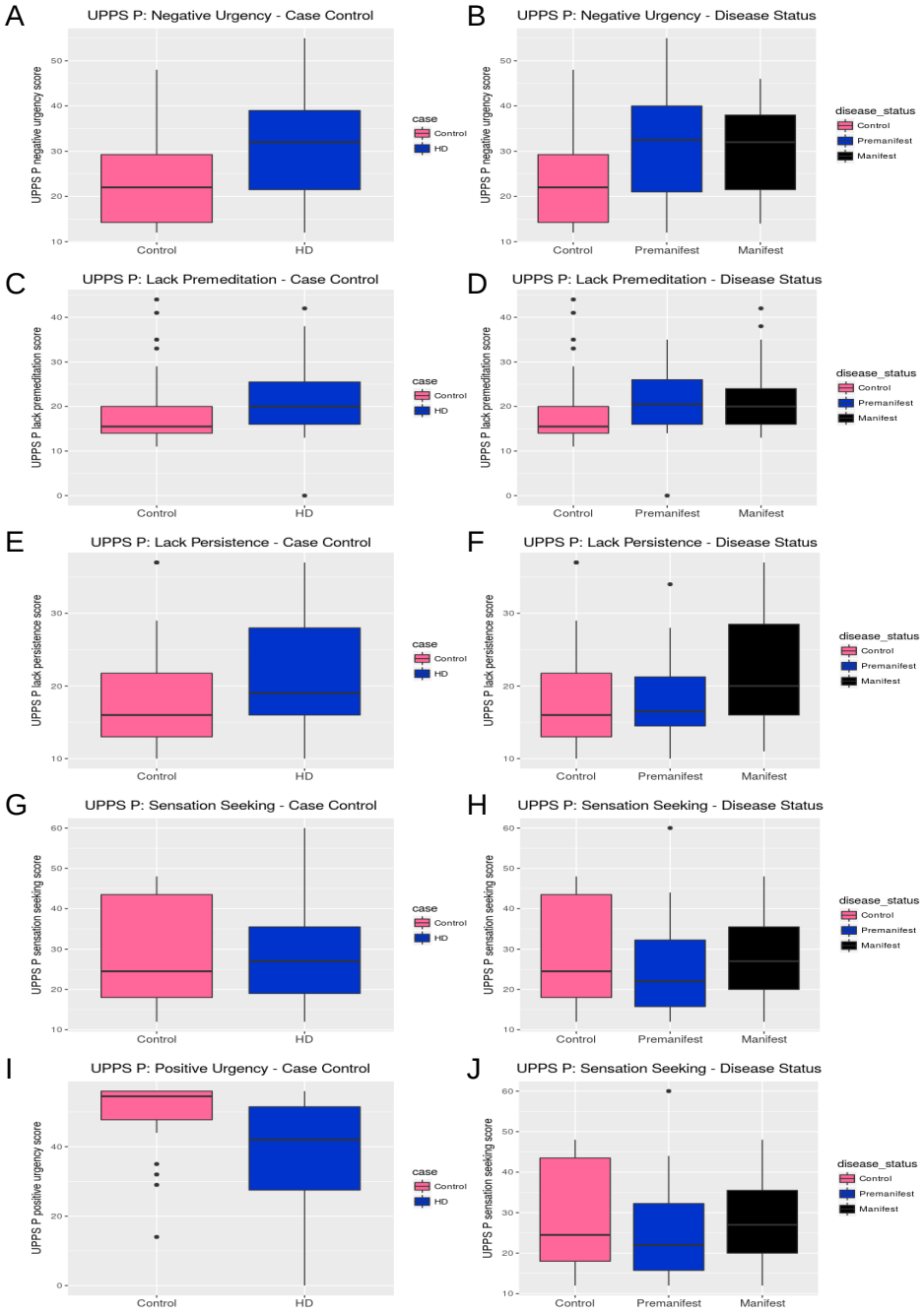


Table 4.6: UPPS P: Negative Urgency

	Dependent variable:	
	UPPS P Negative Urgency	
	Estimate	P Value
(Intercept)	3.34	$<2\text{x}10^{-16}$
Disease Status	0.16	$6.4\text{x}10^{-6}$
Observations	77	
Log Likelihood	−366.49	
Akaike Inf. Crit.	738.98	

	Dependent variable:	
	UPPS P: Negative Urgency	
	Estimate	P Value
(Intercept)	4.23	$<2\text{x}10^{-16}$
Disease Status	0.10	0.015
Age	0.0032	0.070
Gender (Male)	−0.23	$2\text{x}10^{-6}$
Olanzapine Equivalent	0.0045	0.35
Fluoxetine Equivalent	0.00070	0.52
IQ	−0.0093	0.000015
Observations	73	
Log Likelihood	−326.15	
Akaike Inf. Crit.	668.29	

Bonferroni corrected alpha level: 0.01

Tukey Test - Manifest>Control p<0.0001, Premanifest>Control p=0.00057

Table 4.7: UPPS P: Lack Premeditation

	Dependent variable:	
	UPPS P Lack Premeditation	
	Estimate	P Value
(Intercept)	3.022	$<2x10^{-16}$
Disease Status	0.067	0.090
Observations	77	
Log Likelihood	−302.39	
Akaike Inf. Crit.	610.79	

	Dependent variable:	
	UPPS P Lack Premeditation	
	Estimate	P Value
(Intercept)	4.15	$<2x10^{-16}$
Disease Status	0.012	0.81
Age	−0.00070	0.72
Gender (Male)	−0.060	0.27
Olanzapine Equivalent	0.019	0.00048
Fluoxetine Equivalent	−0.0015	0.26
IQ	−0.010	0.000063
Observations	73	
Log Likelihood	−273.25	
Akaike Inf. Crit.	56250973000	

Bonferroni corrected alpha level: 0.01

Table 4.8: UPPS P: Lack Persistence

	Dependent variable:	
	UPPS P Lack Persistence	
	Estimate	P Value
(Intercept)	2.98	$<2x10^{-16}$
Disease Status	0.16	0.000080
Observations	77	
Log Likelihood	−288.43	
Akaike Inf. Crit.	582.85	

	Dependent variable:	
	UPPS P Lack Persistence	
	Estimate	P Value
(Intercept)	4.0012	$<2x10^{-16}$
Disease Status	0.12	0.017
Age	−0.0013	0.52
Gender (Male)	−0.066	0.23
Olanzapine Equivalent	0.0047	0.42
Fluoxetine Equivalent	−0.00062	0.64
IQ	−0.0088	0.00051
Observations	73	
Log Likelihood	−266.79	
Akaike Inf. Crit.	549.58	

Bonferroni corrected alpha level: 0.01

Tukey Test - Manifest>Control p<0.001

Table 4.9: UPPS P: Sensation Seeking

	Dependent variable:	
	UPPS P Sensation Seeking	
	Estimate	P Value
(Intercept)	3.32	$<2\text{x}10^{-16}$
Disease Status	−0.011	0.74
Observations	77	
Log Likelihood	−369.49	
Akaike Inf. Crit.	744.98	

	Dependent variable:	
	UPPS P Sensation Seeking	
	Estimate	P Value
(Intercept)	3.14	$<2\text{x}10^{-16}$
Disease Status	0.015	0.72
Age	−0.0080	$1.3\text{x}10^{-6}$
Gender (Male)	0.23	$1.1\text{x}10^{-6}$
Olanzapine Equivalent	0.017	0.00055
Fluoxetine Equivalent	−0.00096	0.41
IQ	0.0044	0.039
Observations	73	
Log Likelihood	−310.58	
Akaike Inf. Crit.	637.15	

Bonferroni corrected alpha level: 0.01

Table 4.10: UPPS P: Positive Urgency

	Dependent variable:	
	UPPS P Positive Urgency	
	Estimate	P Value
(Intercept)	3.75	$<2x10^{-16}$
Disease Status	−0.18	$<2.11x10^{-11}$
Observations	77	
Log Likelihood	−394.48	
Akaike Inf. Crit.	794.95	

	Dependent variable:	
	UPPS P Positive Urgency	
	Estimate	P Value
(Intercept)	3.23	$<2x10^{-16}$
Disease Status	−0.094	0.0040
Age	−0.0027	0.043
Gender (Male)	0.030	0.43
Olanzapine Equivalent	−0.017	0.0040
Fluoxetine Equivalent	−0.0018	0.065
IQ	0.0065	0.00014
Observations	73	
Log Likelihood	−355.12	
Akaike Inf. Crit.	726.24	

Bonferroni corrected alpha level: 0.01

Tukey Test - Manifest<Control p<0.001, Premanifest<Control p<0.0064

Barratt Impulsivity Scale

Attention

Higher scores on this subscale indicate inability to concentrate or focus on activities. Case-control comparison using the Wilcoxon test showed a higher score among HD cases (mean 17.71, 14.69, p = 0.012). Disease status in the GLM predicted higher scores (p = 0.0011). Post-hoc testing showed a significant relationship between the manifest group and controls alone (p = 0.003). Addition of confounders to the model led to loss of the significance (p = 0.051)(Table 4.11, Figure 4.3).

Motor

Higher scores on this subscale indicate a higher level of acting without thinking. There was no significant difference between cases and controls using the Wilcoxon test, but disease status in the GLM was a significant predictor of higher Motor scores (p = 0.012), post-hoc testing showed a significant difference between manifest subjects and controls, but no other significant group comparisons. Addition of confounders to the model did not result in loss of this significant relationship(Table 4.12, Figure 4.3).

Non-Planning

Higher scores on this subscale are associated with a lack of future planning. There were significantly higher scores among cases compared with controls using the Wilcoxon test (means 26.35, 22.15, p = 0.030). Disease status was predictive of higher scores in the GLM (p = 0.0014). Post-hoc testing showed significantly higher scores in both manifest (p = 0.0042) and premanifest (p = 0.014) groups compared with controls. There were no other significant relationships. However, addition of confounders to the GLM resulted in loss of the significance of the relationship(Table 4.13, Figure 4.3).

Total Score

This is a total of the three subscales. Cases had higher scores compared with controls (means 66.42, 59.27; Wilcoxon test p = 0.034). Disease status was strongly predictive of higher total score (p = 0.00036). Post-hoc testing showed significantly higher scores of both manifest (p = 0.0012) and premanifest (p = 0.023) groups than controls, although there were no other significant comparisons. Adding confounders to the model did not result in a loss of this significant relationship(Table 4.14, Figure 4.3).

Figure 4.3: BIS-11

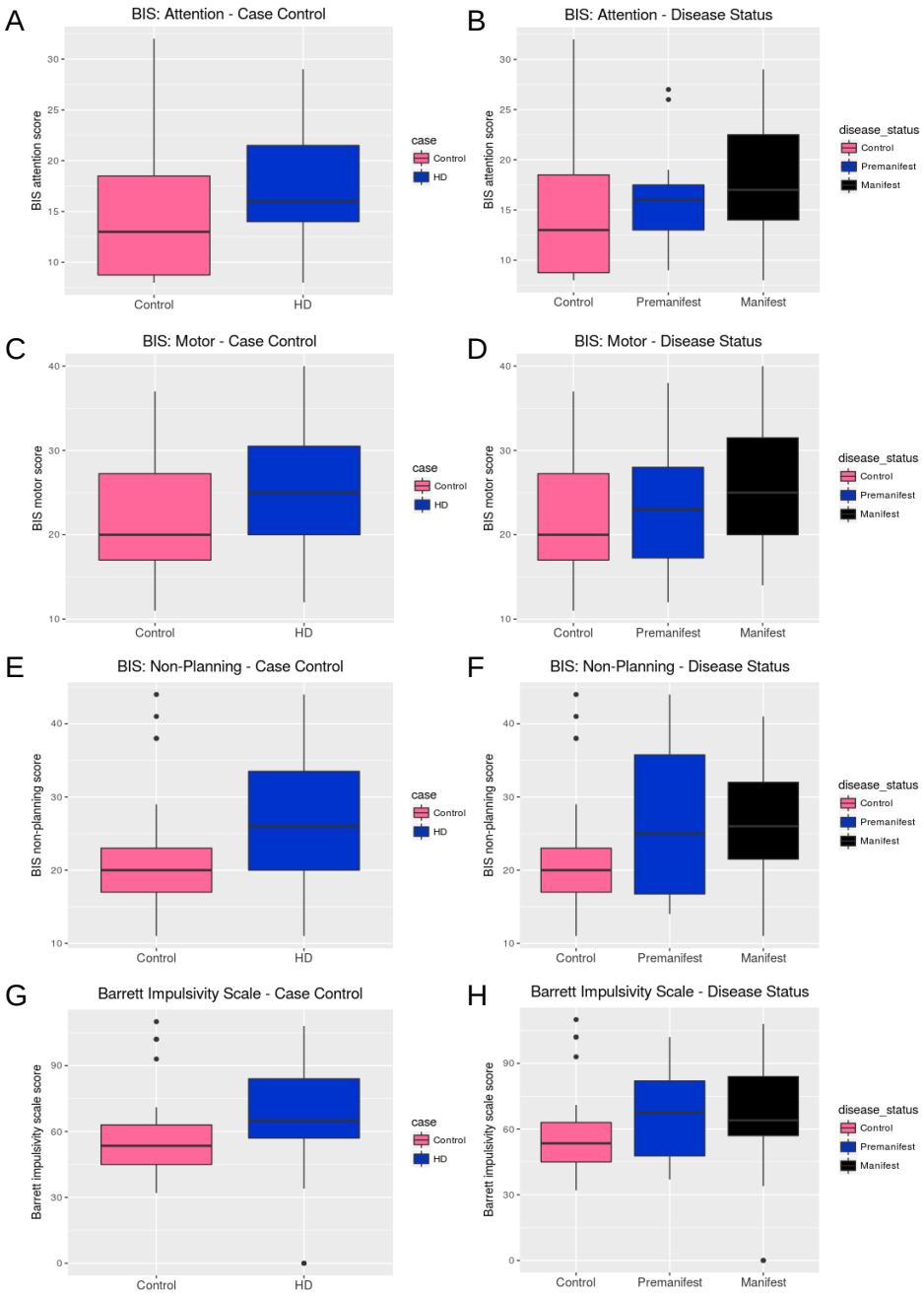


Table 4.11: BIS-11 Attention

	Dependent variable:	
	BIS Attention	
(Intercept)	2.80	$<2x10^{-16}$
Disease Status	0.15	0.0011
Observations	77	
Log Likelihood	−259.80	
Akaike Inf. Crit.	525.61	

	Dependent variable:	
	BIS Attention Estimate	P Value
(Intercept)	4.39	$<2x10^{-16}$
Disease Status	0.11	0.051
Age	−0.0068	0.0024
Gender (Male)	−0.019	0.76
Olanzapine Equivalent	0.0083	0.17
Fluoxetine Equivalent	0.00068	0.64
IQ	−0.012	0.000014
Observations	73	
Log Likelihood	−225.45	
Akaike Inf. Crit.	466.90	

Bonferroni corrected alpha level: 0.013

Tukey Test - Manifest>Control p=0.003

Table 4.12: BIS-11 Motor

	Dependent variable:	
	BIS Motor	
	Estimate	P Value
(Intercept)	3.16	$<2x10^{-16}$
Disease Status	0.093	0.012
Observations	77	
Log Likelihood	−268.68	
Akaike Inf. Crit.	543.36	

	Dependent variable:	
	BIS-11 Motor	
	Estimate	P Value
(Intercept)	4.068	$<2x10^{-16}$
Disease Status	0.099	0.026
Age	−0.0046	0.011
Gender (Male)	−0.046	0.37
Olanzapine Equivalent	0.013	0.018
Fluoxetine Equivalent	−0.0017	0.18
IQ	−0.0061	0.0082
Observations	73	
Log Likelihood	−244.53	
Akaike Inf. Crit.	505.06	

Bonferroni corrected alpha level: 0.013

Tukey Test - Manifest>Control p=0.031

Table 4.13: BIS-11 Non-Planning

	Dependent variable:	
	BIS Non-Planning	
	Estimate	P Value
(Intercept)	3.22	$<2x10^{-16}$
Disease Status	0.12	0.0014
Observations	77	
Log Likelihood	−308.40	
Akaike Inf. Crit.	622.81	

	Dependent variable:	
	BIS Non-Planning	
	Estimate	P Value
(Intercept)	5.03	$<2x10^{-16}$
Disease Status	0.060	0.18
Age	−0.0044	0.015
Gender (Male)	−0.066	0.18
Olanzapine Equivalent	0.010	0.043
Fluoxetine Equivalent	−0.00069	0.57
IQ	−0.015	$8.22x10^{-11}$
Observations	73	
Log Likelihood	−266.85	
Akaike Inf. Crit.	549.69	

Bonferroni corrected alpha level: 0.013

Tukey Test - Manifest>Control p=0.0039, Premanifest>Control p=0.013

Table 4.14: BIS-11 Total

	Dependent variable:	
	Total Score	
	Estimate	P Value
(Intercept)	4.16	$<2x10^{-16}$
Disease Status	0.080	0.00036
Observations	79	
Log Likelihood	−569.12	
Akaike Inf. Crit.	1,144.24	

	Dependent variable:	
	Total Score	
	Estimate	P Value
(Intercept)	5.77	$<2x10^{-16}$
Disease Status	0.06087	0.026
Age	−0.0062	$2.35x10^{-8}$
Gender (Male)	−0.018	0.56
Olanzapine Equivalent	0.0086	0.0056
Fluoxetine Equivalent	−0.000030	0.97
IQ	−0.012	$<2x10^{-16}$
Observations	74	
Log Likelihood	−419.34	
Akaike Inf. Crit.	854.67	

alpha level: 0.05

Tukey Test - Manifest>Control p<0.001, Premanifest>Control p=0.024

Behavioural Inhibition Scale Behavioural Activation Scale

Behavioural Activation Scale –Drive

The subscale measures subjects readiness to work hard for reward. There were no differences between groups, and disease status in the GLMs was not predictive of scores(Table 4.15, Figure 4.4).

Behavioural Activation Scale – Fun Seeking

The subscale measures subjects enjoyment of novel experiences. There were no differences between groups, and disease status in the GLMs was not predictive of subscale scores (Table 4.16, Figure 4.4).

Behavioural Activation Scale – Reward Responsiveness

This subscale measures how much subjects value or enjoy rewarding experience. Cases scored slightly lower compared with controls (means 16.51 & 17.54, Wilcoxon p value = 0.049). However disease status was not predictive of scores with, or without confounding variables (Table 4.17, Figure 4.4).

Behavioural Inhibition Scale

Higher scores indicate higher sensitivity to negative experiences. Group comparisons of cases and controls showed lower scores among cases (means 22.38 & 19.31, Wilcoxon test p value = 0.02). Disease status in the GLM was negatively associated with behavioural inhibition scores ($p = 0.0069$). Post hoc testing revealed significantly lower score in the manifest group compared with controls ($p = 0.018$), but there were no other significant comparisons. Addition of confounders to the model did not change the significance of the result (Table 4.18, Figure 4.4).

Figure 4.4: BISBAS

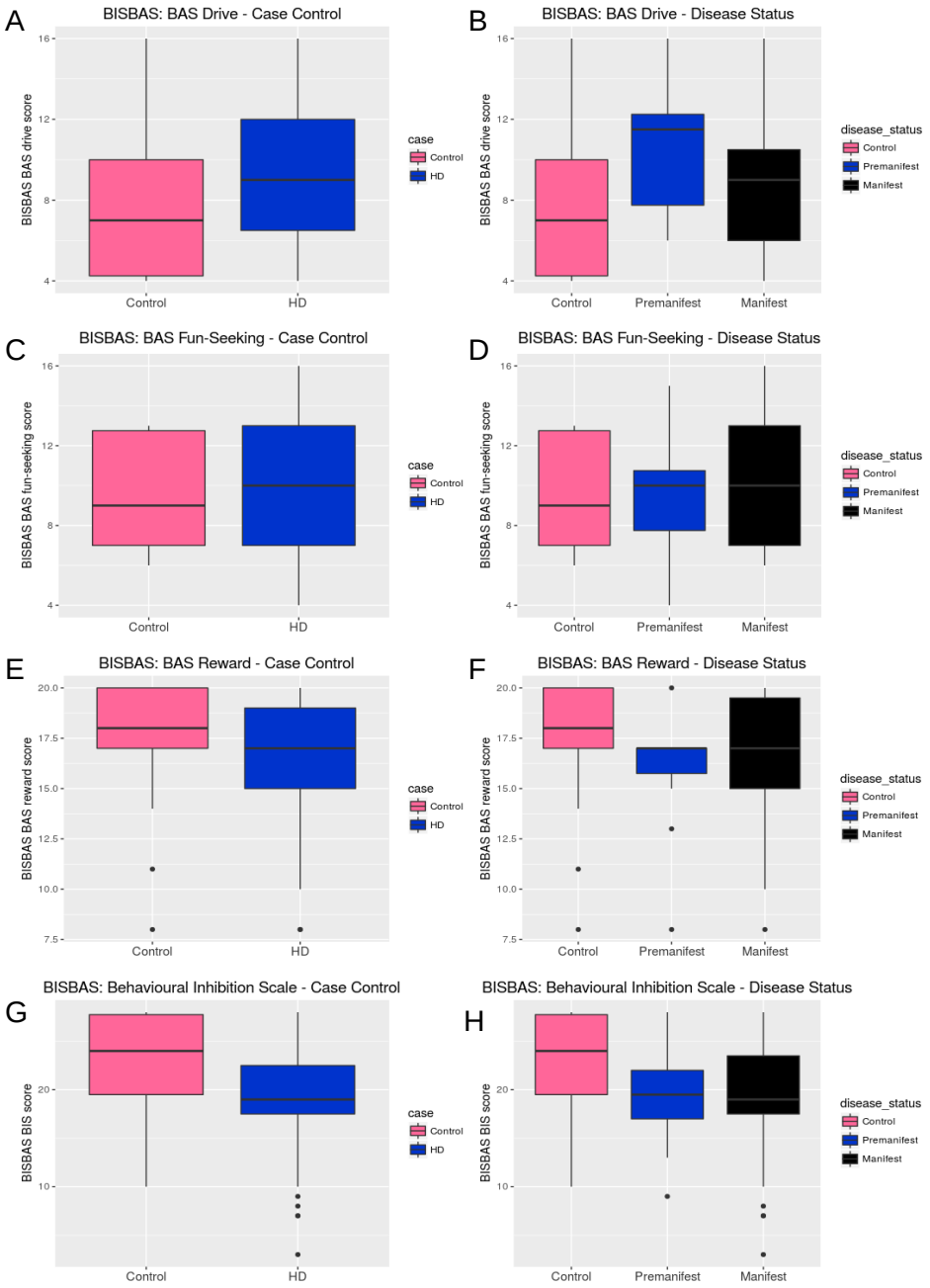


Table 4.15: BISBAS: BAS Drive

	Dependent variable:	
	BAS Drive Estimate	P Value
(Intercept)	2.20	$<2x10^{-16}$
Disease Status	0.057	0.36
Observations	77	
Log Likelihood	−207.041	
Akaike Inf. Crit.	420.082	

	Dependent variable:	
	BAS Drive Estimate	P Value
(Intercept)	2.91	$<2x10^{-16}$
Disease Status	0.083	0.28
Age	−0.0053	0.088
Gender (Male)	0.045	0.60
Olanzapine Equivalent	0.020	0.018
Fluoxetine Equivalent	−0.0026	0.20
IQ	−0.0045	0.24
Observations	73	
Log Likelihood	−188.46	
Akaike Inf. Crit.	392.93	

Bonferroni corrected alpha level: 0.0125

Table 4.16: BISBAS: BAS Fun Seeking

	Dependent variable:	
	BAS Fun Seeking	
	Estimate	P Value
(Intercept)	2.28	$<2\text{x}10^{-16}$
Disease Status	0.087	0.13
Observations	77	
Log Likelihood	−195.29	
Akaike Inf. Crit.	396.59	

	Dependent variable:	
	BAS Fun Seeking	
	Estimate	P Value
(Intercept)	2.99	$<6.84\text{x}10^{-13}$
Disease Status	0.12	0.075
Age	−0.0047	0.10
Gender (Male)	0.047	0.55
Olanzapine Equivalent	0.013	0.13
Fluoxetine Equivalent	−0.0022	0.26
IQ	−0.0046	0.20
Observations	73	
Log Likelihood	−180.66	
Akaike Inf. Crit.	377.33	

Bonferroni corrected alpha level: 0.0125

Table 4.17: BAS Reward

	Dependent variable:	
	BAS Reward	
	Estimate	P Value
(Intercept)	2.82	$<2x10^{-16}$
Disease Status	−0.035	0.42
Observations	77	
Log Likelihood	−201.065	
Akaike Inf. Crit.	408.13	

	Dependent variable:	
	BAS Reward	
	Estimate	P Value
(Intercept)	3.17	$<2x10^{-16}$
Disease Status	0.0069	0.90
Age	−0.0040	0.065
Gender (Male)	−0.079	0.19
Olanzapine Equivalent	−0.0000017	0.99
Fluoxetine Equivalent	−0.00024	0.88
IQ	−0.0012	0.67
Observations	73	
Log Likelihood	−188.69	
Akaike Inf. Crit.	393.37	

Bonferroni corrected alpha level: 0.0125

Table 4.18: BISBAS: Behavioural Inhibition Scale

	Dependent variable:	
	BIS	
(Intercept)	3.011	$<2x10^{-16}$
Disease Status	−0.11	0.0069
Observations	77	
Log Likelihood	−260.67	
Akaike Inf. Crit.	527.35	

	Dependent variable:	
	BIS	
	Estimate	P Value
(Intercept)	3.0041	$<2x10^{-16}$
Disease Status	−0.11	0.026
Age	0.00017	0.93
Gender (Male)	−0.24	0.000021
Olanzapine Equivalent	−0.012	0.065
Fluoxetine Equivalent	0.0031	0.023
IQ	0.00046	0.85
Observations	73	
Log Likelihood	−230.57	
Akaike Inf. Crit.	477.14	

Bonferroni corrected alpha level: 0.0125

Tukey Test - Manifest>Control p=0.018

4.3.4 Task Predictors of Impulsivity Scores in HD group

SSRT

Initial GLMs did not show any associations with questionnaire impulsivity measures. Adding 'Go' signal reaction time to the GLM (in order to account for generalised motor slowing) demonstrated a positive association with BIS Total score ($p = 0.00659$) and a negative association with the Positive Urgency score in the UPPSP ($p = 0.00135$), although only the association with Positive Urgency remained significant after applying the Bonferroni correction(0.005).

IGT

GLMs showed that higher IGT scores were predictive of the Barratt Impulsivity Scale total score ($p = 0.000108$), and had a negative association with the positive urgency subscore of the UPPSP ($p = 0.00143$) both of which remained significant after Bonferroni correction. There were positive associations of the IGT with Lack of Premeditation, Lack of Persistence and Negative Urgency from the UPPSP and the Inhibitory subscale from the BISBAS that did not satisfy the Bonferroni correction(0.005).

Executive function prediction of IGT scores

A GLM studying the effect of PVF score on IGT performance did not demonstrate any significant effect, but the effect of the EDSST was significant ($p = 0.0026$) in a negative direction: more set switches was associated with reduced disadvantageous choices on the IGT.

4.4 Discussion

We have shown higher levels of impulsive behaviour on selected measures in HD, compared to controls, that progresses with disease. Of the tasks, the SSRT had the largest effect size, and was significant even after including 'Go' signal reaction time in the model. The IGT was also significant and had a medium effect size. No differences were seen for the delay discounting measure or the BART. HD patients scored more highly on a number of the impulsivity self-report measures, even after correction for confounders: the 'Negative Urgency' and 'Lack Persistence' subscales from UPPSP, and the total score (and 'Motor' subscore) from the Barratt Impulsivity scale. HD Patients had lower scores on the inhibitory subscale from the BISBAS (suggesting higher levels of impulsivity) and lower scores on the 'Positive Urgency' subscale from the UPPSP. However, after correcting for the family-wise error rate using the Bonferroni method, the only self-report measures to remain significant were the reduced levels of Positive Urgency and the total score on the Barratt Impulsivity Scale. Taken together these findings suggest that HD patients are more

impulsive than controls, but only on selected measures. They have problems with decision making – they were more likely to make disadvantageous choices, and they had problems inhibiting a pre-potent response, compared with control subjects. Furthermore, on a number of self-report measures they score differently to controls, suggesting at least some level of insight into their behavioural change. The higher scores on the total score from the Barratt Impulsivity Scale are consistent with higher 'trait' impulsivity, whilst the disparity between the 'Negative Urgency' and 'Positive Urgency' subscales suggests that impulsive behaviour may be either induced or inhibited dependent on the underlying mood state in subjects with HD. Although other groups have shown stronger associations between one type of urgency, and selected behaviours than the other (for example binge-eating in bulimia is predicted by negative, but not positive urgency), to our knowledge this is the first study that has shown opposite associations in the same patient group.

The SSRT is a well-established and widely used test of inhibition, but has not been used in manifest HD subjects to date. Importantly, the fact that HD patients perform worse on this measure supports the work found in human HD subjects using the Go Nogo task, and confirms that inhibition of motor responses is the neuropsychological process that is impaired, rather than a set shifting or response selection deficit (persistent 'Go' responses might have reflected an inability of HD participants to shift response set and select the 'Nogo' action) , which are well known to occur very early in the disease course of HD(164, 382, 452). The deficit was seen, even after correcting for medication, gender, IQ and reaction time on the 'Go' trials. This suggests that despite a generalised slowing of reaction time, the inhibitory process is disproportionately slowed. Prior work in human HD subjects in a premanifest group(496), did not find a difference on the task compared with controls, but did see changes in attentional networks (inferior parietal and temporal regions) and the inhibition network (cingulate, inferior frontal regions/insula, and the supplementary motor area) during failed inhibition. Successful inhibition was associated with a reducing level of activation in the attentional network with proximity to diagnosis. Disease progression of HD may simply cause a deterioration in these responses to the point where inhibition fails. Early work on the neurobiology of motor inhibition suggested the right inferior frontal cortex as a core region involved in inhibition(287), however behavioural processes are likely to be subserved by multiple regions connected in a network: single brain regions are likely to be necessary, but not sufficient for cognitive processes, and later work has shown a wider range of regions to be involved(289, 497) – encompassing a fronto-basal ganglia network. Later work(498, 499) has not supported the earlier idea of a specific 'inhibitory' circuit, but instead suggests that a distributed network (anterior insula, anterior cingulate, frontal

operculum) is responsible for recognising and responding to infrequent stimuli, that is activated both for inhibitory tasks and tasks of attention. Although other workers, using more precise delineation of the right inferior frontal region have shown a more selective dissection of attentional and inhibitory processes(500). Cortical atrophy in these regions is known in HD, and has been correlated with performance on the Stroop task, which involves an inhibitory component(142, 501).

In our study, the HD patient group were more impaired than controls on the IGT. Post-hoc comparisons demonstrated that the difference was due to the significant disparity between the manifest and control groups in the confounder model, albeit in the model comparing disease status and IGT performance in isolation, the post-hoc comparison between manifest and premanifest was also significant. Notably our data show that IGT performance was also impaired by increasing age, male gender and lower IQ. Published comparisons between HD subjects and healthy controls have generally found IGT differences,(482–484) although none of these studies have clarified what the underlying neuropsychological process mediating the impaired performance might be, and not all groups have found this difference(485). We used the outcome measure shown to be the most reliable (number of selections from the A deck in the final 25 selections), from a meta-analysis of IGT studies(425). This may account for the clear difference between groups seen in our study, compared with published work(485) in which performance was analysed over the whole task. The IGT was originally designed to measure decision making under ambiguity in patients with ventromedial prefrontal cortex lesions(99), however as the task-originators have acknowledged, impaired performance on the task may be caused by deficits in punishment sensitivity (as seen in our work on apathy), learning, 'future blindness' (an insensitivity to the future outcomes of their decisions), or sensation-seeking/enjoyment of risk. IGT performance has been shown to be impaired in groups with high levels of impulsivity(502, 503). In patients with ventro-medial prefrontal cortex lesions, this deficit appears to be caused by 'future blindness' - an insensitivity to future consequences(481). Brand and co-workers have also shown that decisions in early trials are taken under ambiguity, whilst in later trials decision-making is 'under risk'(504). This is supported by Xu et al's finding that performance on later trials correlates with BART performance(505). In our cohort, the BART did not correlate with the IGT outcome, nor did performance on the PVF, but impaired performance was associated with a set-switching deficit. Taken together, this suggests that the impairment seen in HD on the IGT is not part of general executive dysfunction or altered risk-sensitivity, but may be part of HD patients' known set shifting deficit. This is supported by Galvez's work(487) showing normal performance by HD patients on the 'decision making under risk' part of the Cambridge

gambling task, and also Holl's finding of no association between IGT performance in HD patients and verbal fluency(485). Thus HD patients may fail to learn the contingencies of different decks (high win/higher loss for decks A & B, low win/markedly lower loss for decks C & D), have a 'pure' shifting deficit meaning they perseverate on the initially most rewarding decks, reward hypersensitivity or punishment insensitivity; all of which could account for the association between set-shifting and IGT performance.

We did not find differences between our HD group and healthy controls on the delay-discounting measure. This is in marked contrast to findings in HD animal models(506, 507), where animals carrying the HD gene all demonstrate steeper discounting than wild type animals. Immediately available rewards activate the ventral striatum, anterior cingulum, amygdala and orbitofrontal cortex, whilst intertemporal choice activates dorso-lateral PFC, and anterior insula(508–511). These areas are recognised to be affected by HD(108, 166, 415, 437, 512) however, the ventral prefrontal cortex and ventral striatum tend to be affected relatively later in the disease process(18, 58, 79) and hence may be comparatively preserved in our presymptomatic and early manifest cohort, whilst animal models have very high repeat lengths and advanced disease. Alternatively, our findings could be explained by dual degeneration: both of the valuation network activated by immediate reward, and the inter-temporal choice regions meaning that HD patients are unable to value immediate reward over delayed, or calculate expected value. Our study also did not find altered risk behaviour on the BART, although the initial model suggested a relative risk aversion in the HD population: HD patients had a lower average pump value compared with controls, however it did not surpass Bonferroni with the addition of confounders to the model. This is in keeping with Galvez et al's work, who did not find increased risky-decision making on the Cambridge gambling task(487). Notably the model showed that increased IQ, higher fluoxetine dose and male gender all increased risky decision making. Of particular note is that fluoxetine increased risky-decision making, given the wealth of literature on lower serotonergic tone leading to impulsive behaviour (reviewed by Dalley and Roiser, and Pattij and Vanderschuren(513, 514)), this was somewhat surprising, although the fluoxetine may be acting as a risk marker for low serotonergic tone, rather than increasing central nervous system serotonin to normal.

We found a marked disparity between scores on the self-report measures. Firstly, we noted differences between HD patients and controls across a range of instruments (Barratt impulsivity total score; 'positive urgency', 'negative urgency' and 'lack of persistence' from the UPPS P; and the inhibition score from the BISBAS). This suggests that HD patients have some insight into

that fact that their behaviour differs from healthy controls, although whether this difference is correct in size and direction is difficult to ascertain without an objective scoring measure. The majority of these differences did not surpass the Bonferroni and correction for confounders – only the Barratt impulsivity total score, and 'positive urgency' from the UPPS P did so. Notably, HD patients scored much lower than controls on the 'positive urgency', showing a reduced propensity to act rashly under conditions of positive affect, whilst 'negative urgency' showed a trend effect in the opposite direction (the HD group scored more highly on this measure). Negative and positive urgency have been associated with a number of measures of alcohol misuse, which has been widely recognised to be a frequent problem in HD(186, 187). The BISBAS subscores did not surpass Bonferroni after correction for confounders, suggesting that this instrument is not useful for measuring impulsive behaviour in HD.

As we discussed, the self-report measures and tasks are often poorly correlated, and may measure different aspects of impulsivity(277, 278, 515). Nonetheless our exploratory models within the HD sample showed that IGT scores predicted a number of the self-report measures (UPPS P: 'positive urgency' (negative association), 'negative urgency' and 'lack of persistence'; Barratt impulsivity score; and a negative association with the inhibitory score on the BISBAS), all of which surpassed Bonferroni. A major hypothesis regarding the validity of tasks and self-report measures for measuring impulsivity is that the tasks measure 'state' - short-lived, emotion-based and highly variable; whilst the self-report instruments measure 'trait' - long term personality components(276, 279, 514). The IGT is clearly a complex instrument, and can be affected by alterations in a number of different neuropsychological processes: it may be that some of these are 'trait' whilst others are more reflective of a 'state'. The only association with SSRT was a negative association with 'positive urgency'.

In conclusion, we have shown that the failure of inhibition previously seen in HD is robust and not altered by reaction time, medication, age or gender. The IGT is also affected by disease progression in HD, an effect not explained by confounders, which is mediated in part by a set-switching deficit. There is no evidence to suggest altered temporal discounting or risk-sensitivity in HD. This is in keeping with the known dorso-ventral progression of HD pathology. The Barratt impulsivity score is the most robust self-report measure.

Chapter 5

Irritability and Aggression

5.1 Introduction

Irritability is defined as "a temporary psychological state characterised by impatience, intolerance and poorly controlled anger . . . . . expressed outwardly towards others or inwardly towards the self." Some researchers also include aggression (behaviour that is intended to harm another individual(516))and components of impulse control(130, 340) within the definition of irritability. Irritability is common in Huntington's disease(HD). Typically it occurs before motor onset of the disease and initially progresses with the disease course before plateauing (in frequency and intensity), or even declining(209, 211, 212, 465) later in the illness. Factor analyses suggest that in HD, irritability and aggression are part of the same neuropsychiatric construct(211, 401, 517).

Morbidity in neurodegenerative disease is most reliably assessed by deteriorating function, or worsening quality of life. Irritability and aggression in HD have significant, deleterious consequences for HD patients: although these symptoms do not directly cause physical symptoms, this behaviour is responsible for significant deteriorations in quality of life(518) for patients and family members, and is predictive of nursing home admission(519).

There is some converging evidence about the neurobiological basis of aggression and irritability. Aggression in animals has been studied both pharmacologically and using focal lesions; work in cat and rodent models, has shown defensive rage is mediated via the medial hypothalamus and periaqueductal grey. These areas receive input from the amygdala, hippocampus, prefrontal cortex and cingulate cortex which may modulate expression of these symptoms. Furthermore, this behaviour may be provoked by reduced serotonergic tone (see Gregg and Siegel for reviews(520, 521)). Irritability and aggression occur in many psychiatric disorders such as bor-

derline personality disorder, bipolar disorder, attention deficit/hyperactivity disorder, depression and anxiety(301, 522–525). In contrast to the animal literature, there is less published evidence concerning the contribution of the hypothalamus and periaqueductal grey to irritable and aggressive behaviour in humans, though several studies have shown altered activity in healthy subjects exposed to threat or lesions in these regions in clinical groups prone to aggressive behaviour (357, 358, 526, 527). However, there is extensive evidence to suggest involvement of the amygdala and medial temporal structures such as the hippocampus (352, 371, 528); orbito-frontal, anterior cingulate and ventro-medial pre-frontal cortex(355, 361, 529–532); striatum(533–535); and thalamus(352). There are also a wealth of studies showing low serotonergic tone makes a major contribution to irritable and aggressive behaviour: there are low serotonin levels in subjects prone to aggressive behaviour(536–538); subjects undergoing tryptophan depletion (which reduces central serotonergic tone) have increased aggressive responses on behavioural probes of aggression (539–541), whilst drugs which increase serotonergic tone improve aggressive behaviour in some patient groups(542, 543). There is also some evidence to suggest dopaminergic(534) and cholinergic(544) involvement in irritable and aggressive behaviour.

Several behavioural paradigms have been developed to measure aggression, such as tasks measuring the level of punishment (monetary loss, electric shocks) meted out to a competitor, which have been shown to correlate with questionnaire-based assessments of aggression(344, 545). Neuropsychological studies have also shown irritable and aggressive behaviour or personality traits are associated with deficits on tasks of ventro-medial prefrontal cortex function(343, 546), increased impulsivity (both motor inhibition(547–549) and delay discounting(550, 551) and increased sensitivity to unfairness(552).

Despite the impact on quality of life and the socio-economic burden of irritability in HD, comparatively little is known about the neuropsychological and neurobiological basis of irritability in the illness. One study compared emotional responses between patients with HD and controls, on a range of scenarios and pictures designed to induce fear, happiness and disgust. The HD group had lower self-reported fear ratings and higher self-reported anger ratings to the fear inducing scenes and scenarios, but irritability was not measured(553). Deficits in social cognition are common in HD (177-180), and consequent misinterpretation of other peoples' motives or behaviour could conceivably provoke anger or irritation. However, a recent study showed that irritability was not associated with deficits on tests of social cognition(177). A post-mortem study has shown a correlation between globus pallidus atrophy in HD and level of irritability measured in life(554). One study using functional imaging(555), suggested irritability in HD correlates

with increased signal during anger induction in HD subjects in the pulvinar; self-report of irritability correlates with increased amygdala activity, and reduced orbito-frontal activity during a frustrating task (although this study did not correlate the imaging changes with an objective irritability measure(130)); and a structural imaging study has shown correlations between irritability and reduced structural integrity in white matter throughout the left hemisphere(556). Furthermore, there are some treatment guidelines to suggest benefit from serotonergic and antipsychotic medications(557). However, in contrast to the wider psychiatric literature concerning irritability and aggression, these studies do not tell us what the alterations in cognitive processes are, that lead to irritability and aggression in HD.

This study aims to address this deficit by using a task-based approach to probe response to provocation (using both self-report measures, and objective, behavioural measures of aggression and frustration), insensitivity to future consequences, sensitivity to unfairness and impulsive behaviour in order to delineate which processes best predict irritable and aggressive behaviour.

5.2 Methods

5.2.1 Patient Recruitment and Consent

As described in materials and methods, 53 patients were recruited through the South Wales HD service. All participants had a confirmed genetic diagnosis of HD (CAG repeat length >36). Participants were recruited at all stages of disease from pre-symptomatic to moderately symptomatic. Control participants were recruited from family members not at risk of HD and local advertising within Cardiff University.

5.2.2 Gold Standard Assessments of Irritability in HD

Problem Behaviours Assessment (Short form)(165, 211, 221)

This is a clinician scored assessment designed for HD, which is used to rate a range of different neuropsychiatric symptoms over the preceding 4 weeks. Each item is scored on severity (0-4) and frequency (0-4) to produce a compound score (0-16). It includes subscores for aggression (verbally expressed anger, threats or violent behaviour; PBA Aggression) and irritability (how easily the subject loses their temper; PBA Irritability). The assessing clinician interviews the patient and anyone with primary caring responsibility for the subject, to avoid problems with

lack of insight/voluntary concealment.

Snaith Irritability Scale(339, 340)(Snaith)

This is a self-report measure. It consists of 18 questions (e.g. "I lose my temper and shout or snap at others") scored on a Likert scale from 0-3. The final score is a summation of the responses for each sub-item: maximum score 54.

5.2.3 Tasks

Impulsivity Measures

Ultimatum Game(390)

This task is an economic decision-making task. Subjects are told. "There is a sum of £50 to be divided between you and another player. You are the divider, who makes the decision about how much of the sum to offer to the other player. The receiving player then chooses whether to accept the offered sum, or reject it. If the offer is rejected both players get nothing. You will then be asked what is the lowest offer you would accept." Subjects were duly asked how they would divide the money between themselves and the second player, and what the lowest offer they would accept would total. The outcome measures were: 1) the 'offer' made to the second player, 2) the lowest offer they would accept and 3) the difference between the offer made by the subject, and the lowest offer they would accept. If this task is performed purely based economic self-interest, the lowest offer subjects would accept is £1 (as £1 is more than they would receive if the offer is rejected: where both players receive £0). However, previous work has shown that if the disparity between amounts is very large, most subjects will reject the offer, demonstrating that an assessment of fairness is also included in responses on this task(390).

Stop Signal Reaction Task

We used the Verbruggen(389) stop signal reaction task, which assesses motor inhibition as described in Chapter 4. The outcome measure was the stop signal response time (SSRT): a measure of the reaction time for the neural inhibitory response. Longer reaction times are indicative of slower inhibitory neural circuits and hence higher motor impulsivity.

Monetary Choice Questionnaire(384)

This is a 27 item questionnaire described in Chapter 4. The outcome measure was the slope of the hyperbolic discounting function (kD) – a constant which varies between individuals. Higher preference for immediate over delayed reward (indicating higher impulsivity) results in higher kD values. In this work, kD was calculated using an automated scoring system(493, 494).

Computerised Provocation Measures

Klöppel Task(130)

Subjects were told that the task was an assessment of visual perception, and that they had to compete to win points. They were then told "In the first part of the experiment you will be playing alone, in the second half you will be joined by a second player. In the second part of the task, both players have to be correct in order for you to win points. You will be asked to respond after you have viewed both squares, responses before this will not be logged." On each trial, subjects viewed a fixation cross followed by 2 squares presented sequentially in the centre of the screen. They were shown one square, then a second square and asked to say which was larger, the first or the second. They then had a feedback screen saying whether or not they were correct. There were 50 trials in each part of the task (100 in total). Subjects were incorrectly told they were wrong on 14% of trials (experimental verification was used in previously published work, to find the maximum level of erroneous feedback before which subjects (HD and healthy controls(130)) would become suspicious that the feedback was incorrect). The squares were very close in size (28mm, 29mm and 31mm). The first square was displayed for 1000ms, and the second for a range of 500-2500ms. The response and feedback screens were displayed for 3000ms each. Subjects won 5 points for correct answers ("Correct! You win 5 points" was displayed on a yellow background) and lost 2 points ("Incorrect. You lose 2 points" was displayed on a red background). The second player was added to increase subjects' levels of irritability: on 14% of occasions they would be wrong when the subject was correct, thereby losing points for the subject. We hypothesised that as subjects became more frustrated they would respond prematurely more often, and would make repetitive button presses on the response screen. Therefore, the outcome measures were firstly the absolute number of premature responses (button presses) made throughout the task, and secondly the absolute number of button presses made during the response screen.

Tower Task

This was based on the point subtraction aggression protocol(344). Subjects were told they would play a series of 6 games against 2 opponents (12 games in total). During each game, subjects were told "You have to compete against an opponent to win points. The first player to 20 points wins. You will first see a 'Totals' screen displaying your score and your opponents score, before being offered the opportunity to add points to your total or steal points from your opponent.

When you see an 'ADD' screen, press 'L' on the keyboard as many times as you can to win points. When you see a 'STEAL' screen press 'S' on the keyboard as many times as you can, if you want to steal points." Subjects were shown a screen with the totals for themselves and an opponent (zero at the beginning of each game; 'TOTALS' screen), followed by either an 'ADD' screen (80% probability) which read "ADD. Press L to win points", or a 'STEAL' screen (20% probability), which read "STEAL. Press S to steal points."(each lasting 3000 ms). Subjects could win up to 5 points on an ADD screen (random number from 1-5), whilst their opponent would always win either 4 or 5 points, whilst a STEAL screen would result in up to 5 points being deducted from their opponent (random number from 1-5). After each ADD or STEAL screen, the TOTALS screen would be displayed with the cumulative points for each player (5000 ms). Each game finished when either the subject or the opponent reached 20 points. The first opponent never stole from the subject, whilst the second always did (4-5 points on each occasion). The task was designed to be unfair. Outcome measures were the VAS scores, and the frequency of 'STEAL' attempts by the participant.

Frustrative Non-Reward (FNR)

This concept was based on the animal protocol where reward is withdrawn(383). Subjects were told they had to complete a series of demographic questions 'to log this session for our records'(Figure 1). They were then asked a series of questions, to enter name, address (each line had to be entered separately), gender, mother's maiden name and name of first pet. Following the final question "what is your email address", the computer would display a message stating "Runtime error. Data not saved. Please re-enter". Subjects would have to enter their data 4 times before being allowed finish data entry and complete the end of task VAS. Outcome measures were the VAS scores.

Self-Report of Emotion: Visual Analogue Scales (VAS)

Before and after each provocation task, subjects were asked to rate their emotions over different domains (happy, sad, frustrated, angry, irritable) between 0-100, where 0 represented 'not at all', whilst 100 represented 'strongest feeling ever'. The 'happy' and 'sad' scores were included to obscure the fact that the tasks were designed to measure irritable feelings. The scores for "frustrated", "angry" and "irritable" were totalled to create 'pre' and 'post' VAS scores for each task. The 'net' value represents VAS 'post' score minus VAS 'pre' score. Before starting the task battery, subjects were told by the experimenter - "you will be asked to complete some emotional rating scales before and after some of these tasks to measure your emotions at random points throughout the experiment". Before the Klöppel and Tower task , no further explanation

or warning would be given. Prior to the pre-task VAS for the Frustrative Non Reward task, subjects were informed they would be completing a series of questions to record demographic details and 'log this session for our records'.

Measures of Insensitivity to Future Consequences

Iowa Gambling Task(99, 481) (IGT)

This task was designed (and robustly tested) as a measure of ventromedial prefrontal cortex function. The task asks subjects to select cards from 4 different packs. They are told they win money every time they draw a card, but on some trials they will then also lose money; over time some packs result in higher losses than gains and they must learn to avoid these 'bad' packs. The outcome measure is the number of selections from the highest loss pack in the final 25 trials of the game: recently shown to be the most reliable outcome measure from this task(425). This study used the Pebl version of the task(424).

5.2.4 Statistical Analysis

Analyses were run in R, an online statistical software package(427). We compared outcome measures between cases and controls, in addition to using statistical models to predict our gold-standard assessments of irritable behaviour (PBA Aggression, PBA Irritability and Snaith). We used Wilcoxon tests to compare groups, however the comparisons were limited by ties in the data. Consequently the accuracy of the p values produced could not be relied upon. We therefore compared cases and controls using logistic models of case status. We initially fitted multiple linear regression models to compare performance, however, the residuals of the regression models (with the exception of the Net VAS scores, and SSRT) were not normally distributed (Shapiro test of the residuals was highly significant) and the distributions of the data conformed to Poisson distributions; thus the assumptions underlying the regression models were violated. Generalised Linear Models (GLMs) with a Poisson distribution were used for the majority of our analyses initially, we tested each of them independently for over-dispersion (using the AER package in R): all of the tests were significant indicating over-dispersion and hence negative binomial models were used, with the exceptions of the SSRT model and the Net VAS scores, which had Gaussian distributions. Dopaminergic and serotonergic drug doses were converted to Olanzapine and Fluoxetine equivalents based on meta-analyses(379, 380). IQ was calculated

using Crawford's method(377), as reading test estimates of IQ deteriorate in the symptomatic HD population(378, 429, 430). For each variable, we initially created a GLM looking at the effect of case status in isolation (cases versus controls), then added potential confounding variables to each model (age, IQ, gender, Olanzapine dose, Fluoxetine dose, TMS). We then used GLMs to measure the predictive effect of the behavioural measures on gold standard assessments of irritable and aggressive behaviour, to create models with and without confounding variables. Family wise error rate was controlled with the Bonferroni method.

5.3 Results

5.3.1 Demographics

The HD population did not differ from controls on age or gender. The HD group had marginally lower IQ, and higher scores on all the irritability/aggression measures, in addition to higher TMS, and medication doses.

Table 5.1: Demographics

	HD	Controls	
Age	53.92 (33-82)	46.85 (20-75)	
IQ	103.53 (88.75-125.27)	109.73 (89.79-128.51)	*
Gender	26/53 female	17/26 female	
PBA Irritability	3.06 (0-12)	0.38 (0-2)	**
PBA Aggression	2.04 (0-12)	0.31 (0-4)	**
Snaith Irritability Scale	7.51 (0-18)	3.62 (0-10)	***
Olanzapine dose (mg)	1.98 (0-41.25)	0	***
Fluoxetine dose (mg)	21.85 (0-146.5)	2.4 (0-22.2)	***
CAG Repeat Length	42.5 (38-50)	-	
Total Motor Score	36.58 (0-89)	1.48 (0-6)	***

** 0.05 ** 0.01 *** 0.001*

Self-Report of Emotion: Visual Analogue Scales (VAS)

Anticipatory VAS Scores

The anticipatory VAS scores were taken before subjects started the provocation tasks. Notably for the FNR, they were measured following an instruction screen describing the need for subjects to complete some demographic details and security questions, but before beginning answering the questions (Figure 5.1). The generalised linear models (GLMs) comparing the effect of case status on pre-task VAS scores showed a consistent effect across all the tasks: the HD group had higher scores (all p<2x10-16). When potential confounding variables were added to the models, the only effect that was retained was the pre-task VAS score for the FNR task, which was higher in the HD group.

Prediction models comparing VAS scores and gold standard irritability aggression measures in the HD group demonstrated an association between FNR anticipatory VAS scores and all gold standard irritability and aggression scores (at trend level: p=0.062 with PBA Aggression), an effect which was retained, or strengthened (the association with PBA Aggression p=0.013) when confounding variables were included in the model. This association was also seen across all gold standard assessments for the Klöppel anticipatory VAS scores, albeit the association with PBA Irritability was at trend level in the model including confounding variables (p=0.095). The association was less marked for the Tower anticipatory VAS scores, which demonstrated an association in the initial models, but this effect was lost in the GLMs including confounding variables, although a trend level (p=0.082) association was seen with the Snaith(Tables 5.2 - 5.5, Figures 5.2 - 5.4).

Post-Task VAS Scores

In the models comparing cases and controls, the HD group had higher post-task VAS scores across all tasks. However, this effect was lost in the models including confounding variables, except for the FNR.

The post-task VAS prediction models in the HD group, did not show such consistent effects as the pre-task VAS prediction models. The FNR model demonstrated a trend-level association between post-FNR VAS score and the Snaith but neither of the PBA scores in the models including confounding variables. The post-Tower VAS score did not display any significant association with gold standard measures in the models including confounders. The post-task Klöppel VAS scores showed a significant predictive effect on the Snaith, but neither of the PBA measures(Tables 5.6 - 5.9, Figures 5.5 - 5.7).

Net VAS Scores

These scores were calculated from VAS post-task score minus VAS anticipatory score, and measured VAS change over the provocation tasks. The GLMs comparing cases and controls did not demonstrate any difference between the groups. The GLMs looking at association between Net VAS scores on each task, did not demonstrate any associations with the gold standard irritability and aggression measures (Tables 5.6 - 5.9, Figures 5.10 - 5.13).

Figure 5.1: Frustrative Non-Reward Introductory Screen

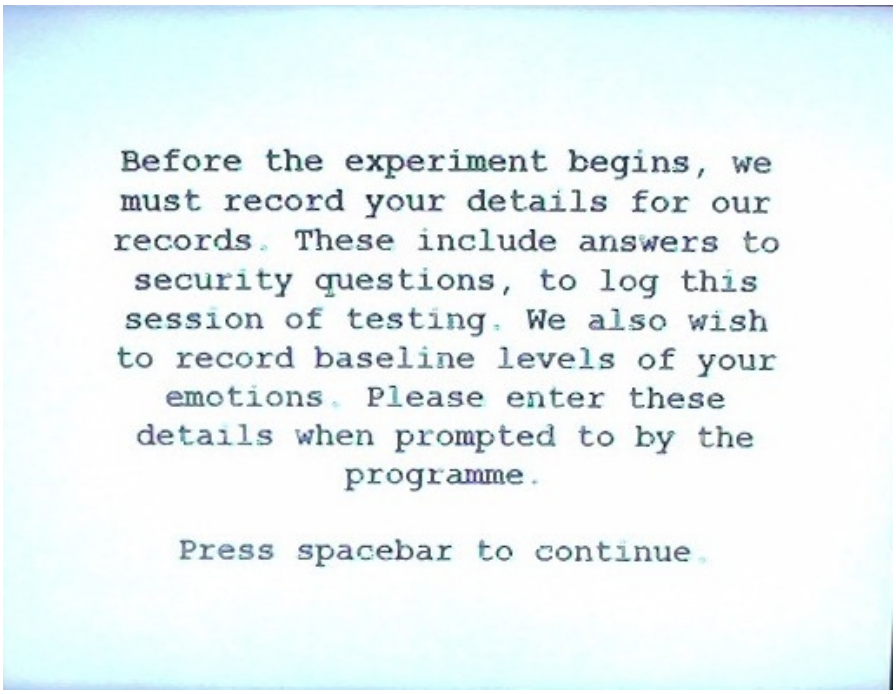


Figure 5.2: Anticipatory VAS Scores- FNR

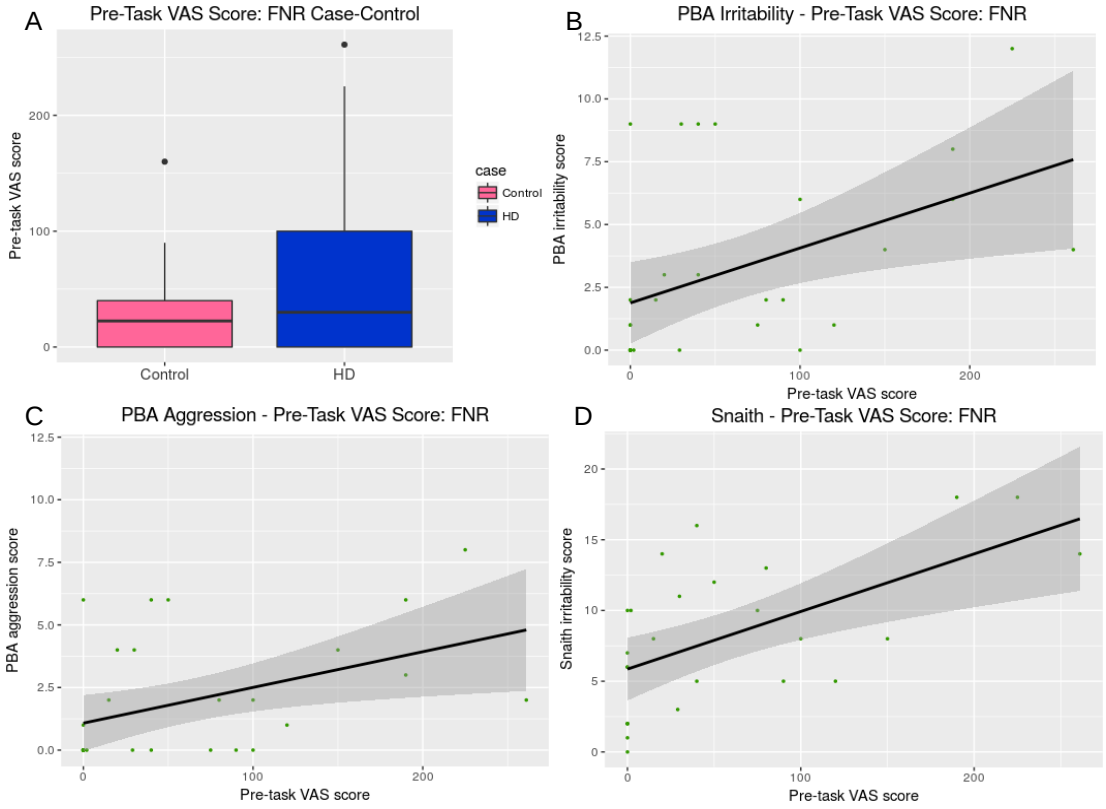


Figure 5.3: Anticipatory VAS Scores- Tower

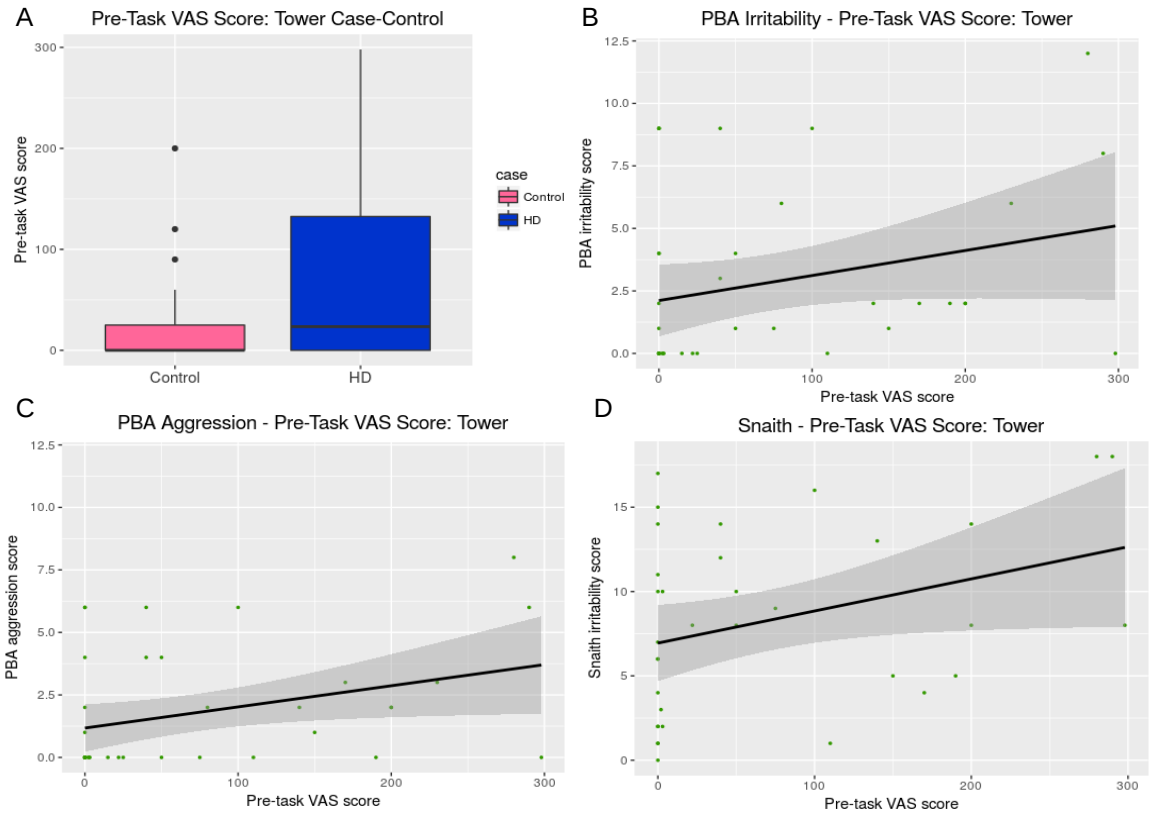


Figure 5.4: Anticipatory VAS Scores- Klöppel

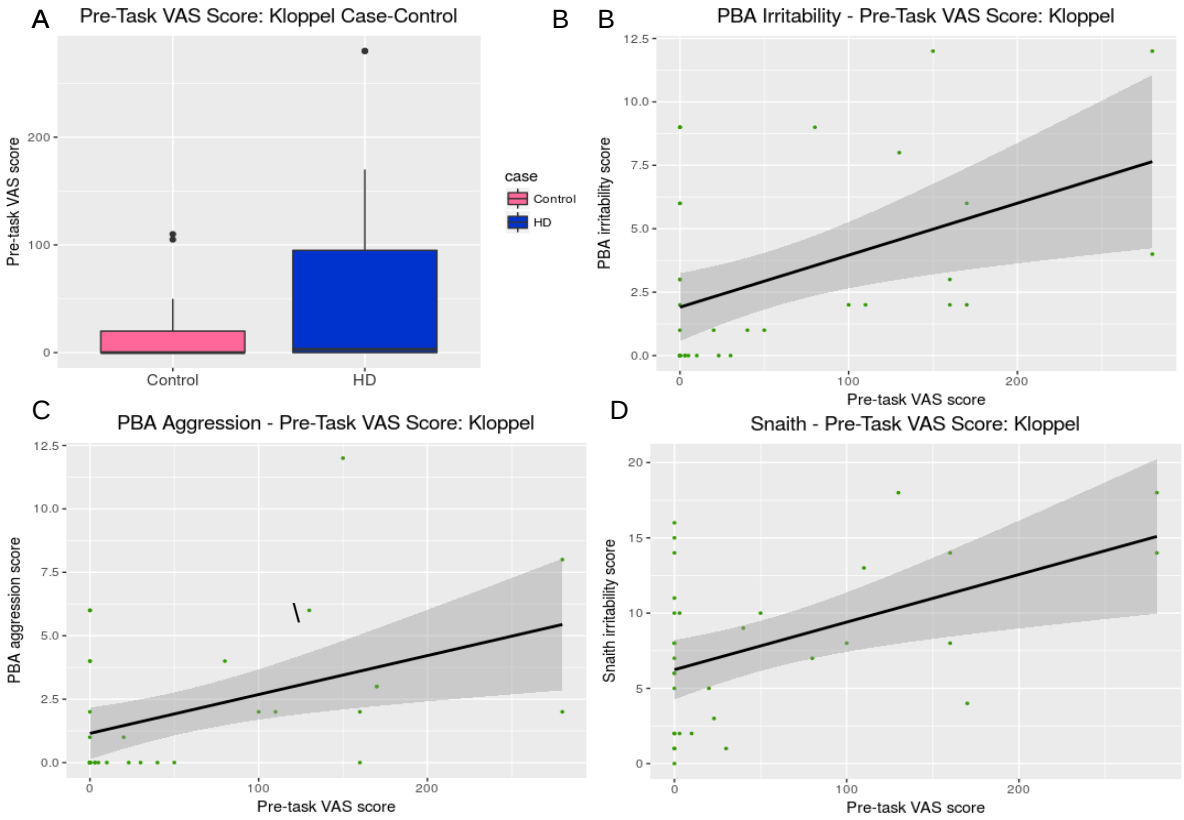


Table 5.2: Anticipatory VAS Scores- Group Comparisons

	Dependent variable:					
	FNR		Tower		Klöppel	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	3.47	$<2x10^{-16}$	3.21	$<2x10^{-16}$	2.91	$<2x10^{-16}$
Case HD	0.66	$<2x10^{-16}$	1.076	$<2x10^{-16}$	1.036	$<2x10^{-16}$
Observations	47		61		59	
Log Likelihood	−1,846.71		−3,200.72		−2,625.38	
Akaike Inf. Crit.	3,697.42		6,405.45		5,254.77	

	Dependent variable:					
	FNR		Tower		Klöppel	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	4.25	$<2x10^{-16}$	6.063	0.14	7.97	0.061
Case HD	0.35	$1.65x10^{-6}$	−0.12	0.91	−0.44	0.69
Age	0.0034	0.060	−0.054	0.051	−0.0090	0.75
IQ	−0.011	$7.81x10^{-8}$	−0.0039	0.91	−0.040	0.25
TMS	0.015	$<2x10^{-16}$	0.044	0.057	0.025	0.25
Olanzapine Equivalent	0.031	$1.32x10^{-14}$	0.040	0.64	0.082	0.32
Fluoxetine Equivalent	−0.0026	0.027	−0.0067	0.72	−0.015	0.41
Observations	44		56		56	
Log Likelihood	−1,497.79		−205.26		−190.29	
Akaike Inf. Crit.	3,009.57		424.51		394.57	

Table 5.3: Anticipatory VAS Scores- FNR

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	0.70	0.017	0.17	0.64	1.80	$<2\text{x}10^{-16}$
VAS Pre FNR	0.0060	0.033	0.0063	0.062	0.0043	0.0036
Observations	29		29		26	
Log Likelihood	−65.78		−53.36		−76.094	
Akaike Inf. Crit.	135.57		110.73		156.19	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	5.72	0.020	4.71	0.10	1.43	0.28
VAS Pre FNR	0.0060	0.040	0.0083	0.013	0.0042	0.0062
Age	−0.029	0.22	−0.012	0.67	0.0013	0.92
IQ	−0.035	0.081	−0.037	0.12	0.00067	0.95
TMS	0.013	0.32	0.0077	0.62	0.0069	0.32
Olanzapine Equivalent	0.049	0.25	0.058	0.27	−0.13	0.21
Fluoxetine Equivalent	−0.019	0.069	−0.025	0.074	0.0048	0.30
Observations	27		27		25	
Log Likelihood	−58.40		−47.75		−72.069	
Akaike Inf. Crit.	130.80		109.49		158.14	

Table 5.4: Anticipatory VAS Scores- Tower

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	0.79	0.0084	0.21	0.53	1.95	$<2\text{x}10^{-16}$
VAS Pre Tower	0.0029	0.23	0.0040	0.13	0.0020	0.098
Observations	38		38		34	
Log Likelihood	−82.33		−67.05		−103.74	
Akaike Inf. Crit.	168.65		138.11		211.48	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	4.11	0.11	4.14	0.14	2.54	0.038
VAS Pre Tower	0.0027	0.38	0.0044	0.18	0.0025	0.082
Age	−0.0084	0.75	−0.0038	0.90	0.0041	0.74
IQ	−0.029	0.20	−0.036	0.15	−0.0087	0.40
TMS	0.0054	0.74	0.00099	0.95	−0.0015	0.84
Olanzapine Equivalent	0.024	0.63	0.015	0.78	−0.096	0.12
Fluoxetine Equivalent	−0.0078	0.50	−0.0066	0.60	0.0080	0.11
Observations	36		36		33	
Log Likelihood	−76.29		−63.0064		−98.63	
Akaike Inf. Crit.	166.57		140.013		211.26	

Table 5.5: Anticipatory VAS Scores- Klöppel

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	0.70	0.011	0.19	0.55	1.85	$<2x10^{-16}$
VAS Pre Klöppel	0.0054	0.050	0.0064	0.042	0.0033	0.020
Observations	38		38		33	
Log Likelihood	−82.32		−67.80		−97.89	
Akaike Inf. Crit.	168.64		139.59		199.79	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	5.51	0.027	4.019	0.17	1.0060	0.40
VAS Pre Klöppel	0.0048	0.095	0.0075	0.024	0.0044	0.0032
Age	0.0046	0.84	0.023	0.40	0.0011	0.92
IQ	−0.057	0.016	−0.054	0.055	0.0059	0.57
TMS	0.013	0.28	0.0029	0.84	0.0021	0.72
Olanzapine Equivalent	−0.033	0.40	−0.046	0.33	−0.13	0.0099
Fluoxetine Equivalent	0.0089	0.33	0.011	0.32	0.0068	0.12
Observations	36		36		32	
Log Likelihood	−73.61		−62.34		−181.077	
Akaike Inf. Crit.	161.23		138.68		197.08	

Figure 5.5: Post-Task VAS Scores- FNR

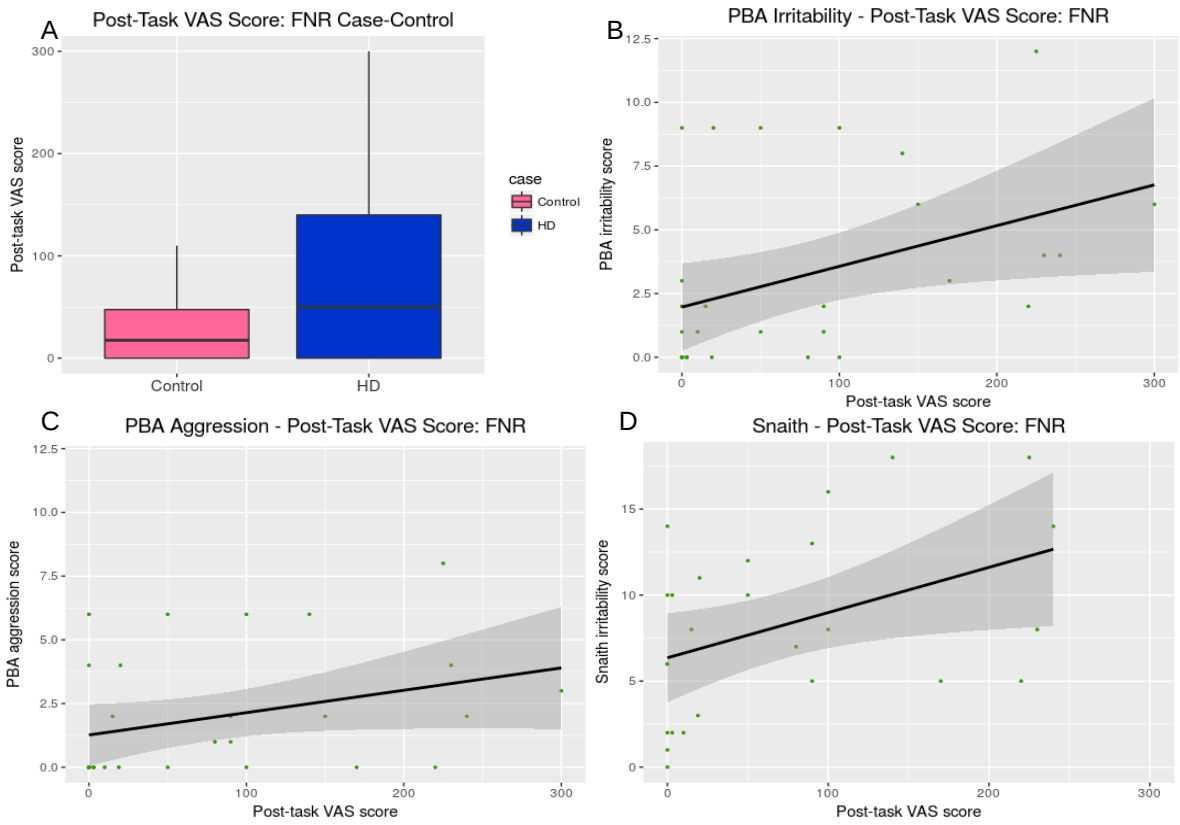


Figure 5.6: Post-Task VAS Scores- Tower

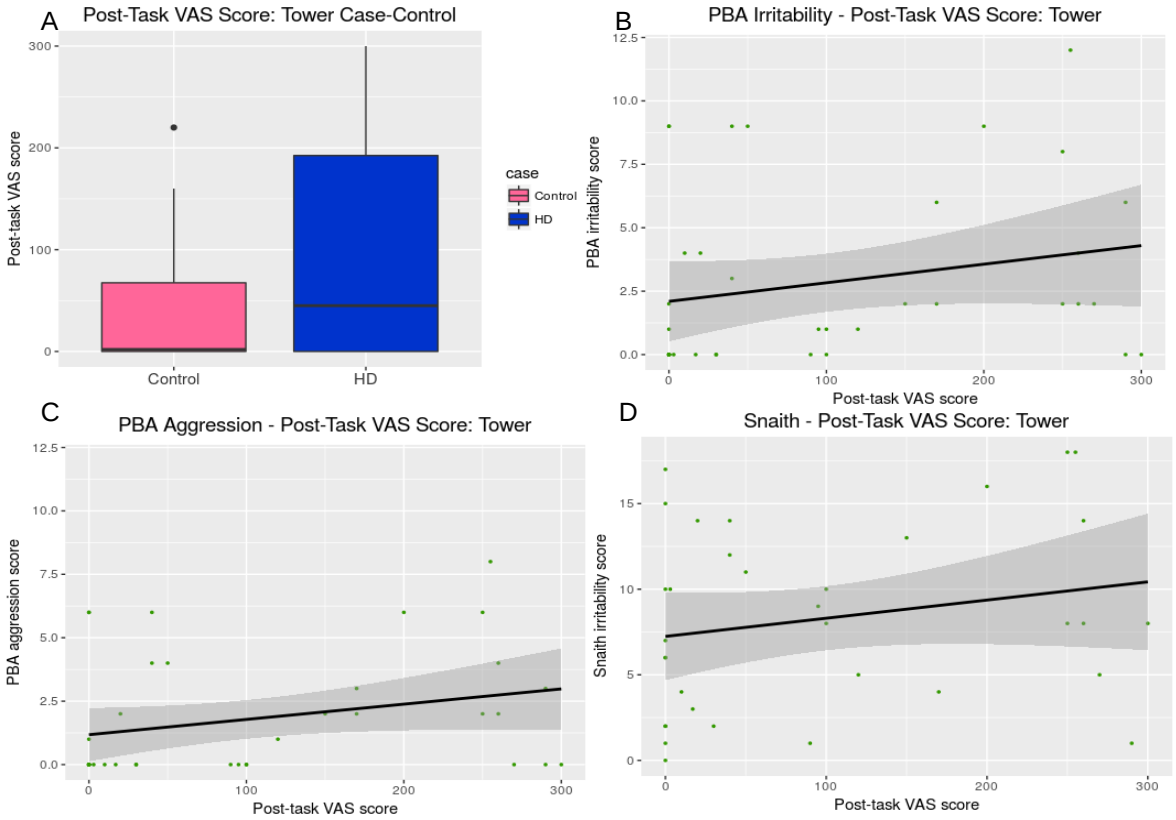


Figure 5.7: Post-Task VAS Scores- Klöppel

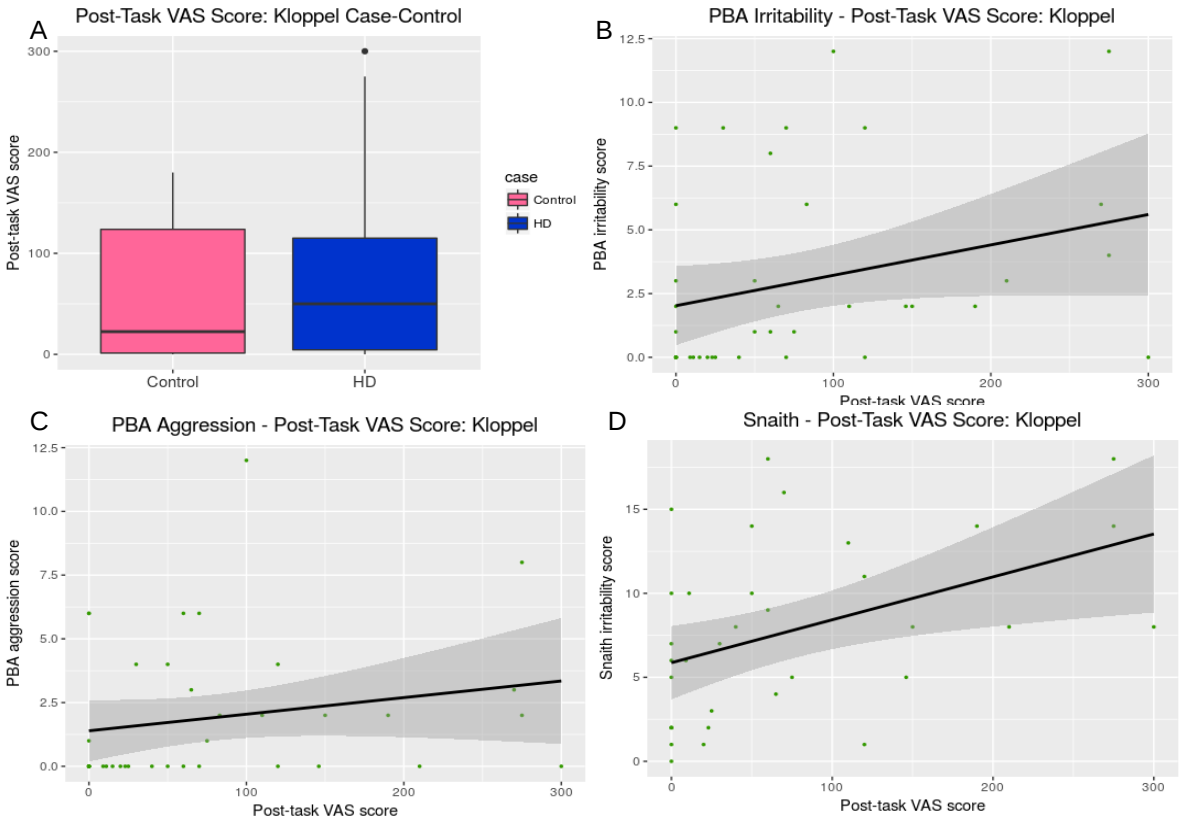


Table 5.6: Post-Task VAS Scores- Group Comparisons

	Dependent variable:					
	FNR		Tower		Klöppel	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	3.37	$<2x10^{-16}$	3.79	$<2x10^{-16}$	4.012	$<2x10^{-16}$
Case HD	1.0025	$<2x10^{-16}$	0.83	$<2x10^{-16}$	0.34	0.47
Observations	47		61		61	
Log Likelihood	−2,043.88		−3,633.36		−296.63	
Akaike Inf. Crit.	4,091.76		7,270.72		597.26	

	Dependent variable:					
	FNR		Tower		Klöppel	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	4.92	$<2x10^{-16}$	3.29	0.3	4.65	0.069
Case HD	0.65	$<2x10^{-16}$	−0.090	0.92	0.18	0.79
Age	−0.0090	$4.88x10^{-7}$	−0.022	0.33	−0.019	0.27
IQ	−0.012	$6.19x10^{-11}$	0.013	0.64	0.0012	0.95
TMS	0.012	$<2x10^{-16}$	0.034	0.73	0.017	0.22
Olanzapine Equivalent	0.025	$3.62x10^{-14}$	0.039	0.59	0.066	0.22
Fluoxetine Equivalent	0.00098	0.30	−0.0062	0.69	−0.015	0.18
Observations	44		56		58	
Log Likelihood	−1,686.63		−248.21		−275.95	
Akaike Inf. Crit.	3,387.27		510.41		565.90	

Table 5.7: Post-Task VAS Scores- FNR

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	0.71	0.020	0.25	0.50	1.85	$<2x10^{-16}$
VAS Post FNR	0.0047	0.049	0.0044	0.14	0.0032	0.033
Observations	29		29		26	
Log Likelihood	−66.13		−54.0051		−77.70	
Akaike Inf. Crit.	136.27		112.01		159.41	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	5.31	0.035	4.20	0.15	1.59	0.26
VAS Post FNR	0.0045	0.11	0.0039	0.23	0.0028	0.073
Age	−0.031	0.19	−0.018	0.51	0.0018	0.88
IQ	−0.031	0.13	−0.030	0.22	−0.00079	0.95
TMS	0.018	0.17	0.019	0.24	0.0078	0.30
Olanzapine Equivalent	0.051	0.24	0.058	0.28	−0.078	0.46
Fluoxetine Equivalent	−0.022	0.050	−0.024	0.082	0.0040	0.42
Observations	27		27		25	
Log Likelihood	−58.82		−48.92		−73.85	
Akaike Inf. Crit.	131.65		111.84		161.70	

Table 5.8: Post-Task VAS Scores- Tower

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	0.75	0.022	0.18	0.64	1.98	$<2\text{x}10^{-16}$
VAS Post Tower	0.0026	0.23	0.0034	0.16	0.0013	0.26
Observations	38		38		34	
Log Likelihood	−82.44		−67.27		−104.50	
Akaike Inf. Crit.	168.87		138.55		213.0042	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	4.31	0.098	4.23	0.14	2.95	0.19
VAS Post Tower	0.0012	0.66	0.0026	0.38	0.0011	0.40
Age	−0.016	0.55	−0.012	0.68	−0.0010	0.94
IQ	−0.028	0.22	−0.034	0.17	−0.011	0.32
TMS	0.011	0.52	0.0069	0.70	0.0023	0.78
Olanzapine Equivalent	0.025	0.62	0.014	0.79	−0.08	0.20
Fluoxetine Equivalent	−0.0068	0.55	−0.0047	0.71	0.0088	0.088
Observations	36		36		33	
Log Likelihood	−76.50		−63.38		−99.56	
Akaike Inf. Crit.	167.0061		140.76		213.12	

Table 5.9: Post-Task VAS Scores- Klöppel

	Dependent variable:					
	PBA Irritability	PBA Aggression	Snaith			
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	0.71	0.020	0.31	0.41	1.79	$<2\text{x}10^{-16}$
VAS Post Klöppel	0.0040	0.11	0.0037	0.24	0.0031	0.019
Observations	39		39		34	
Log Likelihood	−85.42		−69.92		−100.48	
Akaike Inf. Crit.	174.84		143.85		204.96	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	5.50	0.024	5.18	0.084	1.30	0.28
VAS Post Klöppel	0.0020	0.45	0.0011	0.74	0.0032	0.018
Age	−0.0032	0.89	0.0085	0.76	0.0014	0.90
IQ	−0.053	0.017	−0.060	0.032	0.0017	0.87
TMS	0.018	0.14	0.021	0.18	0.0033	0.60
Olanzapine Equivalent	−0.031	0.46	−0.027	0.59	−0.088	0.091
Fluoxetine Equivalent	0.0089	0.33	0.0084	0.46	0.0077	0.095
Observations	37		37		33	
Log Likelihood	−76.90		−64.31		−95.34	
Akaike Inf. Crit.	167.79		142.61		204.68	

Figure 5.8: Change in VAS Scores- FNR

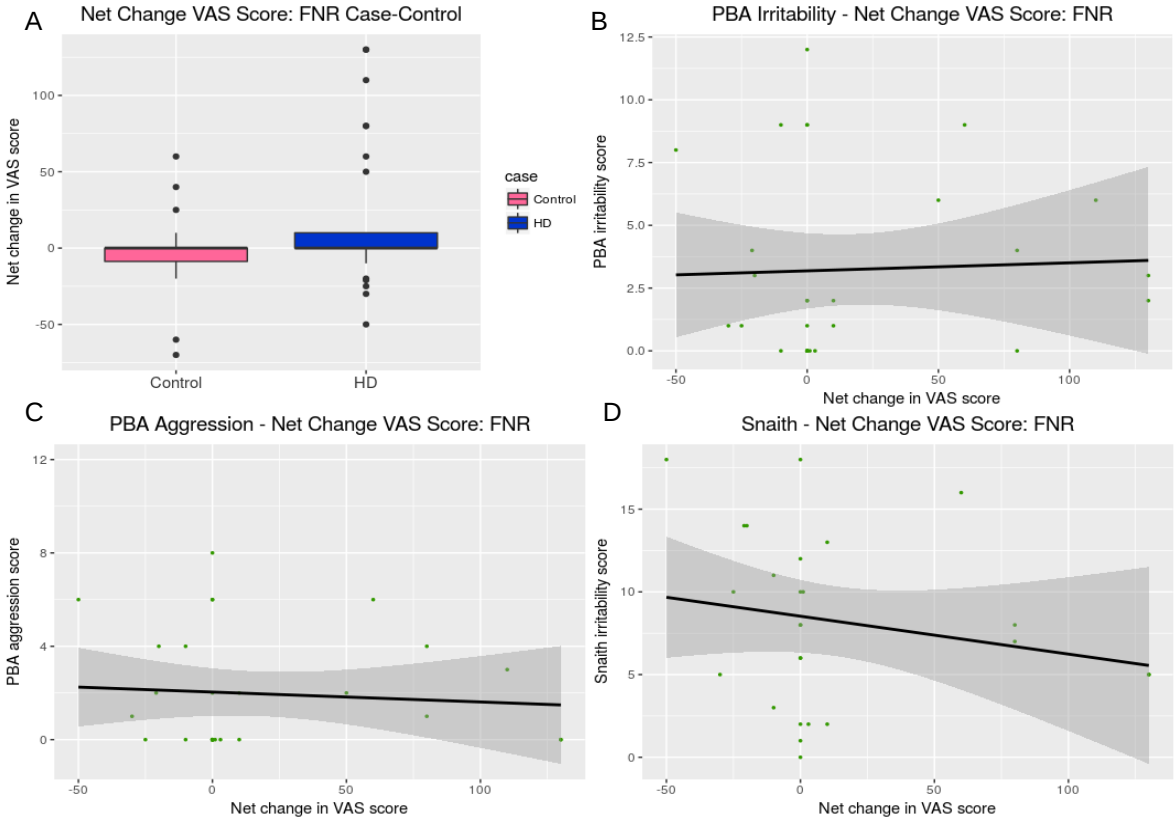


Figure 5.9: Change in VAS Scores- Tower

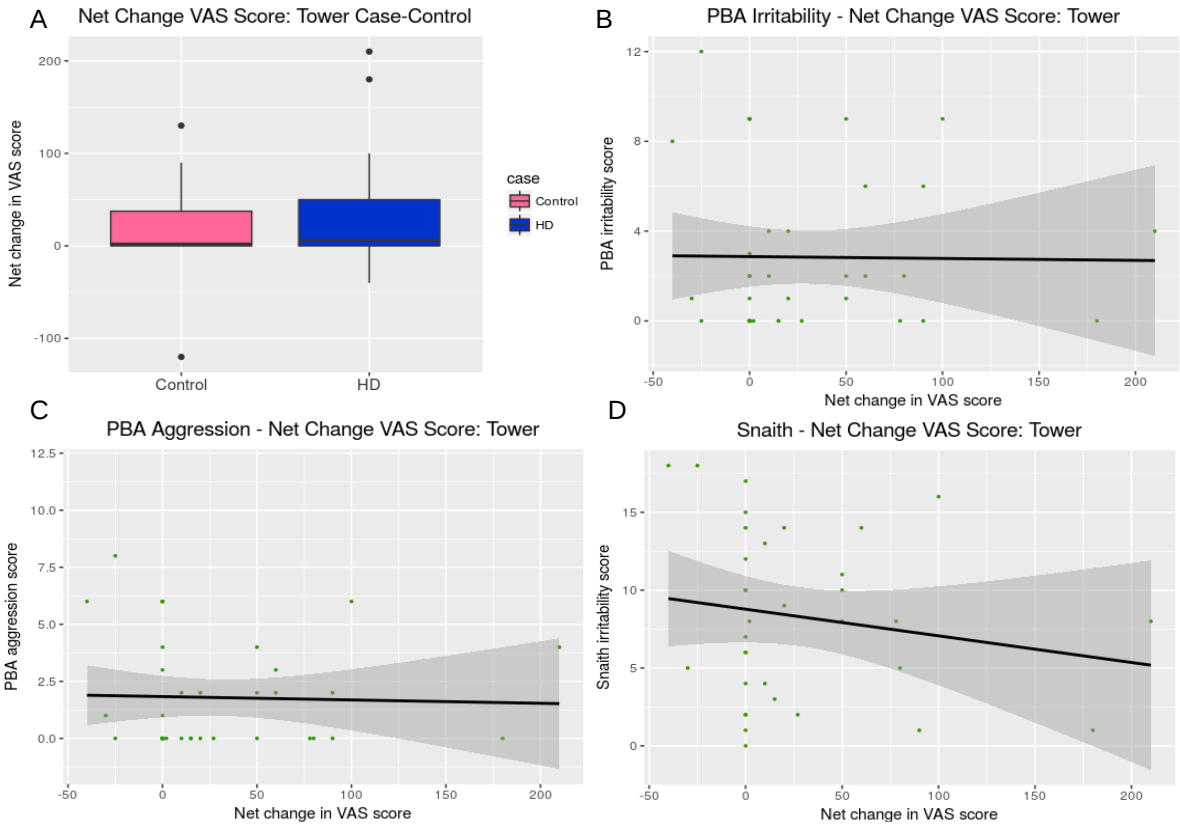


Figure 5.10: Change in VAS Scores- Klöppel

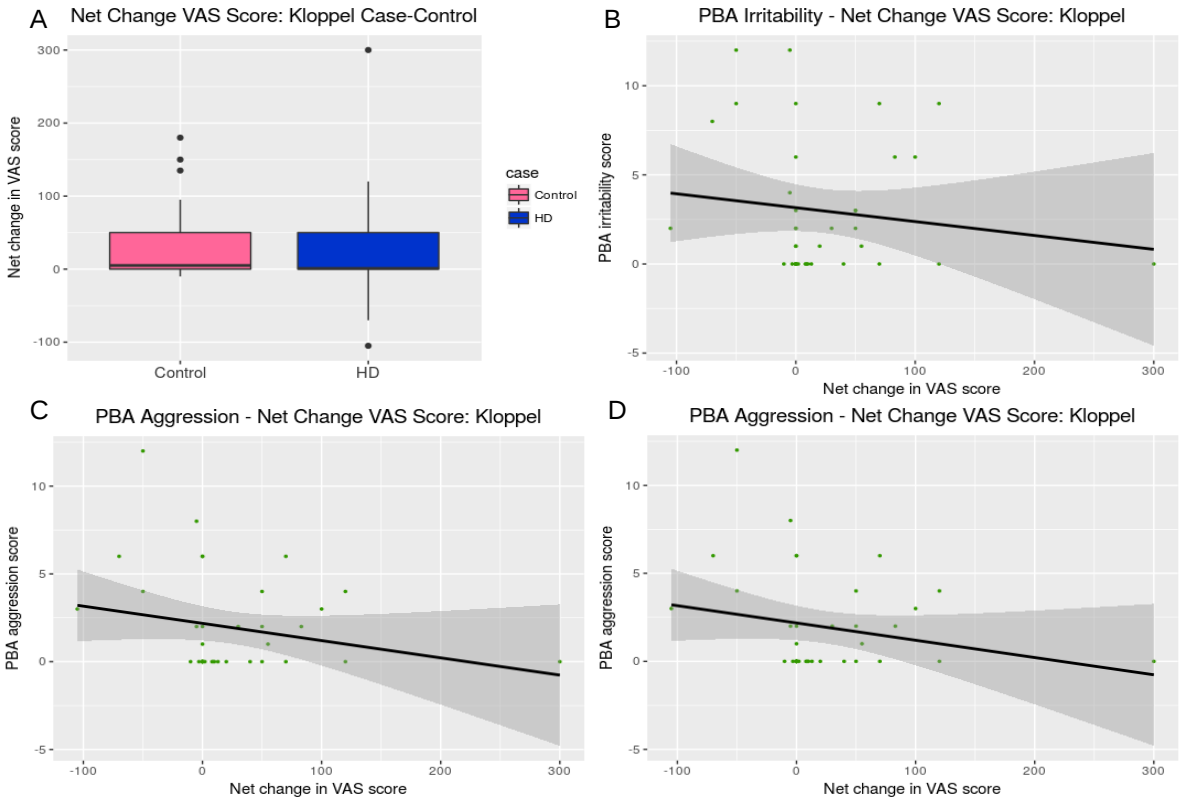


Table 5.10: Change in VAS Scores- Group Comparisons

	Dependent variable:					
	FNR		Tower		Klöppel	
	VAS Net	P Value	VAS Net	P Value	VAS Net	P Value
(Intercept)	−3.056	0.76	19.650.072	38.048	0.0073	
Case HD	20.22	0.11	9.22	0.50	−14.31	0.40
Observations	47		61		59	
Log Likelihood	−241.54		−326.91		−327.79	
Akaike Inf. Crit.	487.082		657.83		659.57	

	Dependent variable:					
	FNR		Tower		Klöppel	
	VAS Net	P Value	VAS Net	P Value	VAS Net	P Value
(Intercept)	45.32	0.49	−36.62	0.66	32.70	0.74
Case HD	12.05	0.49	6.79	0.75	−7.89	0.76
Age	−0.49	0.27	0.16	0.77	−0.64	0.33
IQ	−0.21	0.70	0.38	0.57	0.26	0.75
TMS	−0.045	0.91	0.41	0.38	0.24	0.64
Olanzapine Equivalent	1.47	0.29	1.21	0.50	1.22	0.53
Fluoxetine Equivalent	0.19	0.52	−0.31	00.41	−0.25	0.55
Observations	44		56		56	
Log Likelihood	−222.016		−298.22		−308.38	
Akaike Inf. Crit.	458.032		610.44		630.76	

Table 5.11: Change in VAS Scores- FNR

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	3.17	0.00018	2.038	0.00034	8.53	$3.11\text{x}10^{-8}$
VAS Net FNR	0.0032	0.83	−0.0042	0.68	−0.023	0.33
Observations	29		29		26	
Log Likelihood	−79.017		−67.78		−79.77	
Akaike Inf. Crit.	162.035		139.56		163.55	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	14.47	0.070	9.069	0.094	11.56	0.34
VAS Net FNR	−0.0061	0.73	−0.0087	0.46	−0.030	0.26
Age	−0.041	0.57	−0.013	0.79	0.0076	0.94
IQ	−0.099	0.13	−0.067	0.13	−0.063	0.53
TMS	0.057	0.20	0.038	0.21	0.10	0.14
Olanzapine Equivalent	0.094	0.48	0.056	0.54	−0.69	0.47
Fluoxetine Equivalent	−0.019	0.53	−0.014	0.49	0.043	0.34
Observations	27		27		25	
Log Likelihood	−71.036		−60.67		−74.56	
Akaike Inf. Crit.	156.072		135.33		163.12	

Table 5.12: Change in VAS Scores- Tower

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	2.87	0.00012	1.83	0.00023	8.78	$1.49\text{x}10^{-9}$
VAS Net Tower	−0.00084	0.94	−0.0015	0.85	−0.017	0.33
Observations	38		38		34	
Log Likelihood	−102.42		−87.41		−105.62	
Akaike Inf. Crit.	208.84		178.82		215.24	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	11.021	0.094	7.89	0.075	17.34	0.083
VAS Net Tower	−0.0062	0.62	−0.0041	0.62	−0.024	0.21
Age	−0.029	0.65	−0.021	0.62	−0.020	0.82
IQ	−0.074	0.20	−0.056	0.150	−0.099	0.25
TMS	0.037	0.32	0.030	0.24	0.079	0.17
Olanzapine Equivalent	0.038	0.77	0.011	0.90	−0.66	0.18
Fluoxetine Equivalent	0.00067	0.98	0.00092	0.96	0.059	0.17
Observations	36		36		33	
Log Likelihood	−95.52		−81.24		−99.72	
Akaike Inf. Crit.	205.04		176.47		213.44	

Table 5.13: Change in VAS Scores- Klöppel

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	3.16	0.000022	2.18	0.000064	7.78	$5.65\text{x}10^{-9}$
VAS Net Klöppel	−0.0078	0.41	−0.0098	0.17	0.0016	0.91
Observations	38		38		33	
Log Likelihood	−104.084		−92.91		−102.20	
Akaike Inf. Crit.	212.17		189.81		208.40	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	12.94	0.038	7.58	0.12	11.51	0.24
VAS Net Klöppel	−0.010	0.27	−0.011	0.15	−0.0056	0.74
Age	−0.0072	0.90	0.0081	0.86	−0.023	0.81
IQ	−0.11	0.042	−0.071	0.12	−0.043	0.63
TMS	0.066	0.047	0.036	0.16	0.063	0.24
Olanzapine Equivalent	−0.047	0.67	−0.036	0.69	−0.61	0.16
Fluoxetine Equivalent	0.021	0.38	0.014	0.46	0.029	0.47
Observations	36		36		32	
Log Likelihood	−93.68		−85.54		−97.38	
Akaike Inf. Crit.	201.36		185.07		208.76	

5.3.2 Economic Decision-making and Fairness

Ultimatum Game (UG)

UG Offer

This is the value of the offer made by participants when they were the 'divider'. No differences were seen in the GLMs comparing performance between cases and controls. There was no association within the HD population between UG offer value and any of the gold standard irritability and aggression measures (Tables 5.14 & 5.15, Figures 5.11).

UG Receive

This is the value given by participants, when asked 'what is the lowest offer you would accept'. In the case-control models, no differences were seen between groups. No associations were seen between 'the lowest offer subjects would accept' in the HD group and any of the irritability and aggression measures(Tables 5.16 & 5.17, Figures 5.12).

UG Net

This is the value of the offer made in the 'dividing' part of the UG, minus the lowest offer participants would accept. No differences were seen between cases and controls. The net offer was not predictive of any of the gold standard irritability and aggression measures(Tables 5.18 & 5.19, Figures 5.13).

Figure 5.11: UG Offer

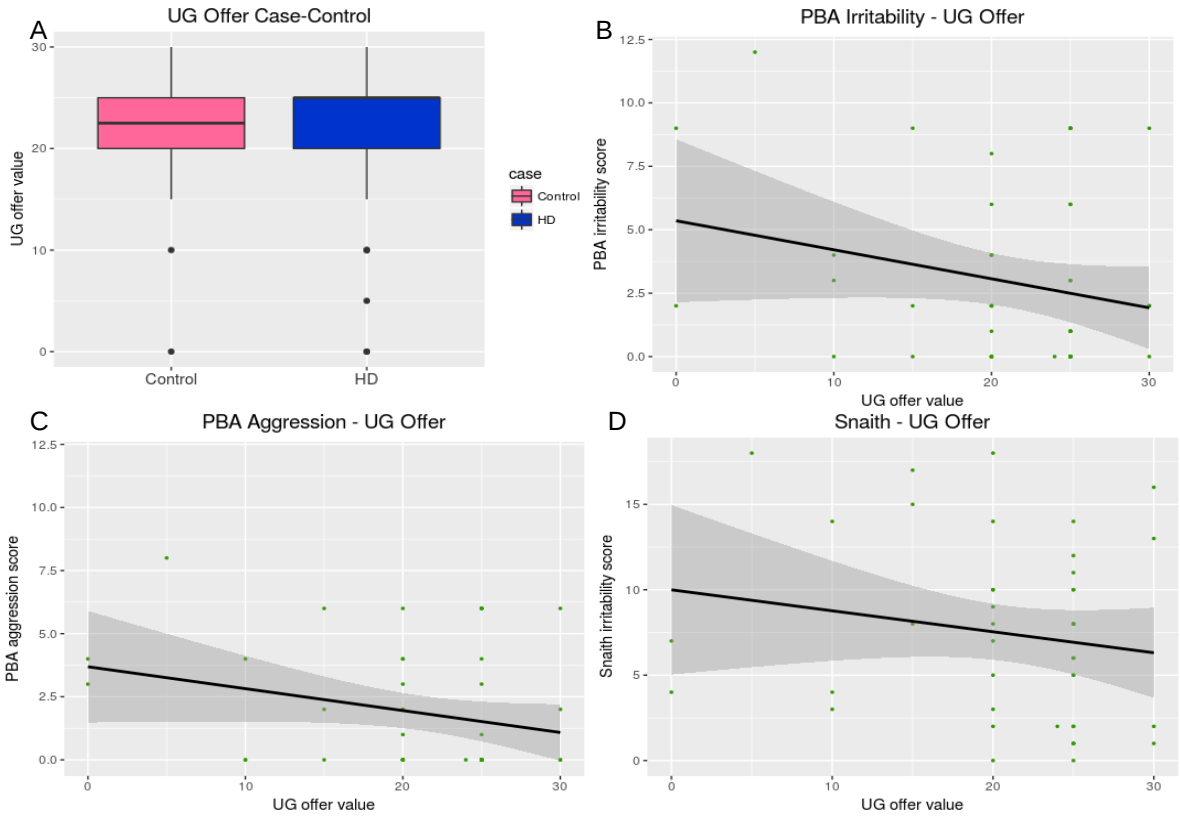


Figure 5.12: UG Receive

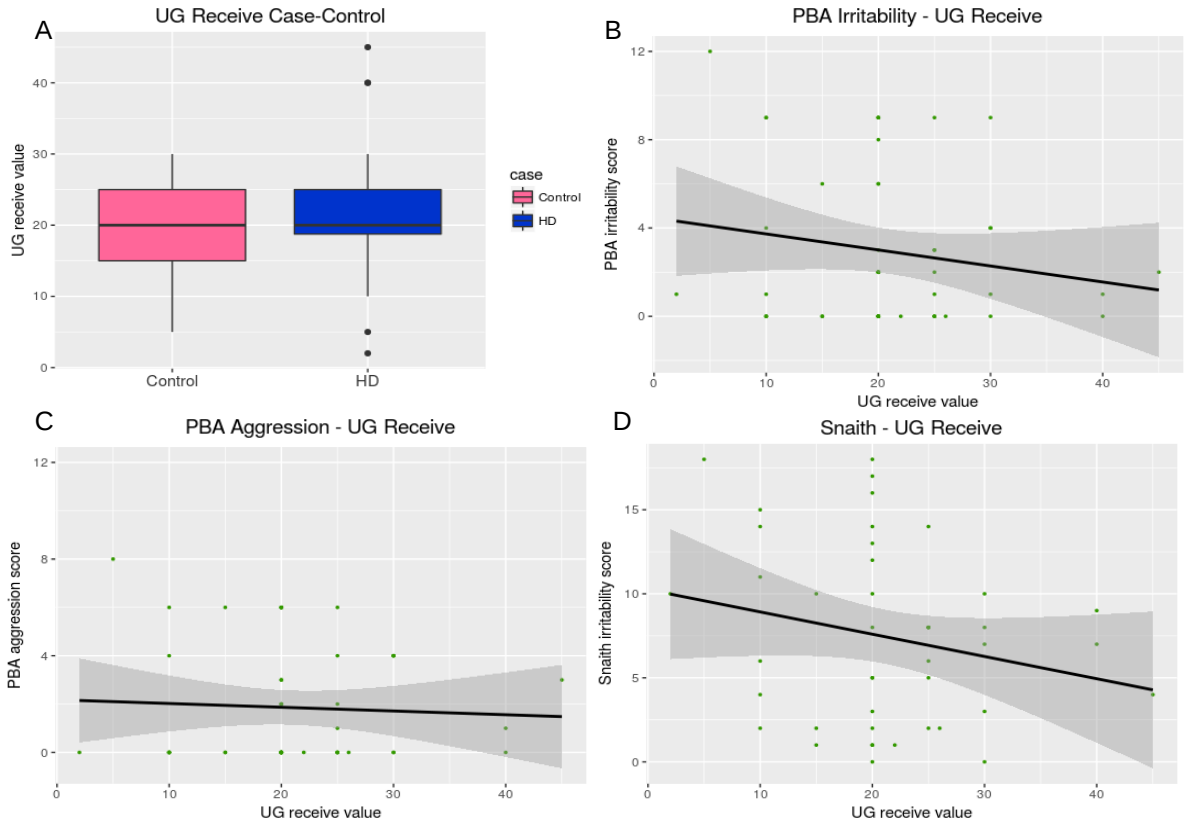


Figure 5.13: UG Net

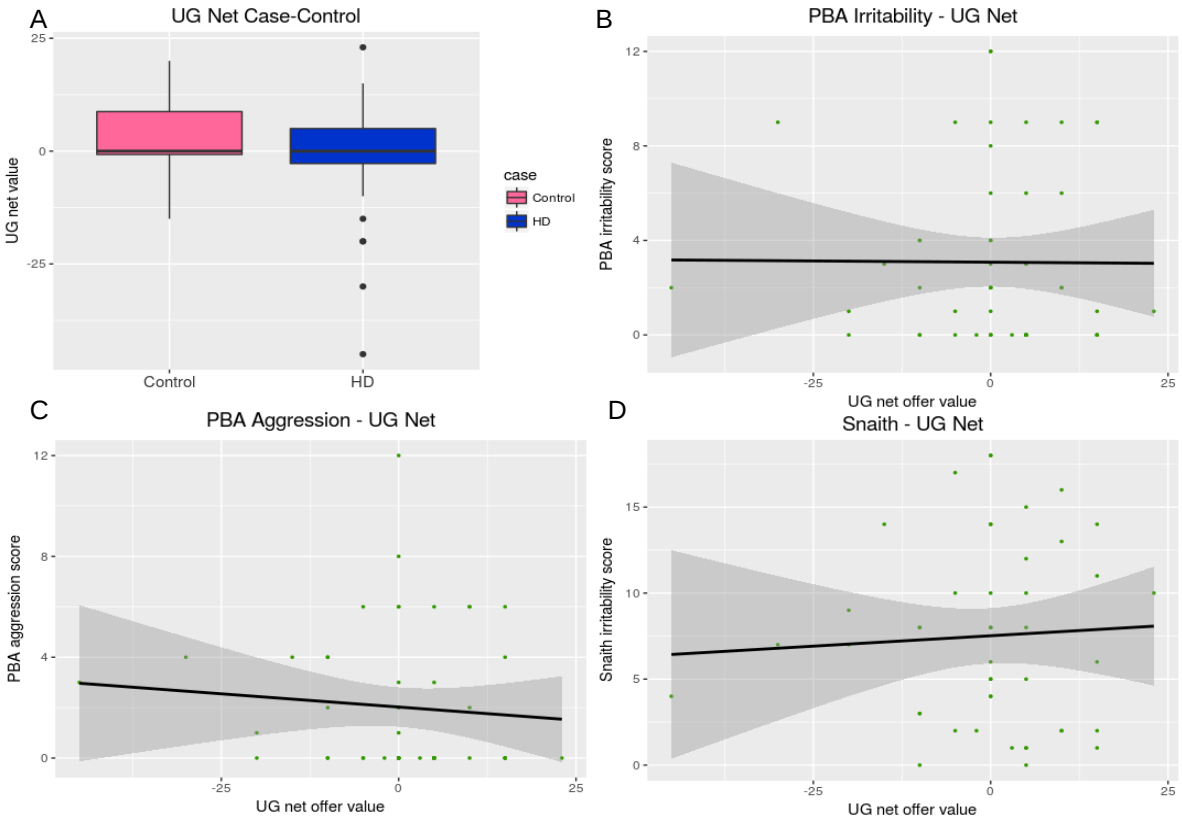


Table 5.14: UG Offer- Group Comparisons

	Dependent variable:	
	UG Offer	
	Estimate	P Value
(Intercept)	3.066	$<2\text{x}10^{-16}$
Case HD	−0.016	0.87
Observations	74	
Log Likelihood	−267.80	
Akaike Inf. Crit.	539.60	

	Dependent variable:	
	UG Offer	
	Estimate	P Value
(Intercept)	2.73	$2.86\text{x}10^{-7}$
Case HD	0.16	0.25
Age	0.00031	0.93
IQ	0.0030	0.50
TMS	−0.0046	0.11
Olanzapine Equivalent	0.0069	0.54
Fluoxetine Equivalent	−0.0015	0.52
Observations	69	
Log Likelihood	−250.032	
Akaike Inf. Crit.	514.064	

Table 5.15: UG Offer

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	1.66	0.0081	1.33	0.079	2.34	$3.59\text{x}10^{-11}$
UG Offer	−0.029	0.31	−0.035	0.30	−0.016	0.31
Observations	48		48		43	
Log Likelihood	−106.027		−85.96		−129.38	
Akaike Inf. Crit.	216.054		175.92		262.77	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	4.33	0.055	5.14	0.062	3.20	0.0089
UG Offer	−0.024	0.42	−0.036	0.31	−0.021	0.21
Age	−0.011	0.56	−0.016	0.52	−0.0062	0.56
IQ	−0.026	0.18	−0.033	0.16	−0.0068	0.51
TMS	0.0077	0.49	0.0068	0.61	0.0041	0.49
Olanzapine Equivalent	−0.016	0.69	−0.018	0.70	−0.13	0.012
Fluoxetine Equivalent	0.0072	0.38	0.0071	0.48	0.010	0.024
Observations	46		46		42	
Log Likelihood	−99.36		−81.72		−122.14	
Akaike Inf. Crit.	212.72		177.43		258.28	

Table 5.16: UG Receive- Group Comparisons

	Dependent variable:	
	UG Receive	
	Estimate	P Value
(Intercept)	2.94	$<2\text{x}10^{-16}$
Case HD	0.10	0.32
Observations	74	
Log Likelihood	−263.48	
Akaike Inf. Crit.	530.96	

	Dependent variable:	
	UG Receive	
	Estimate	P Value
(Intercept)	3.085	$1.47\text{x}10^{-8}$
Case HD	0.11	0.43
Age	−0.00045	0.90
IQ	−0.0013	0.78
TMS	0.0017	0.55
Olanzapine Equivalent	0.011	0.36
Fluoxetine Equivalent	−0.0028	0.24
Observations	69	
Log Likelihood	−240.94	
Akaike Inf. Crit.	495.88	

Table 5.17: UG Receive

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	1.60	0.0028	0.78	0.24	2.35	$1.37\text{x}10^{-14}$
UG Receive	−0.026	0.28	−0.0079	0.79	−0.017	0.21
Observations	48		48		43	
Log Likelihood	−106.093		−86.55		−129.051	
Akaike Inf. Crit.	216.19		177.10		262.10	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	3.94	0.073	3.95	0.15	2.84	0.025
UG Receive	−0.027	0.28	0.00024	0.99	−0.0049	0.73
Age	−0.0084	0.66	−0.0096	0.69	−0.0045	0.67
IQ	−0.024	0.21	−0.033	0.16	−0.0078	0.45
TMS	0.012	0.25	0.012	0.38	0.0055	0.34
Olanzapine Equivalent	−0.0033	0.93	−0.012	0.80	−0.12	0.033
Fluoxetine Equivalent	0.0031	0.71	0.0047	0.65	0.0096	0.039
Observations	46		46		42	
Log Likelihood	−99.13		−82.15		−122.86	
Akaike Inf. Crit.	212.26		178.29		259.72	

Table 5.18: UG Net- Group Comparisons

	Dependent variable:	
	UG Net	
	Estimate	P Value
(Intercept)	2.58	0.24
Case HD	−2.40	0.37
Observations	78	
Log Likelihood	−298.045	
Akaike Inf. Crit.	600.09	

	Dependent variable:	
	UG Net	
	Estimate	P Value
(Intercept)	−5.96	0.69
Case HD	0.77	0.84
Age	0.011	0.91
IQ	0.077	0.54
TMS	−0.12	0.13
Olanzapine Equivalent	−0.064	0.84
Fluoxetine Equivalent	0.025	0.70
Observations	72	
Log Likelihood	−271.60	
Akaike Inf. Crit.	557.20	

Table 5.19: UG Net

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	1.12	$1.51\text{x}10^{-8}$	0.70	0.0040	2.017	$<2\text{x}10^{-16}$
UG Net	−0.00068	0.97	−0.010	0.62	0.0035	0.71
Observations	51		51		45	
Log Likelihood	−115.18		−94.79		−135.97	
Akaike Inf. Crit.	234.36		193.57		275.94	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	3.33	0.12	4.21	0.11	3.16	0.0065
UG Net	0.0041	0.82	−0.015	0.48	−0.0056	0.58
Age	−0.0083	0.67	−0.017	0.48	−0.0045	0.67
IQ	−0.023	0.22	−0.031	0.18	−0.011	0.28
TMS	0.012	0.28	0.011	0.41	0.0030	0.60
Olanzapine Equivalent	−0.023	0.56	−0.041	0.40	−0.12	0.0084
Fluoxetine Equivalent	0.0069	0.41	0.010	0.30	0.0098	0.27
Observations	49		49		44	
Log Likelihood	−108.35		−90.37		−128.85	
Akaike Inf. Crit.	230.71		194.74		271.71	

5.3.3 Impulsivity Measures

Stop Signal Reaction Task

The SSRT is a measure of the speed of inhibitory processes: higher values reflect slower reaction time and hence worse inhibitory processes. The groups differed in the case-control model, where the HD group had longer reaction times than controls. However, addition of confounders to the model resulted in loss of significance of this relationship . SSRT was not predictive of scores on any of the irritability or aggression measures in the HD population (Tables 5.20 & 5.21, Figures 5.14).

Delay Discounting

The kD reflects temporal discounting: valuing immediate over delayed rewards. Higher kD values reflect steeper discounting and hence higher impulsivity. There were no differences between cases and controls. Higher kD values were not predictive of any of the gold standard irritability and aggression measures(Tables 5.22 & 5.23, Figures 5.15).

Figure 5.14: Stop Signal Reaction Task

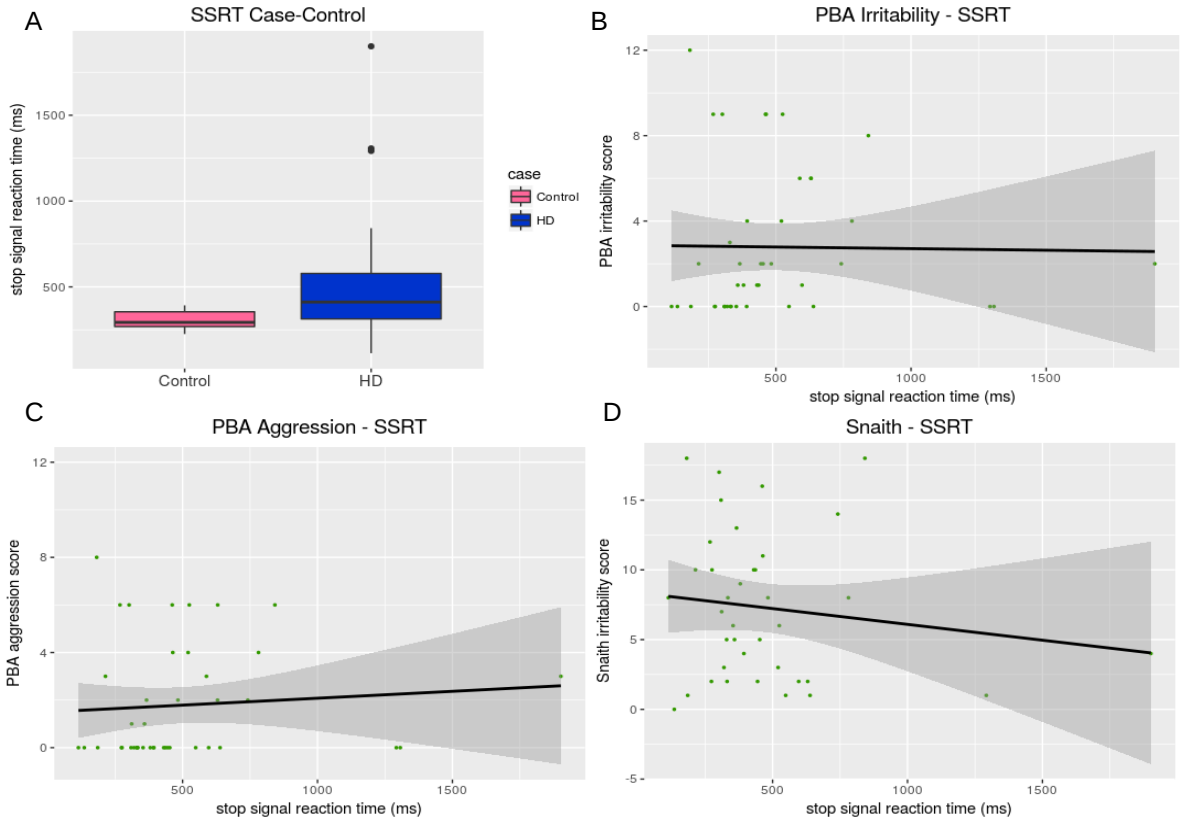


Figure 5.15: Delay Discounting

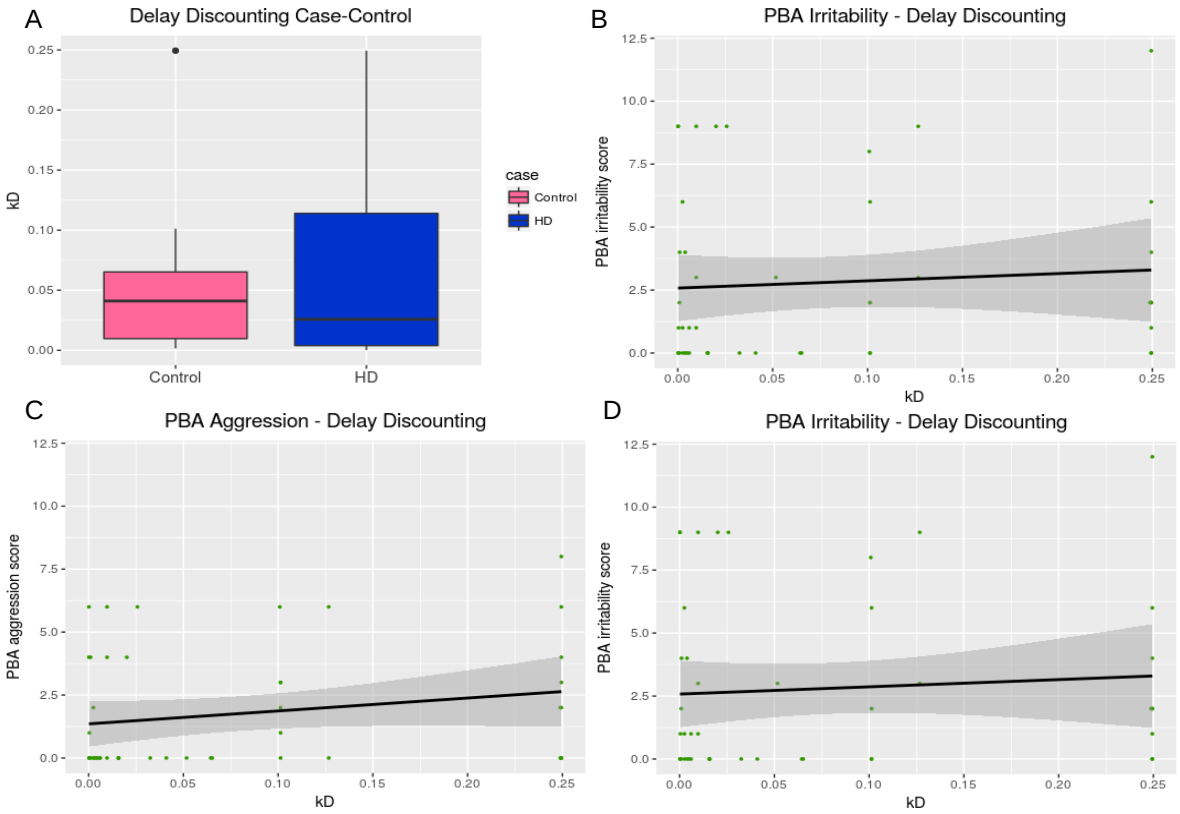


Table 5.20: SSRT- Group Comparisons

	Dependent variable:	
	SSRT	
	Estimate	P Value
(Intercept)	304.42	$1.89\text{x}10^{-7}$
Case HD	191.84	0.0053
Observations	68	
Log Likelihood	−476.33	
Akaike Inf. Crit.	956.66	

	Dependent variable:	
	SSRT	
	Estimate	P Value
(Intercept)	201.84	0.59
Case HD	77.97	0.43
Age	2.61	0.29
IQ	−0.21	0.95
TMS	3.24	0.12
Olanzapine Equivalent	16.26	0.045
Fluoxetine Equivalent	−1.47	0.37
Observations	63	
Log Likelihood	−437.51	
Akaike Inf. Crit.	889.013	

Table 5.21: SSRT

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	1.063	0.0077	0.41	0.40	2.16	$<2\text{x}10^{-16}$
SSRT	$-7.74\text{x}10^{-5}$	0.91	0.00034	0.67	−0.00039	0.34
Observations	42		42		38	
Log Likelihood	−91.44		−74.41		−113.37	
Akaike Inf. Crit.	186.88		152.82		230.75	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	3.75	0.11	5.77	0.044	3.074	0.013
SSRT	−0.00028	0.70	0.00052	0.54	0.00027	0.61
Age	−0.0097	0.67	−0.033	0.24	−0.013	0.28
IQ	−0.025	0.22	−0.043	0.085	−0.0090	0.40
TMS	0.012	0.30	0.017	0.24	0.0081	0.19
Olanzapine Equivalent	0.0020	0.96	−0.020	0.71	−0.13	0.056
Fluoxetine Equivalent	0.0022	0.81	0.0046	0.68	0.0094	0.047
Observations	40		40		37	
Log Likelihood	−84.92		−69.70		−107.31	
Akaike Inf. Crit.	183.84		153.39		228.62	

Table 5.22: Delay Discounting- Group Comparisons

	Dependent variable:	
	kD	
	Estimate	P Value
(Intercept)	−2.88	0.00066
Case HD	0.36	0.72
Observations	72	
Log Likelihood	−17.41	
Akaike Inf. Crit.	38.81	

	Dependent variable:	
	kD	
	Estimate	P Value
(Intercept)	0.11	0.98
Case HD	−0.19	0.90
Age	0.019	0.61
IQ	−0.037	0.45
TMS	0.0083	0.76
Olanzapine Equivalent	0.039	0.71
Fluoxetine Equivalent	−0.0089	0.74
Observations	67	
Log Likelihood	−15.63	
Akaike Inf. Crit.	45.25	

Table 5.23: Delay Discounting

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	0.95	0.00051	0.31	0.35	2.024	$<2\text{x}10^{-16}$
kD	1.0069	0.64	2.73	0.29	−0.46	0.71
Observations	47		47		42	
Log Likelihood	−102.50		−82.27		−126.068	
Akaike Inf. Crit.	209.00060		168.54		256.14	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	3.43	0.15	3.18	0.27	3.052	0.022
kD	0.20	0.94	1.99	0.49	−0.76	0.58
Age	−0.010	0.61	−0.0090	0.71	−0.0068	0.53
IQ	−0.024	0.26	−0.026	0.30	−0.0095	0.41
TMS	0.012	0.28	0.0088	0.52	0.0069	0.25
Olanzapine Equivalent	−0.0077	0.85	−0.0058	0.91	−0.11	0.040
Fluoxetine Equivalent	0.0038	0.67	0.0021	0.85	0.0088	0.064
Observations	45		45		41	
Log Likelihood	−95.88		−78.41		−119.37	
Akaike Inf. Crit.	205.77		170.82		252.75	

5.3.4 Provocation Measures

Tower Task

The outcome variable was the number of 'STEAL' attempts by participants. Only one participant did not make any STEAL attempts (premanifest HD participant). All other participants stole whenever they were offered the opportunity to do so.

Klöppel Premature Responses

This value is the number of responses made prior to the response screen. The HD group made significantly more premature responses than controls, although the effect was lost after inclusion of confounding variables in the model. However, the premature response value was not predictive of the irritability and aggression measures in the models including confounding variables (Tables 5.24 & 5.25, Figures 5.16).

Klöppel Total Responses

This value reflects repeated responses (i.e. repetitive tapping) during the response period of the task. There were no differences between cases and controls in the case status models. Total responses was not predictive of any of the gold standard irritability and aggression measures(Tables 5.26 & 5.27, Figures 5.17).

Figure 5.16: Klöppel Premature Responses

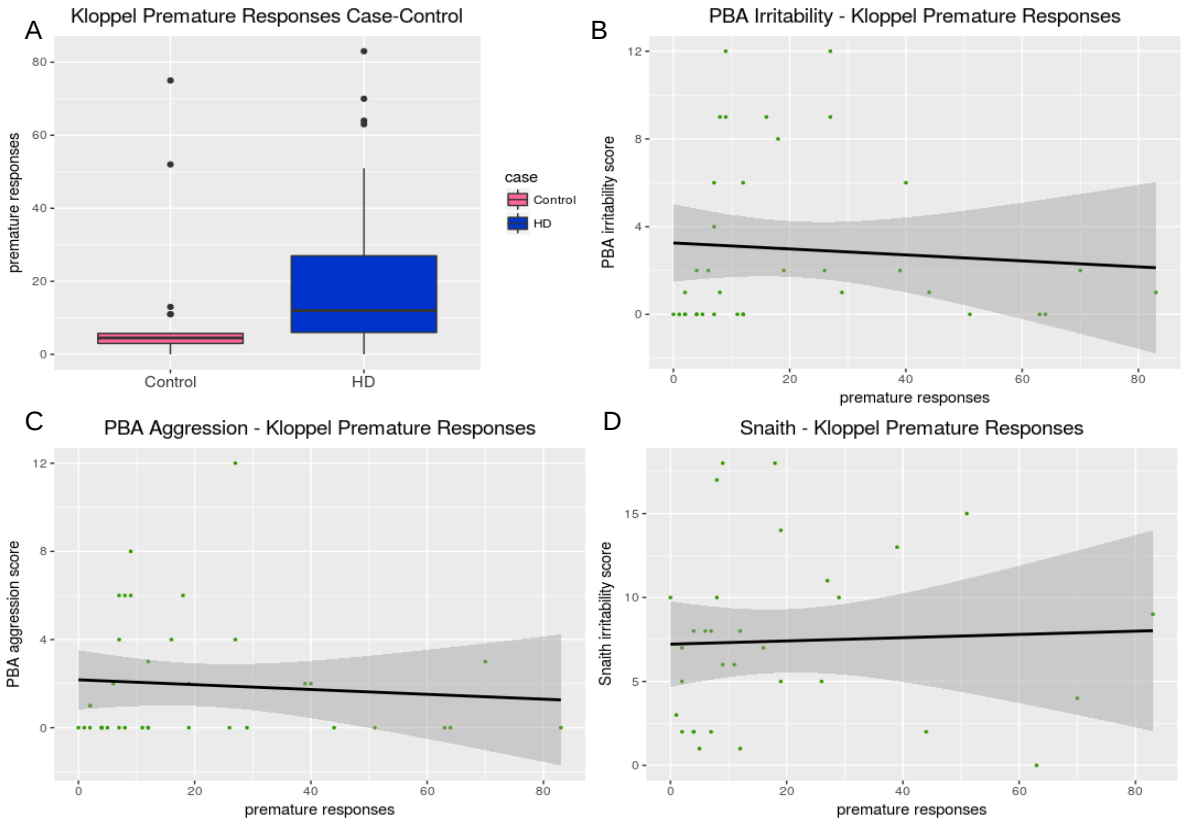


Figure 5.17: Klöppel Total Responses

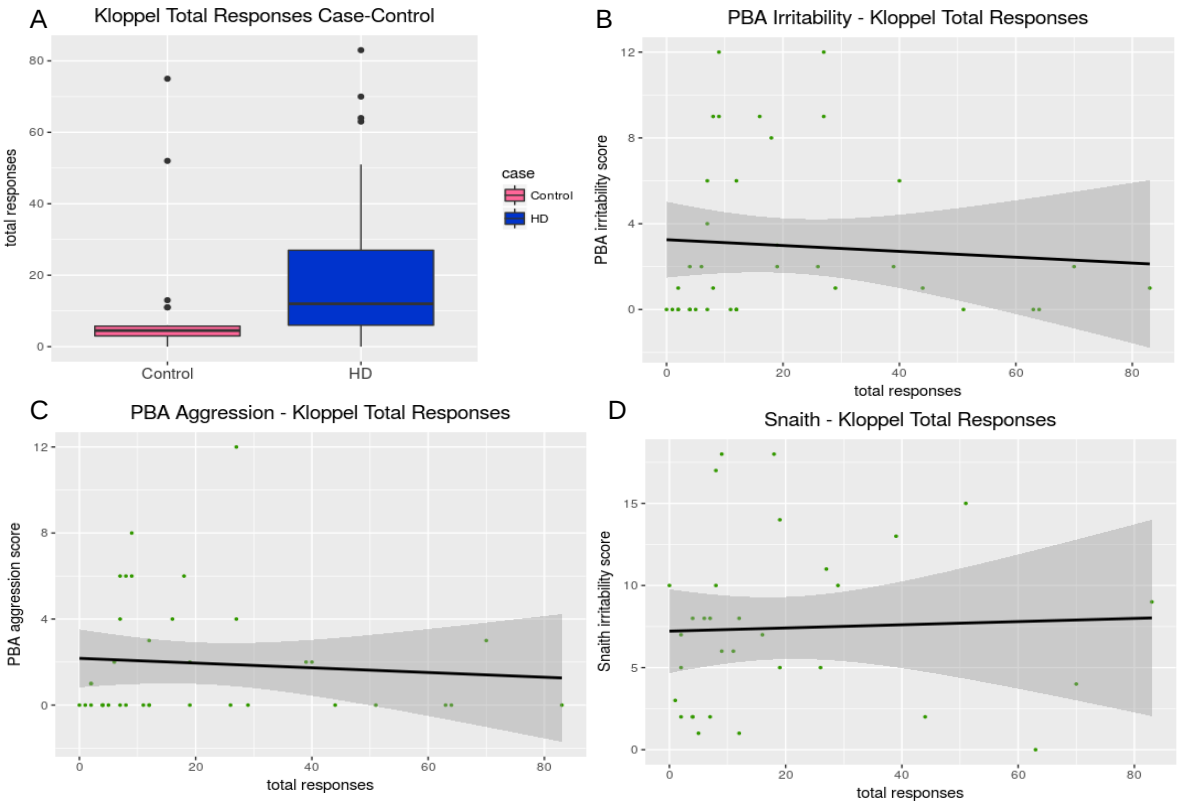


Table 5.24: Klöppel Premature Responses - Group Comparisons

	Dependent variable:	
	Kloppel Premature	
	Estimate	P Value
(Intercept)	2.29	$<2\text{x}10^{-16}$
Case HD	0.74	0.014
Observations	59	
Log Likelihood	−224.26	
Akaike Inf. Crit.	452.52	

	Dependent variable:	
	Kloppel Premature	
	Estimate	P Value
(Intercept)	5.45	0.00061
Case HD	0.62	0.15
Age	0.0023	0.83
IQ	−0.031	0.021
TMS	0.0075	0.41
Olanzapine Equivalent	0.053	0.11
Fluoxetine Equivalent	−0.016	0.028
Observations	56	
Log Likelihood	−207.67	
Akaike Inf. Crit.	429.34	

Table 5.25: Klöppel Premature Responses

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	1.25	0.00019	0.85	0.037	1.97	$<2\text{x}10^{-16}$
Kloppel Premature	−0.0083	0.47	−0.0095	0.50	0.0015	0.81
Observations	37		37		32	
Log Likelihood	−82.065		−67.29		−95.55	
Akaike Inf. Crit.	168.13		138.57		195.10	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	6.31	0.012	6.70	0.031	2.32	0.086
Kloppel Premature	−0.016	0.16	−0.019	0.16	0.0069	0.26
Age	−0.016	0.51	−0.0075	0.80	−0.017	0.16
IQ	−0.053	0.016	−0.066	0.017	−0.0022	0.84
TMS	0.029	0.019	0.036	0.020	0.016	0.017
Olanzapine Equivalent	−0.0078	0.85	−0.0047	0.93	−0.12	0.055
Fluoxetine Equivalent	0.0042	0.66	0.0035	0.77	0.0085	0.071
Observations	35		35		31	
Log Likelihood	−72.067		−60.18		−88.33	
Akaike Inf. Crit.	158.13		134.36		190.66	

Table 5.26: Klöppel Total Responses - Group Comparisons

	Dependent variable:	
	Kloppel Total	
	Estimate	P Value
(Intercept)	4.69	$<2x10^{-16}$
Case HD	−0.083	0.50
Observations	59	
Log Likelihood	−308.13	
Akaike Inf. Crit.	620.25	

	Dependent variable:	
	Kloppel Total	
	Estimate	P Value
(Intercept)	4.32	$<2x10^{-16}$
Case HD	−0.0035	0.98
Age	−0.00029	0.93
IQ	0.0037	0.34
TMS	−0.0039	0.15
Olanzapine Equivalent	0.0043	0.65
Fluoxetine Equivalent	−0.0012	0.55
Observations	56	
Log Likelihood	−270.059	
Akaike Inf. Crit.	554.12	

Table 5.27: Klöppel Total Responses

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	0.94	0.027	0.62	0.23	2.064	$2.04\text{x}10^{-9}$
Kloppel Total	0.0014	0.68	0.00042	0.92	−0.00070	0.85
Observations	37		37		32	
Log Likelihood	−82.11		−67.43		−95.55	
Akaike Inf. Crit.	168.22		138.85		195.10	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	6.18	0.016	6.44	0.041	2.72	0.037
Kloppel Total	0.0038	0.61	0.0047	0.61	0.0020	0.61
Age	−0.018	0.47	−0.014	0.65	−0.016	0.19
IQ	−0.057	0.013	−0.068	0.016	−0.0074	0.52
TMS	0.027	0.039	0.033	0.042	0.016	0.018
Olanzapine Equivalent	−0.018	0.66	−0.024	0.63	−0.088	0.15
Fluoxetine Equivalent	0.0072	0.45	0.0083	0.48	0.0085	0.072
Observations	35		35		31	
Log Likelihood	−72.58		−60.70		−88.75	
Akaike Inf. Crit.	159.17		135.39		191.50	

5.3.5 Measures of Insensitivity to Future Consequences

Iowa Gambling Task (IGT)

The outcome variable is the number of disadvantageous selections in the final 25 trials of the task. Cases had significantly more disadvantageous selections than controls, however this did not survive the inclusion of confounders in the model. IGT performance did not predict any of the irritability or aggression measures (Tables 5.28 & 5.29, Figures 5.18).

Figure 5.18: Iowa Gambling Task

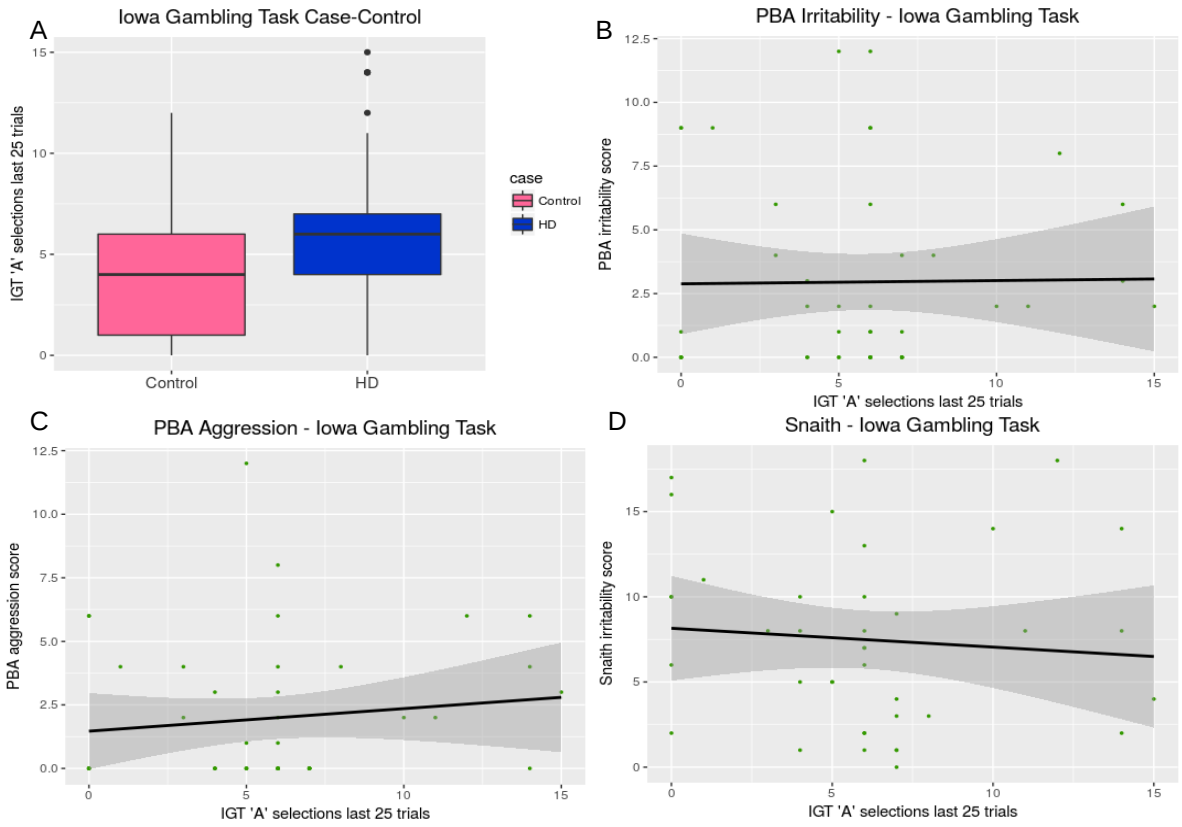


Table 5.28: Iowa Gambling Task- Group Comparisons

	Dependent variable:	
	IGT	
	Estimate	P Value
(Intercept)	1.32	$<2\text{x}10^{-16}$
Case HD	0.44	0.040
Observations	71	
Log Likelihood	−188.99	
Akaike Inf. Crit.	381.99	

	Dependent variable:	
	IGT	
	Estimate	P Value
(Intercept)	2.67	0.010
Case HD	0.039	0.89
Age	0.0084	0.23
IQ	−0.017	0.060
TMS	0.010	0.059
Olanzapine Equivalent	0.022	0.29
Fluoxetine Equivalent	−0.0043	0.37
Observations	66	
Log Likelihood	−171.33	
Akaike Inf. Crit.	356.65	

Table 5.29: Iowa Gambling Task

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	1.062	0.0058	0.46	0.32	2.089	$<2\text{x}10^{-16}$
IGT	0.0037	0.95	0.036	0.59	−0.013	0.67
Observations	45		45		39	
Log Likelihood	−100.057		−82.82		−116.92	
Akaike Inf. Crit.	204.11		169.64		237.84	

	Dependent variable:					
	PBA Irritability		PBA Aggression		Snaith	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	4.34	0.045	5.59	0.040	2.66	0.027
IGT	−0.0073	0.90	0.027	0.70	0.016	0.63
Age	0.0035	0.86	−0.00067	0.98	0.0021	0.84
IQ	−0.044	0.025	−0.059	0.017	−0.011	0.30
TMS	0.022	0.050	0.023	0.092	0.0044	0.47
Olanzapine Equivalent	−0.020	0.62	−0.024	0.63	−0.12	0.039
Fluoxetine Equivalent	0.0076	0.39	0.0054	0.63	0.0096	0.038
Observations	43		43		38	
Log Likelihood	−90.83		−76.96		−110.69	
Akaike Inf. Crit.	195.66		167.91		235.39	

5.3.6 Exploratory Models

Generalised Linear Models demonstrated highly significant, positive relationships between all 3 irritability and aggression measures in the HD population, suggesting that these instruments are all measuring a similar underlying construct (PBA Irritability and PBA Aggression, estimate=1.19, p<2x10-16; PBA Irritability and Snaith, estimate=0.38, p=4.56x10^{-5}; PBA Aggression and Snaith, estimate=1.24, p=3.22x10^{-5}).

5.4 Discussion

In this work, we have demonstrated that irritable and aggressive behaviour in HD is most strongly predicted by anticipatory VAS scores following negative affect induction (being asked to undertake an onerous form-filling task). Anticipatory VAS scores under condition of negative affect were significantly higher in HD patients compared with healthy controls, and predicted scores on our gold standard assessments. Post-task scores did not reliably distinguish between cases and controls, although there were some associations with gold-standard measures in the HD group. There were no group differences between patients and healthy controls on Net VAS scores, or associations with the irritability and aggression measures. Measures of impulsivity, fairness and frontal control showed no differences between cases and controls, and were not predictive of irritability and aggression in the HD population. The behavioural outputs from the provocation tasks, did not show any increase in repetitive or premature responding, or 'punishment' of a competitor in HD, nor were these variables predictive of irritability and aggression.

Similar VAS scores of negative affect were also used in the study by Klöppel and colleagues(130). They did not find group differences of VAS scores of negative affect between pre manifest HD gene carriers and controls, nor did they find an association with the Snaith irritability scale (although there was a trend level effect). In contrast to our work, the Klöppel study involved testing VAS scores throughout the task, but not prior to starting. There was no negative affect induction – subjects were told they would perform a task which 'examines how the brain responds when doing tasks and getting feedback'. Furthermore, in this work the pre-manifest HD group did not differ on gold standard assessments of irritability from the controls. The sample size (16 premanifest HD subjects and 15 controls) may not have been large enough to demonstrate an effect, in contrast to our larger cohort. We also included a spectrum of HD subjects (from premanifest to motor manifest), which is likely to include a higher proportion of subjects with irritability, given the known progression of irritability early in the disease course(211, 212). Previous work has shown that HD subjects have higher anger responses during mood induction than controls(553) however, this study did not look for an association with irritability. Studies in healthy subjects have shown that mood induction effectively induces irritability in healthy subjects – in particular dealing with difficult bureaucracy or frustrating social situations(558, 559). There are a number of neurobiological mechanisms that may mediate the effect of increased susceptibility to negative mood induction. In the work by Klöppel et al(130), there was a lack of correlation between BOLD signal in the amygdala and negative affect ratings in the HD group, whilst there was a strong correlation between these variables in the control group, the HD group also demonstrated reduced functional coupling between the amygdala and orbito-frontal cortex.

However, the paper does not report an association with gold standard measures of irritability. Singh-Bains and co-workers(554) showed an association between irritability on a self-designed questionnaire and atrophy in the globus pallidus. Globus pallidus lesions have not previously been linked with irritable behaviour in case series and meta-analyses of focal basal ganglia lesions, although disinhibition is reported in a small minority(238, 241). The most convincing neurobiological locus for irritability in HD was found by van den Stock and colleagues(555). They showed that during anger induction, HD subjects showed markedly increased BOLD signal in the pulvinar compared with controls, this signal change correlated with scores on the Snaith irritability scale.

In our study we found VAS ratings of negative emotion strongly predicted gold standard assessments of irritable and aggressive behaviour. The strong associations between self-rating measures and gold-standard clinical measures is somewhat surprising, as lack of insight (anosognosia) into irritability in HD is widely reported by clinicians and number of previous studies have found that anosognosia is a significant problem in HD, affecting motor, cognitive and neuropsychiatric symptom domains(560). The mechanism for anosognosia is unclear, but it has been correlated with impaired executive function(561, 562). Self-assessment of irritability has been shown to be vulnerable to this problem(563), in addition to other psychiatric symptoms, such as depression, apathy and disinhibition(206, 563). There are a number of possibilities which might explain our findings: firstly, it is possible that our cohort had relatively well-preserved executive function, although this seems unlikely given the advanced disease stage as indicated by the mean TMS in the HD group of 36.58. Secondly, HD subjects may be able to rate their emotions accurately 'in the moment' but because of the widely-recognised impairments in working memory, struggle to recall these feelings when questioned about them later. This explanation would be in keeping with the historical nature of the gold-standard assessments, which ask subjects to rate their behaviour over the preceding weeks or months. Finally, irritable subjects in HD may not realise that the emotional intensity they experience is different to others, or different to how they were before irritability developed in them.

Tests of ventro-medial prefrontal cortex function and motor inhibition showed some group differences between HD patients and healthy controls, but these differences were (at best) only retained at trend level after inclusion of confounding variables in the GLMs. Furthermore, they were not predictive of PBA or Snaith measures of irritability and aggression. The other impulsivity assessment (delay discounting) did not demonstrate any differences between cases and controls, nor was it predictive of irritable and aggressive behaviour. Impairments in motor inhi-

bition and on IGT performance are widely recognised in HD(171, 444, 478, 482, 483), which is consistent with our data. Studies suggesting a contribution of motor impulsivity to aggression in disease groups (borderline personality disorder, attention deficit hyperactivity disorder and conduct disorder), have compared impulsivity task performance between cases and controls(548, 549), but not correlated task performance with gold-standard irritability measures in the patient groups. A possible explanation is that impulsivity and aggression co-exist in these disorders, but the impulsive behaviour does not contribute to the aggression.

In contrast to irritability and aggression in other neuropsychiatric diseases and personality disorders, we did not find higher rates of directed aggression (inflicting punishment on a competitor), or aggressive behaviour directed at an inanimate object (repetitive button presses on the Klöppel task). Our aggression task was based on the point subtraction aggression protocol(344), however, a noted difference was that our task did not allow subjects to choose how much punishment was meted out to a competitor in the task. Thus we may have lost important nuanced information about degree of punishment. The lack of excessive or premature responses in the HD group may reflect motor impairment and bradykinesia known to be seen with disease progression. Finally we did not see a difference between the HD group and controls in the level of offer they were prepared to accept in the ultimatum game, although in contrast to others we did note an association between lower accepted offers and higher PBA Irritability scores, albeit this was not supported by an association between the Snaith or PBA Aggression scores.

In conclusion, we have shown that irritability and aggressive behaviour in HD is predicted by increased sensitivity to negative mood induction, and is not related to impulsivity, impaired frontal control, excessive sensitivity to unfairness or task-based punishment measures.

Chapter 6

Depressed Mood and Suicidal Ideation

6.1 Introduction

The first description of HD by George Huntington in 1872(181) particularly remarks on the "tendency to insanity, and sometimes that form of insanity which leads to suicide" indicating an awareness of depression and suicidal ideation forming part of the phenotype from the earliest accounts.

Estimates of the prevalence of depression in HD vary in epidemiological studies depending on the instrument used, the sample size, and the population studied. The frequency of symptoms of depression or major depressive disorder in prevalence studies of the general population have found rates of between 3% and 12%, with higher risk in women, smokers and people suffering from a chronic medical condition(564, 565). However, in HD, the evidence is that depression is more common. Using the neuropsychiatric inventory(222) and the behavioural scale of the unified Huntington's disease rating scale (UHDRS (422)), Paulsen and co-workers found symptoms of dysphoria or depressed mood in up to 69% in motor-manifest HD patients(465, 566). Using the Composite International Diagnostic Instrument (567) (CIDI – diagnoses are based on formal psychiatric criteria from the Diagnostic and Statistical Manual of Mental Disorders(154)) higher rates of depressive symptoms were found in pre-manifest HD gene carriers compared with non-carriers(209). A meta-analysis(196) found rates of between 33 and 69% in 7 studies, whilst more recent studies using larger cohorts (of pre-manifest and motor manifest patients) found depressive symptomatology or major depressive disorder in 42-64%(197, 401). Suicide and suicidal

ideation is also significantly more common in HD with rates of suicidal ideation in up to 20% of mutation carriers in cross-sectional studies(214, 568). Suicidal ideation is predicted by depressive symptoms, but also agitation and irritability. The frequency of depressive symptoms in HD varies throughout the disease course, with some studies finding that it occurs more frequently in the pre-manifest and earlier motor-manifest stages(211, 212). The psychological burden of knowing that one is at risk of developing, or has symptoms of, an incurable neurodegenerative disorder, has often been presumed to be the trigger for depressive symptoms in HD families. However, work comparing rates of psychiatric symptoms in gene carriers and non-gene carriers, blinded to their own genetic status, has shown that in fact, the risk of neuropsychiatric symptoms, is higher in gene carriers(147, 210, 569).

Assessing depressive symptomatology in HD is made more difficult by the criteria for vegetative symptoms in major depressive disorder(154) – changes in sleep, movement, slowed thinking and weight are all common in HD, as part of disease progression and are not necessarily related to depressive symptomatology. Rickards and co-workers(570, 571), compared self report measures of depressive symptoms, and found that the Hospital Anxiety and Depression scale (HADS), and Depression Intensity Scale Circle(DISCS) had good predictive ability of formal diagnosis of major depressive disorder, whilst the Beck depression inventory performed relatively poorly. A comparison of the Hamilton and Beck depression scales, showed that the items best predictive of depression included "guilt" and "loss of interest", but items relating to agitation or vegetative symptoms such as sleep and weight change were not strongly predictive of depression in HD(571). Depressive symptoms also have significant effects on quality of life and function in HD(198, 572, 573). Despite the frequency, and significant effects on quality of life and functional decline, little is known about the neurobiology or neuropsychological antecedents of depression in HD.

In major depressive disorder (MDD), cognitive mechanisms have been investigated in terms of cognitive biases and cognitive deficits. As a prime example of a cognitive bias, Beck(295) describes depressive cognition – interpreting experiences in a negative light, with selective attention to negative stimuli. Standard neuropsychological test batteries in patients with MDD emphasise the deficits in processing speed, executive function, attention and memory(574–578): a recent meta-analysis confirmed the central nature of executive function in MDD(309). However, in light of Beck's theory of depressive cognition, other groups have used specific tasks to measure some more specific neuropsychological deficits. Murphy(579) and co-workers demonstrated hypersensitivity to negative feedback in patients with MDD compared with controls. Deficits in tasks

measuring sensitivity to reward and altered effort in response to reward have also been described in MDD cohorts, with reports of either reduced reward value, or reduced effort for equivalent reward in the literature. Specific findings have included reduced effort for equivalent reward on a progressive ratio task(316), and reduced reward responsiveness in patients with MDD(313, 314). A task mediating reward and effort (the 'EefRT' – energy expended for reward task) has been shown to predict trait anhedonia in healthy controls in addition to demonstrating reduced effort and impaired processing of reward-related information in patients with MDD(315, 580). Functional imaging studies of patients with MDD often report deficits in responses to reward, particularly in the striatum, and orbitofrontal cortex, but also hypoactivity in prefrontal cortex(326–328, 581, 582), however, a recent meta-analysis(583) did not find any consistent areas of functional changes in these regions, and noted the lack of consistency in prior, less rigorous meta-analyses.

Depressive symptomatology in HD has shown an association with cognitive decline, with poorer performance on working memory tasks(584), as well as predicting worse performance on tasks assessing visuo-motor function, planning and inhibition(585). Imaging studies of depressive symptomatology in HD have found increased dorso-lateral prefrontal activity during a shifting response set task(414) pathological reductions in raphe integrity(586); reduced fractional anisotropy (FA) in the corpus callosum(556), in addition to FA reductions in the anterior cingulate cortex, insula and cerebellum(587); and increased functional connectivity, but reduced structural connectivity in a distributed network involving pre-frontal and limbic regions(417). The disparity of these findings suggests that either a distributed network or networks are at fault, depression in HD is a heterogenous entity, or the differences relate to methodological inconsistencies. A major contributor to our lack of understanding of the neurobiology of depression in HD is a lack of understanding about exactly what cognitive processes contribute to depressive symptomatology in HD.

This work addresses these inconsistencies, by attempting to map the potential contributors to depressed mood in HD, namely depressive cognition and negative bias, altered reward valuation, altered reward-effort calculations and impaired executive function using a battery of novel and existing tasks.

6.2 Methods

6.2.1 Participants

As described in materials and methods, 53 participants known to carry a CAG repeat expansion in the Huntingtin gene on chromosome 4 (>36 repeats) were recruited, along with 26 control participants from family members either not at risk of HD or with a negative genetic test, and local advertising in Cardiff university.

6.2.2 Questionnaires

Behavioural Inhibition System, Behavioural Activation System (BISBAS)(394)

This is a self-report Likert-type questionnaire based on the theories of competing neural systems developed by Gray(489, 490). The BAS Reward was used in this study as a self-report measure of reward value (to isolate this from reward-effort calculations involved in most behavioural tasks).

Hospital Anxiety and Depression Scale (HADS)

This is a short, self report-questionnaire of 7 questions on depressive symptoms such as "I feel cheerful" and 7 questions on anxiety "I get a sort of frightened feeling as if something awful is about to happen", employing a Likert-type scale from 0-3 (not true to very true). It has previously been shown to have good sensitivity and specificity for depression symptoms in HD patients when compared to gold standard diagnostic instruments (ICD-10 diagnosis of depression)(588). It is also used as a standard assessment as part of the Enroll-HD worldwide observational study of HD(589).

Problem Behaviours Assessment (short form; PBAs)(165, 211)

This is a clinician-scored instrument developed specifically for the neuropsychiatric symptoms in HD. Information is gathered during a semi-structured clinical interview with both the subject, and carers. Symptoms are rated for severity and frequency over the previous 4 weeks, and then these scores are combined to form a product score. The domains of 'depressed mood' (PBA Depression) and 'suicidal ideation' (PBA Suicidality) are included in this study.

Mini International Neuropsychiatric Interview (MINI)(307)

The MINI is a short neuropsychiatric interview covering 16 different neuropsychiatric symptoms. The interview was administered by a trained clinician (DMcL), and consists of screening questions followed by sub-questions if the screening criteria for possible neuropsychiatric symptoms are met: for example one of the screening questions for major depressive disorder is "Have you

been consistently depressed or down, most of the day, nearly every day, for the past two weeks?" The MINI uses the DSM IV criteria for psychiatric diagnosis. This study employed the Major Depressive Episode ('Major Depression') and Dysthymia domains, which are scored as either present or absent.

6.2.3 Tasks

Depressive Cognition and Negative Bias

Optimistic Influence Test - Depressive Cognition

This is a novel task designed by DMcL. Subjects first complete a repetitive tapping assessment – they are asked to tap as quickly as possible on the space-bar for 10 seconds. Participants are told they will see a race between two people on the computer, which they can influence with repetitive tapping on the space-bar key – the faster they tap, the more they can speed up one of the runners. They are asked to watch the race first without pressing any buttons. Following the race, they are asked "Do you think you can make the slower runner win?" They are told the computer accounts for their motor performance (to avoid lower estimates among subjects with worse motor symptoms, and avoid bias between cases and controls), using the baseline tapping speed. They are asked to give an estimate on a scale of 0-100, how likely it is that with their influence, they can make the slower runner win, 0 being 'definitely not' and 100 representing 'absolutely certain'. They then have a chance to help the slower runner, by repetitive tapping (the slower runner still loses the race), and are then asked again after the race about whether they thought they could make the slower runner win if given a second chance (again scored from 0-100). This task was designed to test if depression in HD results in lower estimates of their own ability, and whether this is modified by experience, either on an absolute or relative basis: outcome measures are the pre-task estimate, post-task estimate and change in estimate (pre-task estimate – post-task estimate).

Reward and Effort Measures

Progressive Ratio(387)

This task was based on the animal protocol, in which increased effort is required to gain a fixed reward. Subjects are asked to search through a series of boxes (16 in total), to win points. When they open the winning box, they can move on to the next level. They are told that early in the game, the winning box will arrive early in the search, whilst on higher levels, they must search through more boxes to find the winning box. They are told that they must keep playing

until the game stops – the number of levels will not be revealed. The final instruction is 'If you wish to quit the level you are playing and move on to the next level, you can press 'Q' on the keyboard at any point. If you press 'Q', you will not win points, but you will finish the game more quickly." There were 18 levels in total, early levels had a winning box within the first 5 boxes, whilst in the second half of the task, the winning box arrived in the final 5 boxes, with occasional completely empty levels. The outcome variable was the first level on which subjects chose to quit – higher levels reached before quitting would imply higher effort for fixed reward.

Reward Ratio

This task was based on the cued reinforcement reaction time task(388). Subjects were asked to respond as quickly as possible when shown a visual stimulus. They were told that there would be a baseline practice condition of 30 trials, and then the opportunity to win points. Furthermore, they were told that the quicker they reacted in the rewarded condition, the more points they would win. There were 30 practice trials, used to derive a baseline reaction time (subjects were told react as quickly as you can", feedback was "well done!", but no points were awarded). In the rewarded condition, to win points, subjects had to react more quickly than the mean reaction time in the unrewarded condition – slower reaction times won 0 points, reaction times up to 30% faster than baseline scored 5 points, whilst reaction times shorter (hence faster) than 70% of baseline reaction time scored 10 points. The outcome measure was the ratio of mean reaction time in the rewarded condition to mean reaction time in the baseline condition.

Executive Function Measures

Phonemic Verbal Fluency (PVF)

This task required subjects to generate as many words beginning with the same letter as they could over the course of 1 minute. Proper nouns were not permitted. The task was repeated three times with a different letter on each occasion (F, A and S). The outcome variable was the total number of novel words from all three trials.

Extra-Dimensional Set Shift Task (EDSST)

We created a modified version of a reversal learning task(426) chosen for the simplicity of the instructions and the task. Subjects were shown 2 houses and asked to choose one to search for gold coins. They were told there was a rule for which house was correct, and that this rule would change after a certain number of correct selections. The dimensions were colour: 'orange' versus 'blue' house and presence of a cat or not. The rule changed after 7 correct answers in a row and cycled from 'orange house' to 'cat' to 'blue house' to 'no cat'. The task terminated either when

20 set shifts were made, or if the rule was not learned after 20 trials. The outcome measure was the number of completed set shifts.

6.2.4 Statistical Analysis

All statistical analyses were conducted in R(427), a widely available statistical package. I first compared performance between the HD group and controls using two tailed t-tests for normally distributed data, whilst for non-normally distributed data, we used the Wilcoxon test. We then compared the predictive power of each outcome variable on our gold standard assessments (PBA Depression and PBA suicidality, HADS Depression score, and presence of Major Depression or Dysthymia from the MINI) within the HD population using multiple linear regression or GLM if the assumptions underlying multiple linear regression were not met (normal distribution of residuals, homoskedasticity, absence of auto-correlation or multi-collinearity). Logistic outcome data (Major Depression and Dysthymia from the MINI) used logistic GLMs. Otherwise to decide on the family and link function, histograms of the data were visualised, and characteristics of the data appraised before the distribution chosen accordingly: for discrete, non-negative data that was positively skewed we used Poisson, non-discrete, non-negative data used the Gamma family. Over-dispersion was corrected for by using negative binomial models (from the R package MASS(590)) if there was evidence for this (positive dispersion test using AER package(591) in R, or degrees of freedom markedly lower than residual deviance). We calculated Pseudo R2 using McFadden's method (1-residual deviance/null deviance). IQ was calculated from demographic variables using Crawford's method(377), as previous analyses have shown reading tests to be unreliable in the manifest HD population(378, 430). We calculated Olanzapine and Fluoxetine equivalent doses from meta-analyses(379, 380) to correct for medication effects. We initially created models comparing the predictive effect of the outcome variable on the gold standard assessment, before adding potential confounding variables (age, IQ, TMS, medication doses and PBA apathy score). Family wise error rate was controlled using the Bonferroni correction.

6.3 Results

6.3.1 Demographics and Gold Standard Assessments

There were no significant differences between the HD group and controls on age or gender balance. As expected, HD patients had higher doses of serotonergic and dopaminergic medications, in addition to higher TMS scores on formal UHDRS examination. HD patients had marginally lower premorbid IQ scores (means 103.53, 109.73; p=0.019). Comparison of HD patients' and controls' scores on the gold standard assessments (MINI Major depression and Dysthymia, HADS

Depression score, PBA Depression and PBA Suicidality) only showed significant differences for the HADS depression score, although Dysthymia and Major depression were both more common in the HD group, and the HD group had higher mean scores than controls on all of the other measures.

Table 6.1: Demographics

	HD	Controls	
Age	53.92 (33-82)	46.85 (20-75)	
IQ	103.53 (88.75-125.27)	109.73 (89.79-128.51)	*
Gender	26/53 female	17/26 female	
PBA Depressed Mood	3.08 (0-12)	1.81 (0-9)	
PBA Suicidality	0.37 (0-6)	0.04 (0-1)	
HADS Depression	5.82 (0-17)	1.88 (0-9)	***
Major Depressive Episode	10/53	2/26	
Dysthymia	8/53	0/26	
Olanzapine dose (mg)	1.98 (0-41.25)	0	***
Fluoxetine dose (mg)	21.85 (0-146.5)	2.4 (0-22.2)	***
CAG Repeat Length	42.5 (38-50)	-	
Total Motor Score	36.58 (0-89)	1.48 (0-6)	***

* 0.05 ** 0.01 *** 0.001

6.3.2 Optimistic Influence Task

Pre-Task Estimate of Performance

The HD group had lower pre-task estimates of performance than controls (means 48.07, 67.31, t-test p value 0.0044). Within the HD cohort, there were effects at trend level: higher pre-task score predicted PBA suicidality score. The R^2 and pseudo R^2 values were uniformly low in the models, with none suggesting an explanatory effect of more than 0.06 of the variation in the data. Adding confounding variables to the models improved the explanatory power of the models (0.20-0.52 R^2/pseudo R^2). However, the trend level association between PBA suicidality and pre-task estimate of performance was lost in the confounder model.

Post-Task Estimate of Performance

Group comparison again showed lower mean values in the HD group than controls (means 35.3, 43.04), but this difference was not significant. There was a highly significant positive relationship between post-task estimate of performance and PBA suicidality . The R^2 and pseudo R^2 values were uniformly low, explaining 10% or less of variation in the data. The models that included confounding variables improved the R2 and pseudo R2 values, but the relationship between PBA suicidality and post-task estimate of performance was lost. There were no other significant associations between post-task estimate of performance and gold standard measures of mood.

Change in Estimate of Performance

Change in estimate was calculated from pre-task score minus post-task score. The control group had a larger change in estimate (and in a positive direction) than the HD group (means 11.2, 24.27, $p = 0.04$). Comparisons within the HD cohort, did not demonstrate any significant findings. The models had low explanatory scores (R^2 and pseudo R^2 all less than 0.05). Including confounding variables again improved the explanation of variation in the data (R^2 and pseudo R^2 0.18-0.53), but no significant relationships between mood scores and change in estimate of performance were revealed in the more complex models.

Figure 6.1: Pre-Task Estimate of Performance

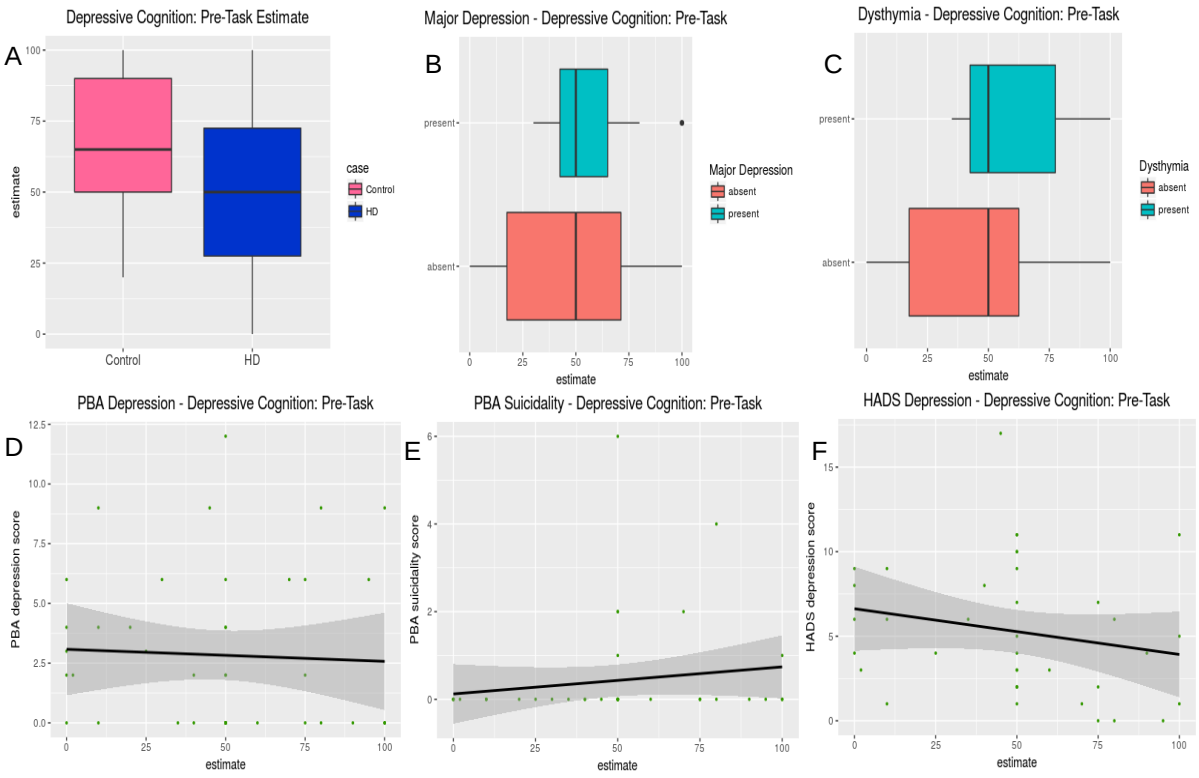


Figure 6.2: Post-Task Estimate of Performance

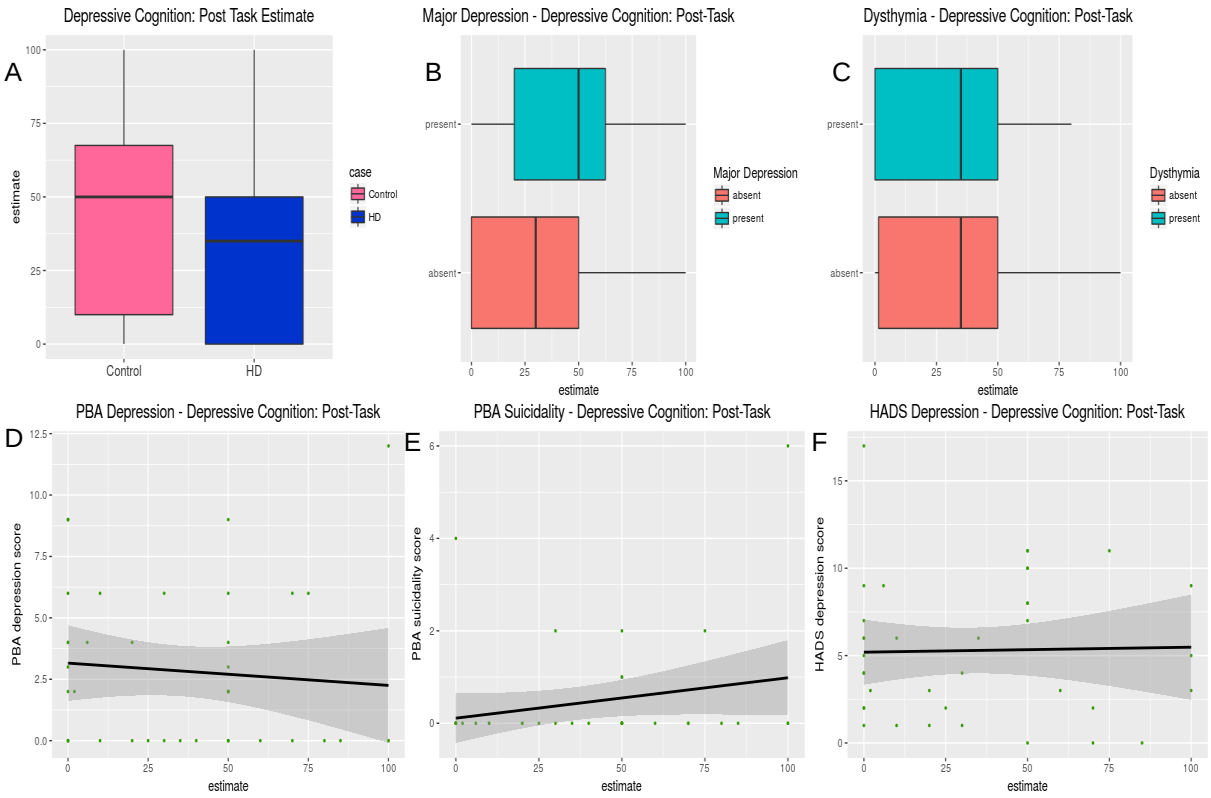


Figure 6.3: Change in Estimate of Performance

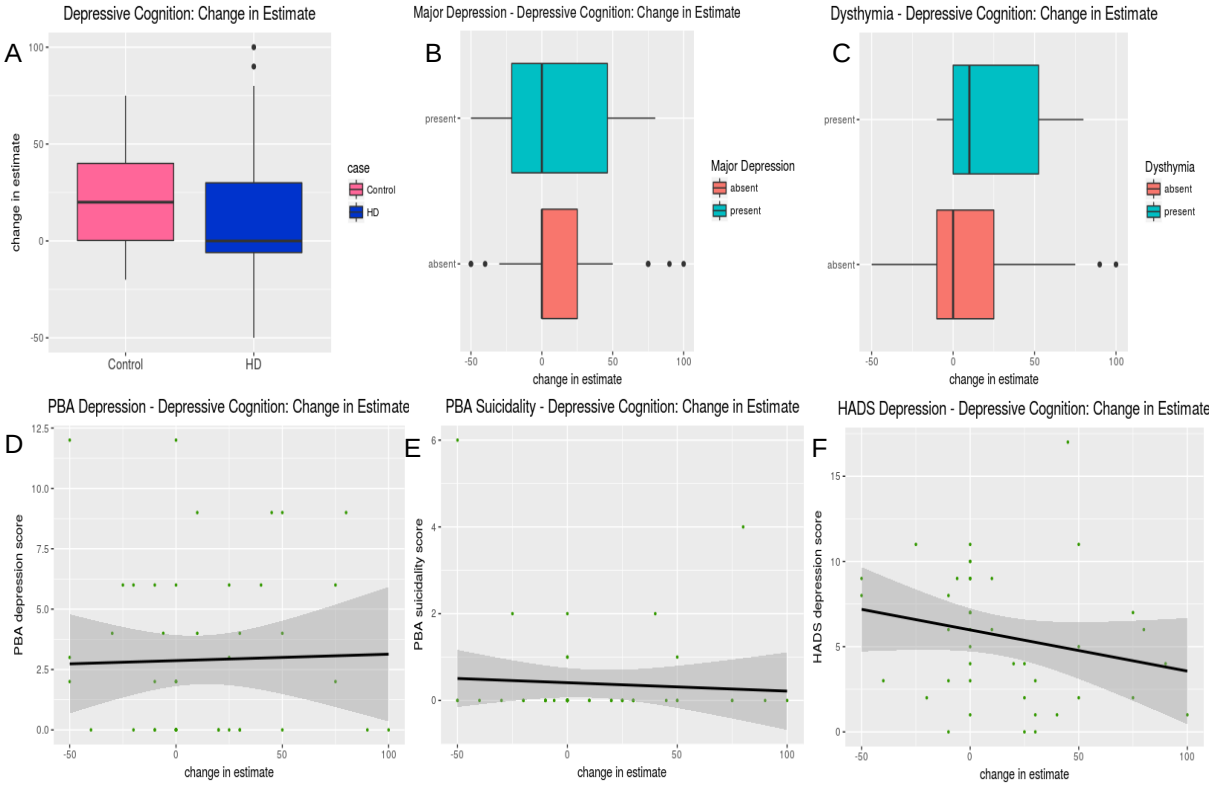


Table 6.2: Optimistic Influence Task: Pre-Task Estimate

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	negative binomial		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	1.12	0.0086	−1.70	0.002	6.63	4.57^{-6}	−2.20	0.011	−2.55	0.0068
Pre-Task Estimate	−0.0017	0.82	0.015	0.06	−0.027	0.21	0.011	0.43	0.017	0.24
R^2					0.043					
Adjusted R^2					0.016					
F Statistic					1.60 (df = 1; 36)					
Log Likelihood	−185.54		−43.68				−18.78		−18.36	
Akaike Inf. Crit.	191.54		91.37				41.57		40.73	
Pseudo R^2	0.0012		0.051				0.017		0.039	

Table 6.3: Optimistic Influence Task: Pre-Task Estimate Confounder Model

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	negative binomial		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	7.44	0.0010	10.82	0.005	12.52	0.083	13.15	0.14	−5.82	0.34
Pre-Task Estimate	-0.0067	0.34	0.010	0.39	−0.026	0.29	0.040	0.12	0.010	0.63
Age	−0.049	0.026	−0.066	0.11	−0.050	0.43	−0.013	0.85	−0.031	0.58
IQ	−0.036	0.056	−0.10	0.0012	−0.057	0.34	−0.120	0.043	0.025	0.61
TMS	0.0032	0.81	−0.009	0.64	0.048	0.26	0.085	0.099	0.054	0.18
Olanzapine Equivalent	−0.11	0.12	−0.49	0.017	−0.14	0.64	0.056	0.64	−0.27	0.36
Fluoxetine Equivalent	0.0035	0.71	−0.026	0.12	0.032	0.28	0.010	0.74	0.062	0.019
PBA Apathy	0.030	0.64	0.43	0.0024	0.15	0.46	−0.14	0.33	−0.18	0.32
R^2					0.20					
Adjusted R^2					0.007					
F Statistic					1.035 (df = 7; 29)					
Log Likelihood	−105.32		−26.40				−10.82		−12.66	
Akaike Inf. Crit.	226.64		68.80				37.63		41.32	
Pseudo R^2	0.20		0.52				0.42		0.32	

Table 6.4: Optimistic Influence Task: Post-Task Estimate

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	negative binomial		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	1.14	0.00086	−1.76	0.00018	5.20	2.05e-06	−2.079	0.0027	−1.45	0.015
Post-Task Estimate	−0.0028	0.70	0.020	0.0070	0.0029	0.89	0.011	0.38	−0.0057	0.68
R^2					0.00057					
Adjusted R^2					−0.027					
F Statistic					0.02040 (df = 1; 36)					
Log Likelihood	−185.43		−41.81				−18.72		−19.013	
Akaike Inf. Crit.	191.43		87.62				41.44		42.027	
Pseudo R^2	0.0038		0.10				0.02		0.0047	

Table 6.5: Optimistic Influence Task: Post-Task Estimate Confounder Model

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	negative binomial		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	7.81	$6.72\text{x}10^{-4}$	11.86	0.0018	11.91	0.11	14.82	0.092	−5.83	0.35
Post-Task Estimate	−0.0078	0.25	0.007	0.26	−0.009	0.70	0.00	0.69	0.005	0.76
Age	−0.043	0.050	−0.093	0.017	−0.043	0.51	−0.019	0.78	−0.031	0.58
IQ	−0.044	0.025	−0.10	0.0025	−0.066	0.30	−0.18	0.056	0.030	0.56
TMS	0.010	0.94	−0.010	0.60	0.056	0.19	0.057	0.15	0.049	0.18
Olanzapine Equivalent	−0.98	0.14	−0.61	0.0016	−0.053	0.85	0.011	0.92	−0.30	0.36
Fluoxetine Equivalent	−0.0014	0.88	−0.025	0.13	0.025	0.38	0.019	0.47	0.065	0.016
PBA Apathy	0.052	0.41	0.52	0.00031	0.13	0.51	−0.12	0.40	−0.19	0.33
R^2					0.173					
Adjusted R^2					−0.027					
F Statistic					0.865 (df = 7; 29)					
Log Likelihood	−167.97		−26.086				−12.31		−12.73	
Akaike Inf. Crit.	185.97		68.17				40.62		41.45	
Pseudo R^2	0.21		0.53				0.34		0.32	

Table 6.6: Optimistic Influence Task: Change in Estimate

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	negative binomial		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	−1.055	$5.7\text{x}10^{-6}$	−0.90	0.00011	5.98	$5.4\text{x}10^{-12}$	−1.62	$5.89\text{x}10^{-5}$	−1.87	$4.94\text{x}10^{-5}$
Change in Estimate	0.00078	0.90	−0.0053	0.45	−0.024	0.16	−0.0012	0.91	0.014	0.19
R^2					0.048					
Adjusted R^2					0.025					
F Statistic					2.081 (df = 1; 41)					
Log Likelihood	−212.058		−48.54				−21.80		−20.94	
Akaike Inf. Crit.	218.06		101.088				47.60		45.87	
Pseudo R^2	0.00034		0.0076				0.00027		0.040	

Table 6.7: Optimistic Influence Task: Change in Estimate Confounder Model

Table 4B - Optimistic Influence Task: Change in Estimate Confounder Model

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	negative binomial		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	6.01	0.0056	10.74	0.0011	12.97	0.044	14.56	0.070	−2.29	0.63
Change in Estimate	0.00075	0.91	−0.003	0.57	−0.016	0.44	0.010	0.51	0.003	0.85
Age	−0.025	0.20	−0.080	0.040	−0.062	0.27	−0.020	0.74	0.009	0.84
IQ	−0.035	0.076	−0.095	0.0013	−0.060	0.30	−0.18	0.025	−0.003	0.94
TMS	−0.0037	0.75	−0.0076	0.58	0.049	0.15	0.073	0.042	0.003	0.91
Olanzapine Equivalent	−0.11	0.12	−0.77	0.0010	−0.072	0.78	−0.018	0.86	−0.15	0.29
Fluoxetine Equivalent	−0.0038	0.66	−0.014	0.33	0.023	0.38	0.029	0.21	0.038	0.038
PBA Apathy	0.036	0.48	0.52	0.00039	0.088	0.62	−0.14	0.31	−0.11	0.46
R^2					0.18					
Adjusted R^2					0.010					
F Statistic					1.060 (df = 7; 34)					
Log Likelihood	−196.083		−30.13				−13.051		−17.31	
Akaike Inf. Crit.	214.08		76.26				42.102		50.61	
Pseudo R^2	0.16		0.53				0.39		0.19	

6.3.3 Reward and Effort Measures

Reward Ratio Task

Smaller values on this task indicate increased effort for reward. No differences in performance were seen between the HD patient group and healthy controls (p=0.86). Within the HD cohort, there were negative associations between all the gold-standard mood measures and the reward ratio, however none of these relationships were significant, furthermore, the explanation of variation in the data, was poor (R^2 and pseudo R^2 all less than 0.05). Adding confounding variables to the models improved the explanation of variation, but did not demonstrate any significant relationships between task performance and mood assessments, although trend level effects suggested smaller ratios (higher effort for reward) were associated with increased likelihood of major depression, and increased scores on the PBA suicidality and HADS depression assessments.

Progressive Ratio

A higher breakpoint on the task is associated with increased effort for a fixed reward. The HD group had lower mean and median breakpoints than controls (means 11.11, 13.29; medians 13, 14.5) but this difference was not significant ($p = 0.24$). Models within the HD group showed that higher breakpoint was associated with higher PBA depression score (p=0.045) and at trend level with presence of major depression ($p = 0.065$). Non-significant positive associations were seen with the other gold standard mood assessments. None of the models had R^2 or pseudo R^2 values greater than 0.11. In the models including confounding variables, a trend level effect was maintained, associating higher breakpoint with higher scores on the PBA depression, and higher likelihood of presence of major depression.

BAS Reward

HD patients had lower BAS reward scores than the healthy control group, demonstrating reduced reward value in the HD population (means 16.51, 17.54, medians 16, 17; $p = 0.049$). Modelling of the relationship between BAS reward score and gold-standard mood assessments, showed a significant (p=0.037) positive relationship between PBA suicidality and BAS reward score. None of the models provided a good explanation of variation in the data (R^2 or pseudo R^2 values all less than 0.07). Adding confounding variables to the models did not show any significant relationships.

Figure 6.4: Reward Ratio

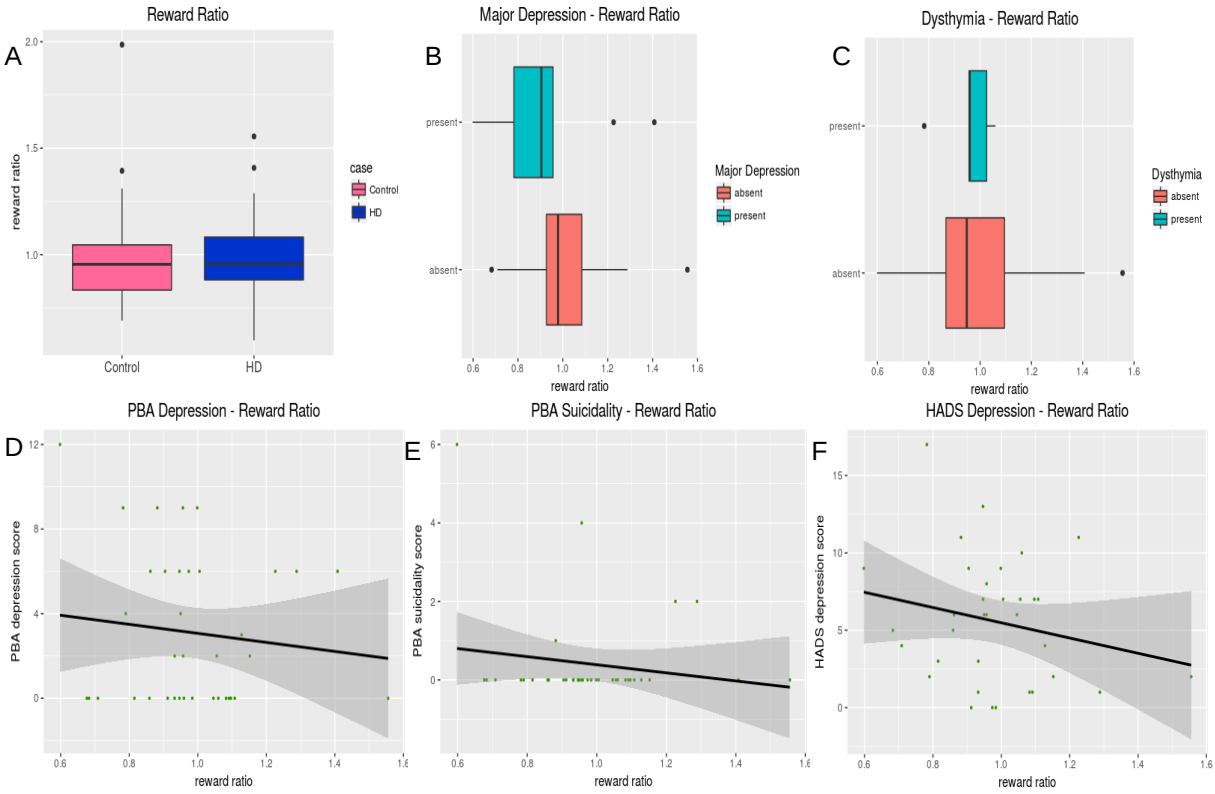


Figure 6.5: Progressive Ratio

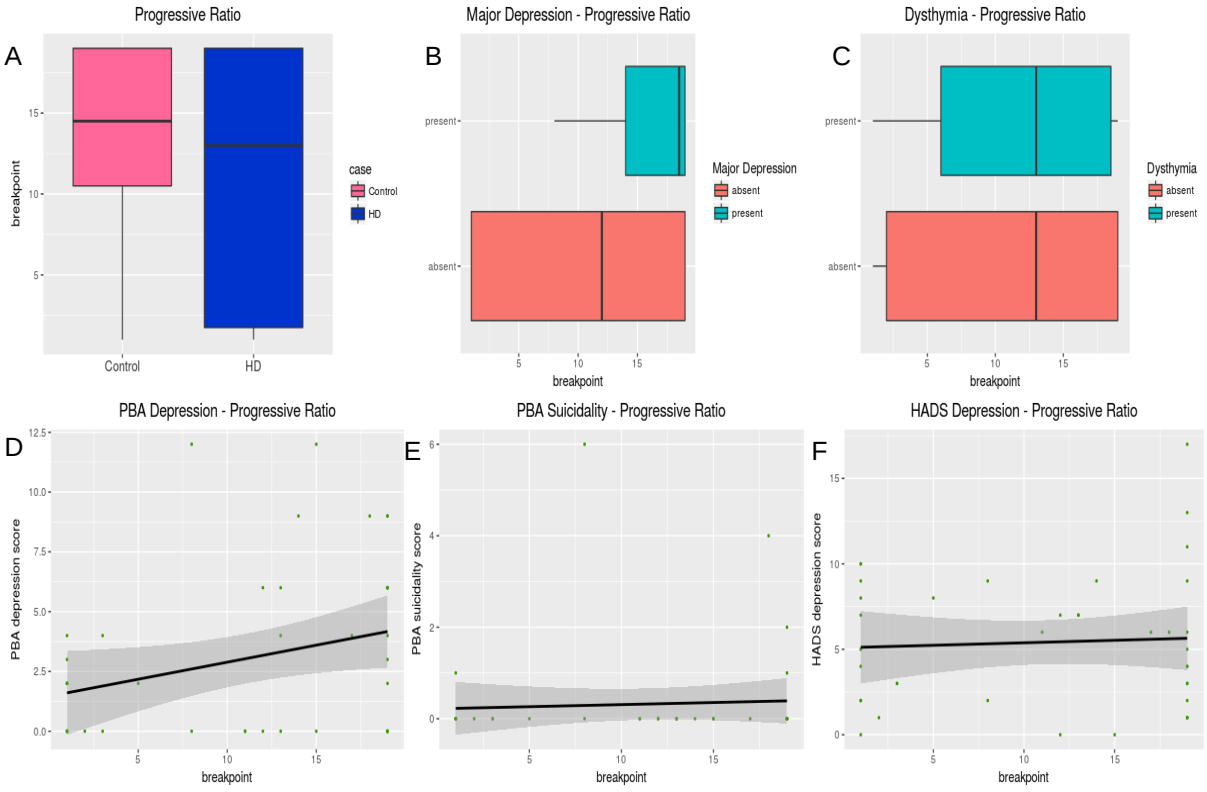


Figure 6.6: BAS Reward

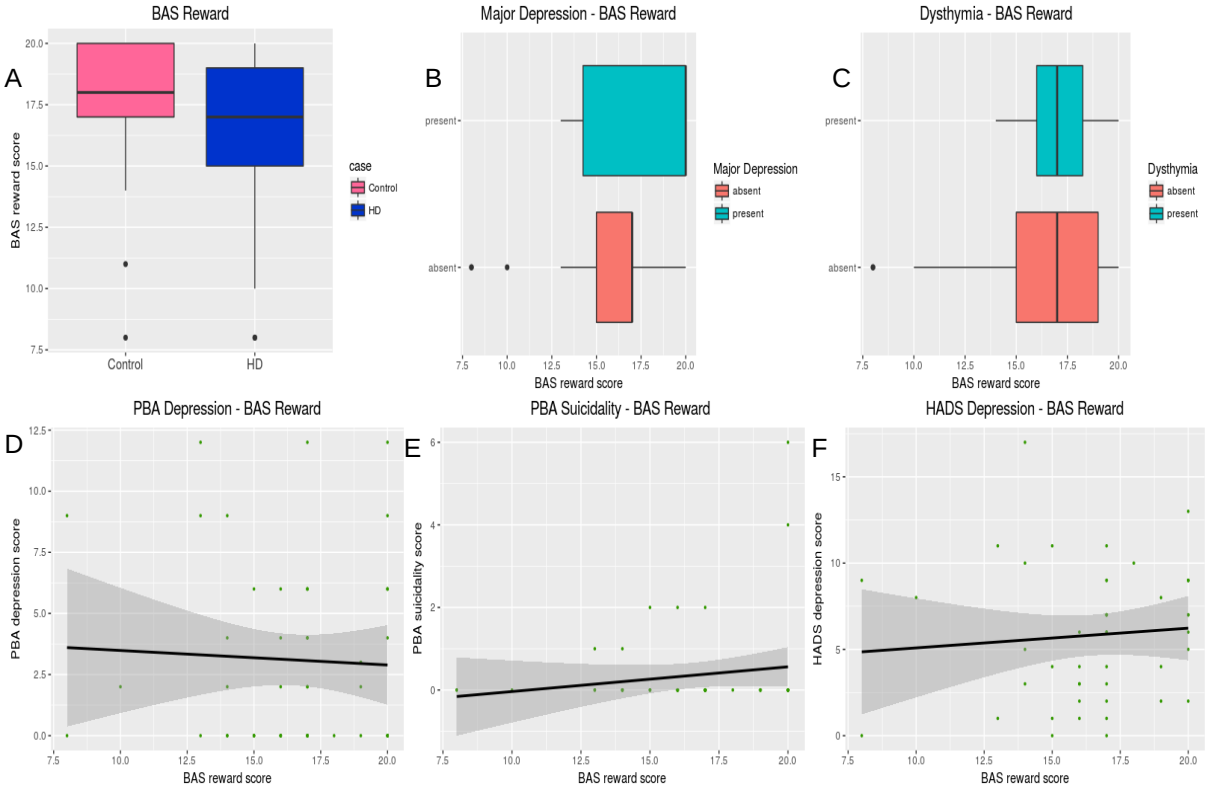


Table 6.8: Reward Ratio Task

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	OLS		*negative binomial*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	5.21	0.10	0.41	0.90	10.41	0.011	0.78	0.716	−0.96	0.67
Reward Ratio	−2.14	0.49	−1.41	0.67	−4.93	0.22	−1.98	0.370	−0.51	0.82
R^2	0.014				0.047					
Adjusted R^2	−0.015				0.018					
F Statistic	0.48 (df = 1; 35)				1.59 (df = 1; 32)					
Log Likelihood			−49.16				−20.09		−17.9	
Akaike Inf. Crit.			55.16				44.19		39.84	
Pseudo R^2			0.026				0.021		0.0040	

Table 6.9: Reward Ratio Task: Confounder Model

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	OLS		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	18.87	0.022	12.85	0.012	19.93	0.030	31.65	0.054	−3.90	0.54
Reward Ratio	−5.54	0.11	−4.01	0.082	−7.19	0.091	−5.84	0.080	−2.30	0.46
Age	−0.099	0.16	−0.11	0.084	−0.12	0.15	−0.053	0.56	−0.012	0.84
IQ	−0.059	0.32	−0.071	0.082	−0.044	0.51	−0.32	0.055	0.033	0.48
TMS	0.043	0.26	0.046	0.23	0.10	0.024	0.17	0.040	0.034	0.30
Olanzapine Equivalent	−0.19	0.13	−8.85	0.99	0.18	0.75	0.11	0.48	−0.21	0.33
Fluoxetine Equivalent	0.0017	0.94	−0.010	0.64	0.025	0.35	0.043	0.22	0.046	0.032
PBA Apathy	−0.042	0.82	0.37	0.0046	−0.077	0.75	−0.14	0.48	−0.11	0.50
R^2	0.20				0.29					
Adjusted R^2	−0.005				0.085					
F Statistic	0.97 (df = 7; 28)				1.42 (df = 7; 25)					
Log Likelihood			−19.41				−9.36		−13.54	
Akaike Inf. Crit.			54.81				34.73		43.086	
Pseudo R^2			0.62				0.54		0.19	

Table 6.10: Progressive Ratio Task

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	OLS		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	1.46	0.12	−1.50	0.0062	5.088	5.33×10^{-5}	−3.36	0.0062	−1.81	0.018
Breakpoint	0.14	0.045	0.030	0.43	0.029	0.73	0.14	0.065	0.013	0.82
R^2	0.092				0.0033					
Adjusted R^2	0.071				−0.024					
F Statistic	4.27^{**} (df = 1; 42)				0.12 (df = 1; 37)					
Log Likelihood			−40.15				−18.48		−19.25	
Akaike Inf. Crit.			84.31				40.95		42.50	
Pseudo R^2			0.0098				0.11		0.0014	

Table 6.11: Progressive Ratio Task: Confounder Model

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	OLS		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	9.22	0.13	13.98	0.0088	12.45	0.068	23.65	0.21	−5.69	0.30
Breakpoint	0.14	0.087	−0.011	0.833	0.094	0.34	0.52	0.058	0.046	0.49
Age	−0.038	0.52	−0.074	0.15	−0.081	0.23	−0.041	0.71	0.0041	0.94
IQ	−0.064	0.22	−0.12	0.0043	−0.069	0.23	−0.40	0.117	0.015	0.76
TMS	0.012	0.74	0.0040	0.86	0.078	0.055	0.14	0.12	0.026	0.42
Olanzapine Equivalent	−0.19	0.096	−0.54	0.014	0.24	0.40	−0.31	0.26	−0.21	0.22
Fluoxetine Equivalent	0.021	0.39	−0.012	0.51	0.036	0.20	0.12	0.12	0.055	0.015
PBA Apathy	0.11	0.47	0.30	0.0036	−0.090	0.65	0.30	0.23	−0.10	0.49
R^2	0.20				0.25					
Adjusted R^2	0.031				0.071					
F Statistic	1.185 (df = 7; 34)				1.40 (df = 7; 30)					
Log Likelihood			−27.82				−8.35		−13.95	
Akaike Inf. Crit.			71.63				32.69		43.90	
Pseudo R^2			0.26				0.59		0.27	

Table 6.12: BAS Reward Score

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	negative binomial		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	−1.39	0.27	−4.93	0.011	3.94	0.25	−4.35	0.090	−3.28	0.20
BAS Reward	−0.016	0.83	0.22	0.037	0.11	0.57	0.17	0.24	0.095	0.52
R^2					0.0075					
Adjusted R^2					−0.016					
F Statistic					0.32 (df = 1; 43)					
Log Likelihood	−113.73		−45.95				−24.45		−21.93	
Akaike Inf. Crit.	95.91		95.91				52.87		47.86	
Pseudo R^2	0.0010		0.067				0.031		0.010	

Table 6.13: BAS Reward Score: Confounder Model

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	negative binomial		*Poisson*		*OLS*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	9.16	0.0030	7.071	0.13	14.96	0.090	11.035	0.14	−5.61	0.44
BAS Reward	−0.096	0.21	0.14	0.19	−0.029	0.90	−0.0043	0.98	0.10	0.60
Age	−0.038	0.068	−0.034	0.27	−0.063	0.27	−0.048	0.35	0.017	0.72
IQ	−0.046	0.023	−0.098	0.0087	−0.079	0.17	−0.13	0.032	0.011	0.81
TMS	0.0037	0.76	−0.0066	0.68	0.064	0.068	0.065	0.029	−0.0033	0.91
Olanzapine Equivalent	−0.14	0.091	−0.53	0.0049	−0.019	0.94	−0.039	0.63	−0.16	0.31
Fluoxetine Equivalent	0.0053	0.52	−0.020	0.20	0.018	0.47	0.026	0.17	0.039	0.033
PBA Apathy	0.026	0.65	0.35	0.00024	0.071	0.68	−0.058	0.60	−0.13	0.36
R^2					0.18					
Adjusted R^2					0.023					
F Statistic					1.15 (df = 7; 36)					
Log Likelihood	−207.78		−32.29				−17.81		−17.55	
Akaike Inf. Crit.	225.78		80.59				51.62		51.11	
Pseudo R^2	0.18		0.40				0.28		0.20	

6.3.4 Executive Function Measures

Phonemic Verbal Fluency (PVF)

Higher scores indicate better task performance and hence better executive function. As described in previous chapters HD patient group had markedly lower scores on this task than healthy controls (means 29.29, 45.46, p = 7.048 x10^{-5}). Modelling of the relationships between task performance and the gold-standard mood measures within the HD population showed an association between worse PVF performance and higher levels of PBA suicidality (p=0.016) and depression measured by the HADS at trend level (p=0.083). The model of PVF and PBA suicidality showed reasonable explanation of variation (pseudo R^2 0.33), but the others did not (R^2 or pseudo R^2 all less than 0.05). Owing to strong co-variances between PBA apathy score, Olanzapine equivalent dose, TMS and PVF, convergence of the GLMs necessitated exclusion of the variables from the PBA suicidality Poisson GLM. However, no significant associations were found.

Extra-Dimensional Set Shift Task (EDSST)

As described in previous chapters the HD group made fewer set shifts than healthy controls (means 6.08, 9.31) but this was not significant (p= 0.17). Within the HD group, better scores on the EDSST indicated higher scores on all mood measures, except for PBA suicidality, although none of these relationships approached significance. There were no significant relationships when confounding variables were added to the models. The explanation of variation in the initial GLMs was poor (R^2 or pseudo R^2 0.12 or less).

Figure 6.7: Phonemic Verbal Fluency

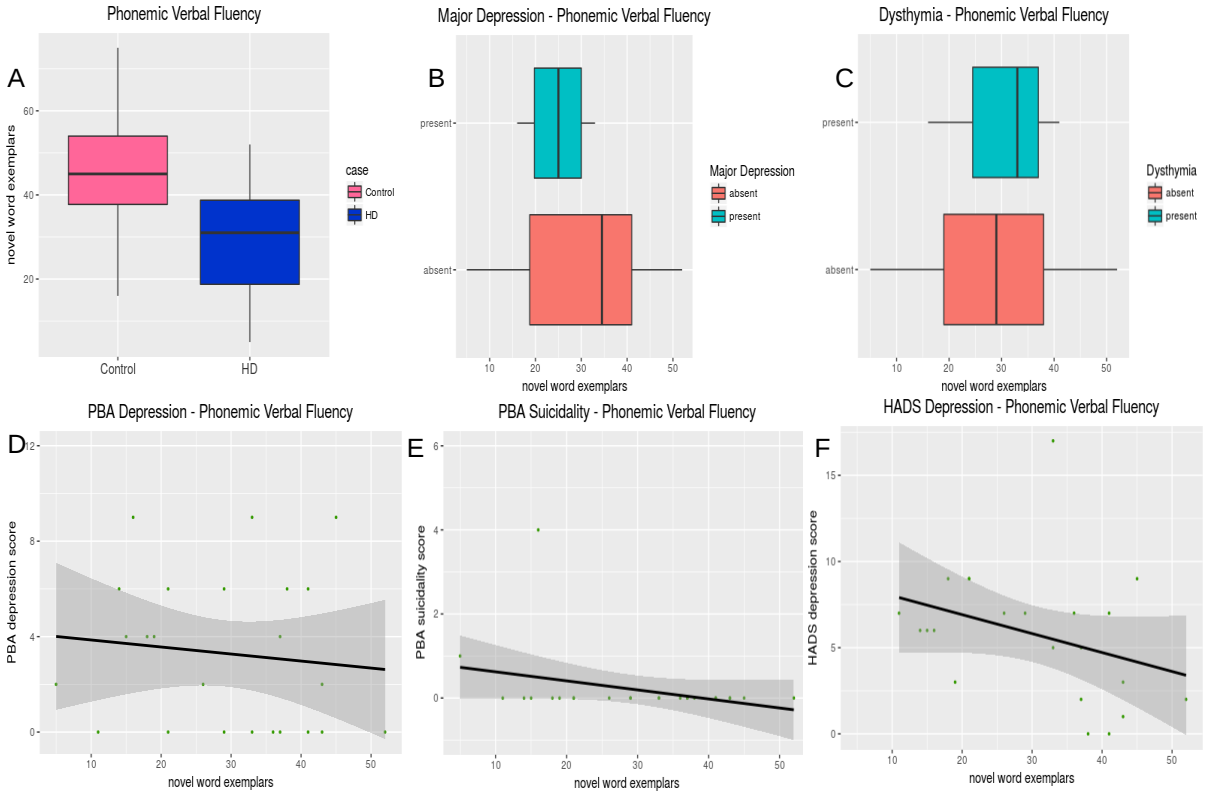


Figure 6.8: Extra-dimensional Set Shift Task

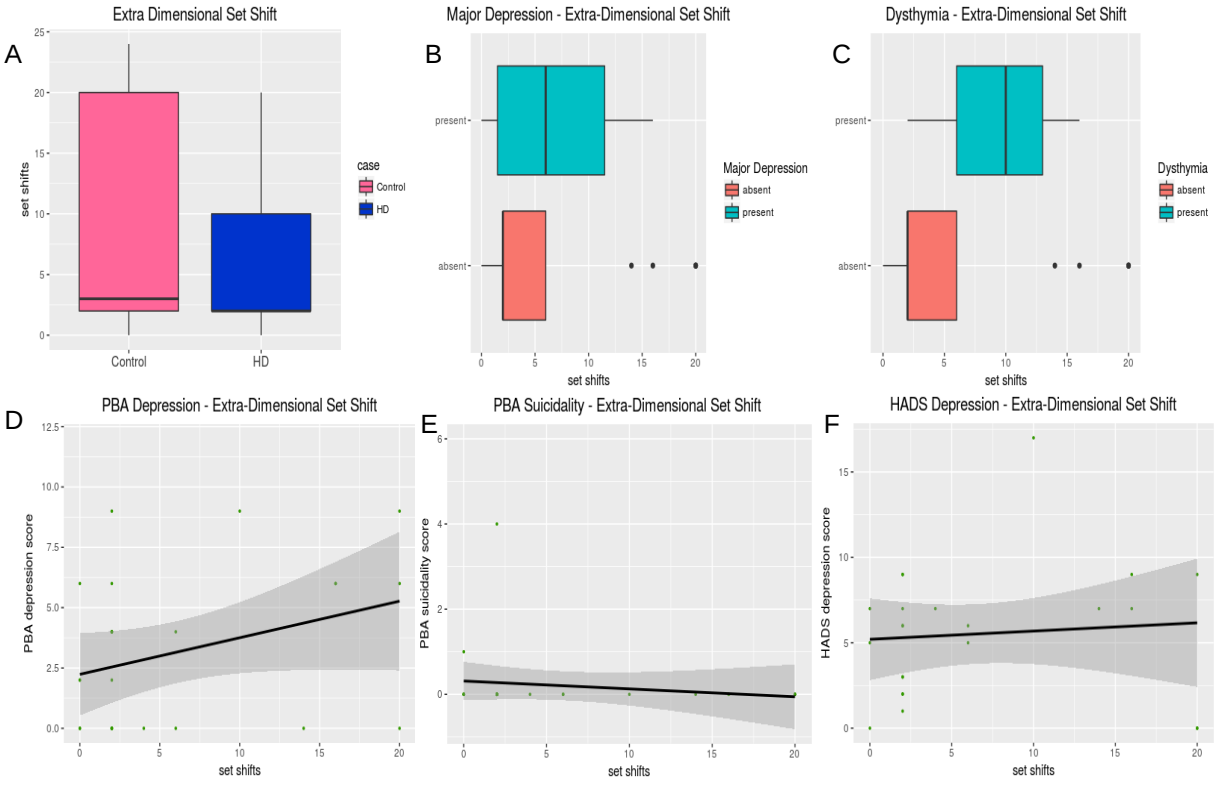


Table 6.14: Phonemic Verbal Fluency

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	OLS		*Poisson*		*negative binomial*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	4.15	0.025	1.10	0.20	2.36	$4.21 \text{x} 0^{-10}$	−0.60	0.64	−2.11	0.20
PVF	−0.029	0.59	−0.13	0.016	−0.021	0.083	−0.037	0.42	0.0054	0.91
R^2	0.013									
Adjusted R^2	−0.032									
F Statistic	0.29 (df = 1; 22)									
Log Likelihood			−11.65		−59.20		−10.48		−9.037	
Akaike Inf. Crit.			27.29		122.40		24.97		22.07	
Pseudo R^2			0.33		0.094		0.031		0.0006	

Table 6.15: Phonemic Verbal Fluency: Confounder Model

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	OLS		*Poisson*		*negative binomial*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	8.38	0.26	15.05	0.095	4.01	0.0038	19.75	0.22	−1.67	0.75
PVF	−0.067	0.44	−0.18	0.12	−0.0016	0.92	−0.018	0.89	0.018	0.80
Age	−0.022	0.77	0.065	0.50	−0.030	0.024	−0.048	0.80	−0.0025	0.97
IQ	−0.010	0.90	−0.16	0.18	−0.013	0.36	−0.22	0.15	−0.0087	0.88
TMS	−0.011	0.82			0.015	0.044	0.065	0.42	0.0081	0.82
Olanzapine Equivalent	−0.44	0.38			−0.027	0.75	−7.71	0.99	0.0055	0.99
Fluoxetine Equivalent	0.024	0.43	−0.038	0.28	0.0081	0.079	0.070	0.24	0.027	0.19
PBA Apathy	−0.10	0.71			0.0034	0.94	−0.14	0.75	0.012	0.95
R^2	0.23									
Adjusted R^2	−0.12									
F Statistic	0.65 (df = 7; 15)									
Log Likelihood			−10.99		−52.88		−4.80		−7.67	
Akaike Inf. Crit.			29.98		121.76		25.61		31.33	
Pseudo R^2			0.50		0.35		0.55		−0.53	

Table 6.16: Extra-Dimensional Set Shift Task

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	OLS		*Poisson*		*negative binomial*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	2.24	0.012	−0.90	0.11	1.64	$2.49\text{x}10^{-13}$	−1.67	0.010	−2.24	0.0084
EDSST	0.15	0.10	−0.24	0.26	0.010	0.66	0.028	0.70	0.065	0.38
R^2	0.11									
Adjusted R^2	0.073									
Log Likelihood			−14.57		−63.47		−11.0046		−8.91	
F Statistic	2.89 (df = 1; 23)									
Akaike Inf. Crit.			33.15		130.95		26.0091		21.81	
Pseudo R^2			0.12		0.0058		−0.25		−0.23	

Table 6.17: Extra-Dimensional Set Shift Task: Confounder Model

	Dependent variable:									
	PBA Depression		PBA Suicidality		HADS Depression		Major Depression		Dysthymia	
	OLS		*Poisson*		*negative binomial*		*logistic*		*logistic*	
	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value	Estimate	P Value
(Intercept)	10.11	0.17	10.93	0.12	4.32	0.0034	6.91	0.24	−1.98	0.72
EDSST	0.12	0.41	−0.34	0.38	0.0055	0.83	0.031	0.78	0.011	0.92
Age	−0.034	0.64	0.093	0.23	−0.039	0.0085	−0.016	0.77	−0.0049	0.93
IQ	−0.057	0.44	−0.16	0.12	−0.014	0.32	−0.082	0.17	0.0025	0.96
TMS	0.022	0.61			0.021	0.0035	0.050	0.13	0.0091	0.76
Olanzapine Equivalent	−0.35	0.47			0.0015	0.99	0.22	0.59	0.015	0.97
Fluoxetine Equivalent	0.012	0.65	−0.061	0.16	0.0052	0.30	0.016	0.47	0.022	0.24
PBA Apathy	−0.068	0.77			−0.026	0.59	−0.23	0.26	−0.048	0.78
R^2	0.23									
Adjusted R^2	−0.10									
F Statistic	0.69 (df = 7; 16)									
Log Likelihood			−11.48		−56.18		−7.16		−8.021	
Akaike Inf. Crit.			32.96		128.36		30.33		32.042	
Pseudo R^2			0.34		0.31		−0.12		−0.58	

6.3.5 Exploratory relationships

To assess validity of the reward based measures, we compared scores on the BAS reward, progressive ratio and reward ratio tasks using GLMs (assumptions underlying linear regression were not met). Higher breakpoint on progressive ratio and faster reaction time on the reward ratio task were significantly associated (pseudo R^2 0.077, AIC 183.54, estimate -0.88, p = 0.012), higher breakpoint was also associated with higher scores on the BAS reward (pseudo R^2 0.051, AIC 185.73, estimate 0.038, p = 0.0438), but there was no association between the reward ratio and BAS reward score (pseudo R^2 0.0084, AIC 141.71, estimate -0.068, p = 0.72).

6.4 Discussion

In this sample, HD cases had more frequent diagnoses of major depression and dysthymia, higher scores on the PBA measures and higher HADS depression scores than the control group, however, the only comparison to reach significance was the HADS depression score. On the assessment of depressive cognition, HD patients scored significantly lower (suggesting reduced optimism compared with controls about their potential performance) pre-task. This score only showed an association with PBA suicidality at trend level, which was not maintained in the model containing confounding variables. None of the other outcome measures from this task showed significant differences between cases and controls, although higher scores post-task were significantly predictive of PBA suicidality in the model without confounding variables. The BAS reward score, and tasks mediating reward and effort, only showed group differences for the BAS reward score, with the HD group scoring lower than controls on BAS reward, whilst the models within the HD group suggested a positive predictive effect of higher BAS reward score on PBA suicidality. There were trend level (or borderline significant) associations between higher effort on both the reward ratio task, and progressive ratio task, and higher scores on the gold standard mood measures, which were not maintained in the models including confounding variables. The executive function measures showed group differences on the PVF task alone. The poorer scores on the PVF (suggestive of impaired cognition) were predictive of increased suicidality and HADS depression score (trend level only), although these associations were not maintained in the confounder models.

In this study, we did not find differences in the prevalence of depression or suicidality between HD cases and controls, apart from the HADS depression score. We considered whether this might reflect a higher risk of depression in the familial controls, as this is well recognised(592), however, the point prevalence of depression, dysthymia and scores on the dimensional instruments in our control cohort were lower than reported population studies(165, 308, 564, 565, 593), alternatively, we considered whether the scores might represent an under-estimate of the prevalence or severity of depression in the HD group (more depressed subjects, may well be less likely to volunteer for studies), however the rates of major depression and PBA scores were similar, or even higher compared with previous reports(165, 197, 214). Notably, several other studies have shown a lack of difference on mood scores between cases and controls(153, 165). Furthermore a number of studies following predictive testing have not found a difference between subjects with a positive predictive test compared with negative one(594–596), although the PHAROS study (a comparison of motor, cognitive and behavioural measures, in a cohort at risk of HD, blinded to their own genetic status) did find higher scores on the depressed mood item of the UHDRS

behavioural score among gene positive compared with gene negative subjects.

The task of depressive cognition demonstrated significantly lower scores in the HD patients compared with controls. As part of the task, clear instructions were given to participants that their performance took in to account their baseline tapping speed. This may reflect depressive cognition in the HD group, however, it may be that the HD group found it more difficult to ignore their known motor deficit. Furthermore, the only association between any of the gold standard mood assessments and task performance, was with PBA suicidality; which occurred in the opposite direction to what we had anticipated: higher estimates of performance both pre and post task were associated with higher scores on the PBA suicidality item. It is not clear what underlies this association (which was not sustained in the model including confounding variables). It is possible that higher estimates of subjects abilities are more likely to lead to disappointment and low mood, whilst several meta-analyses have shown that extroversion is linked to suicide attempts, and may explain some of this association(597, 598). Alternatively poor understanding of the requirements of the task may have limited interpretation in the HD group. This task has not been independently verified in subjects with depressed mood drawn from the general population, and hence may not measure what we hypothesised.

Our reward and effort measures only showed differences between HD and control participants on the BAS reward score, where HD subjects had lower scores than controls. Previous work has shown deficits in reward based tasks in manifest HD(88), and in ventral striatal activity during reward anticipation in presymptomatic HD subjects(437). Within the HD group, higher BAS reward score was predictive of higher PBA suicidality, although this relationship did not survive the inclusion of confounding variables in the model. This relationship may also be mediated by the personality trait of extraversion highlighted above, as increased reward responsiveness is associated with the personality trait of extraversion(599–601). The lack of association between the reward-effort tasks and gold standard measures of depression is not in keeping with the wider literature about depressed mood, reward and effort. Treadway and co-workers, have demonstrated associations between lower effort and diagnosis of depression, as well as anhedonic trait in healthy controls(315, 580, 602). Moreover there is a large body of literature demonstrating reduced reward responsiveness in major depressive disorder(603, 604). Our tasks were based on standardised instruments, previously shown in animal and human studies to be effective measures of effort and reward. Nonetheless, we compared predictive value between all three related measures, and found strong relationships, except for BAS reward score and performance on the reward ratio task. It is possible that some of the other cognitive or psychiatric features of HD are

acting as confounders in this; for example perseveration may lead to inappropriate persistence of responses leading to apparently preserved effort for reward.

In our study, impaired performance on one measure of executive function, the PVF, was associated with higher scores on the PBA suicidality instrument, and a trend to higher scores on the HADS depression. Wetzel et al(568), did not find an association between symbol digit modality test scores and suicidality in HD, whilst other large studies of suicidality in HD did not report cognitive tests in their analyses(214, 605, 606). Deteriorating cognition has been a predictor of suicide in other neurodegenerative diseases(607–610). Although the epidemiological work suggests that depression is the major predictor of suicidality in HD, narrative accounts point to suicide as being a rational response to physiological deterioration caused by HD(611), which may explain this association.

Notably in the models including confounding variables, apathy was not strongly related to any of the mood instruments except for the PBA suicidality score. This may reflect the contribution executive function makes to apathy in HD(456). The distinction between depressed mood and apathy in HD has previously been clearly drawn(612, 613). Reward deficits are only seen later in the disease course(88), in keeping with the relative preservation of the ventral striatum and orbito-frontal cortex. In keeping with this, we did not find links between reward or effort and either apathy or depression in our study.

Our study does have several limitations. We used demographic instruments to measure premorbid IQ, and some workers have advocated reading tests such as the National Adult Reading Test (NART)(614), or combined demographic and reading tests(615). However, work in pre-manifest and motor manifest HD subjects has shown, that whilst in the pre-manifest state, reading test performance is preserved, with motor onset, it declines, underestimating premorbid IQ systematically in this group(377, 378, 429, 430). Given our mixed sample of pre-manifest and manifest individuals, this created a high risk of systematic bias. Therefore we adopted the demographic method of Crawford. Furthermore, there may have been unknown confounders we were unable to correct for in our models. The high degree of auto-correlation between the executive function measures, apathy and olanzapine dose precluded their inclusion in the models. However, despite this, no significant result for the independent variable was found and hence it is unlikely to influence the conclusions of the study.

In summary, we found differences between HD patients and healthy controls on measures of

reward value, estimated performance and executive function, however these were only weakly predictive of scores on the PBA suicidality instrument (and no other depressed mood measure) within the HD cohort, and none survived inclusion in a model with confounding variables.

Chapter 7

Concluding Remarks

7.1 Overview of the Findings of the Work

To my knowledge this is the first attempt to systematically delineate the cognitive processes leading to common neuropsychiatric symptoms in HD. I have shown that apathy in HD is associated with insensitivity to negative stimuli, furthermore, that whilst there is a reward deficit in HD, it is not as marked as that seen in relation to aversive stimuli, and makes little to no contribution to apathy in HD. Impulsivity in HD is related to impaired performance on the Iowa gambling task, suggesting either impairments in future perspective or insensitivity to aversive stimuli; and also that inhibitory deficits contribute to impulsive behaviour, whilst risk-taking and inter-temporal discounting do not. Irritability and aggression in HD are related to increased negative emotional reaction to 'real-life' negative stimuli, but not to failure of frontal control, measures of unfairness or impaired motor inhibition. Finally suicidality in HD is in part linked to deteriorating cognition, and overestimate of performance, however, measures of reward and effort do not make a major contribution to mood disorders in HD.

7.2 Strengths of the Work

In this work I have attempted to definitively link task performance and behaviour. I explicitly sought evidence for differences between cases and controls, and prediction of gold-standard measures of neuropsychiatric symptoms within our HD cohort by task performance or impairment. A major problem in some of the published literature, that has been exposed by this work is a variant of the ecological fallacy: the co-occurrence of high rates of a particular characteristic

in a group and altered task performance in the same group, does not necessarily imply that the characteristic is caused by (or even related to) the characteristic in question, despite any biological plausibility. This issue is particularly pertinent when performance on a particular task is affected by two or more cognitive processes each of which affect task performance in different ways. An example of this phenomenon in this thesis is the co-occurrence of a reward deficit and aversive stimulus insensitivity and their influence on performance in the BART. Applying the ecological fallacy would have led to a conclusion that as cases were less effective at exploiting reward than controls, a reward deficit explained the higher levels of apathy seen in the HD cohort. However the use of a mixed-modelling approach using data from individual trials, allowed the delineation of cognitive processes and revealed the contribution of aversive stimulus insensitivity to apathy in HD. However, this approach becomes more difficult when there is no definitive gold-standard assessment for the characteristic in question. In this scenario, strategy I employed was to map the change in task performance with increasing biological burden of disease (using controls, presymptomatic HD and manifest HD), and compare performance between tasks and questionnaire assessments of the characteristic in question, in order to look for overlap.

The ecological fallacy in neuropsychology, can also be seen in the imaging literature, when changes in cerebral perfusion, task activation or volume within an affected cohort in isolation, or between cases and controls are presumed to explain neuropsychiatric symptoms or cognitive deficits. For example in the paper by Massimo et al(254), (that uses a novel task they hypothesise measures apathy, and apathy scores on the Neuropsychiatric Inventory - NPI) in a cohort of fronto-temporal dementia patients they relate NPI apathy scores to smaller volume in the grey matter of the orbito-frontal cortex, but then relate task performance to imaging changes in many more regions. However, there is no assessment in the study of how well the gold-standard apathy measure is predicted by their novel task and all of these analyses are completed within a disease cohort, with no controls. Without a control cohort, the grey matter changes cannot be interpreted – the low apathy cases, may have had a disproportionately bigger orbito-frontal cortex than controls, for example.

The approach of comparing task performance between groups, and then predicting neuropsychiatric scores using models has the advantage of being able to correct for confounding variables. Other groups have excluded participants with depression from apathy tasks for example, whilst this approach allows robust correction for any mood disorder. The use of meta-analytic data for drug dose equivalents (Olanzapine and Fluoxetine) to include in models (rather than exclude participants on medication) meant that no data were discarded, and the cases were more repre-

sentative of the wider HD population, very few of whom are not on some form of neuropsychiatric treatment.

7.3 Extending our Findings to Explore the Neurobiology

I plan to take this work forward using imaging techniques to further delineate the neurobiology. The published literature to date on neuropsychiatric symptoms in HD has not shown any consistency regarding the networks or anatomical locations involved in the core behavioural symptoms in HD. This may reflect methodological techniques or the heterogeneity of cognitive processes underlying these symptoms. The majority of published studies are negative, and there is no consistency in the anatomical regions involved between the publications that have shown an effect. Imaging studies (because of the number of statistical tests involved) are very vulnerable to type I error. The most reliable neuropsychological imaging studies demonstrate a behavioural deficit on a task (ideally in a double dissociation), that predicts symptomatology reliably, then go on to demonstrate that neuro-imaging changes associated with task performance predict gold standard measures of symptoms.

7.4 Rationale for the Statistical Approach

In this work, I have employed a range of statistical techniques: group comparisons using standard two tailed t-tests or Wilcoxon tests, in addition to modelling techniques – multiple linear regression, generalised linear models using Poisson distributions, logistic regression and mixed modelling techniques. Each of these tests have underlying assumptions which must be satisfied to ensure the validity of the test and consequent reliability of the results. When the assumptions underlying linear regression were not met, I plotted the data, and tested whether it met the assumptions of an alternative distribution; often this would be the Poisson distribution, non-negative, positively skewed whole numbers. This distribution is most commonly found in count data, which did represent some of the dependent variables. I used dispersion tests and changed Poisson models to negative binomial models to account for the excess variance (causing overdispersion) when these were significant. This approach is robust, but an alternative would have been to log transform or inverse the dependent variable. I chose not to do this primarily because of the methodological principle that data should be analysed as they are, rather than attempting to amend them in some way to make the assumptions underlying statistical tests

valid. Furthermore, many of the transformations change the nature of what is being measured and invalidate inferences about the biology. In more practical terms, data transformation often does not sufficiently change the data to make the test assumptions valid(616). Where I have used models to study the effect of case (HD compared with controls), instead of Wilcoxon tests, this is because of ties in the data (equivalent values at the same rank) meaning an exact P value could not be calculated. Furthermore, discarding information about the numerical differences between ranks in the Wilcoxon test limits the power to detect a difference.

7.5 Apathy Findings

Our findings regarding apathy are likely to be robust: a disparity between punishment and reward sensitivity has been shown in other diseases(436) and also in HD(88), but this work is the first to demonstrate that a deficit in sensitivity to aversive stimulus leads to apathy in any disease. I found large group effects for the PVF task, and prediction of apathy in simple linear regression, but the addition of confounders meant the relationship was no longer significant. There are a number of potential reasons for this; firstly the HD sample size was smaller than that completing the other tasks; secondly the Stroop, Trails tasks and symbol digit modality test are more sensitive measures of cognitive decline in HD, and were the tasks that showed an association with apathy in previous works(165, 166, 213, 456). The letter fluency and set shifting tasks were chosen for theoretical (there is good evidence that they are impaired in HD(136, 164, 382)) and practical reasons: the executive function tasks known to show deficits in HD were more difficult to computerise, and in the case of the Stroop, predominantly measured processes that were partly assessed by other tasks in our battery i.e. inhibition. However, what remains unclear is whether the executive function tasks measure a cognitive process that directly leads to apathy, or whether cognitive decline in HD occurs in parallel with apathy. In any future studies of apathy in HD, it would be helpful to include a specific task of planning such as the towers of London task, which I did not use in our battery because some groups have found it less sensitive to executive function in premanifest HD than other measures(136), albeit in manifest HD the Towers of London task is much more sensitive to decline (382). I did not include a measure of time perception in our analysis, which is known to be abnormal in HD(617, 618), and may also contribute to apathy in HD: patients may not act or change action because they are unaware of the passage of time, and consequently sit in an inactive state without realising how long they have been there for. The Maze task showed strong association with both the EDSST and par-

ticularly the PVF in our battery, however the R^2 value of these regressions showed that there remained a significant degree of unexplained variation in the data: clearly the task is reliant on executive function, but idea generation may have more 'creative' processes underlying it too.

7.6 Impulsivity Findings

Our findings regarding impulsivity in HD: deficits in decision making and inhibition, but not in inter-temporal discounting or measures of risk-taking, have been shown in part by other groups(136, 171, 478, 483, 486). The literature on inter-temporal discounting and risk-taking in HD is sparse, with one conference abstract, and one publication regarding the Cambridge gambling task, but these studies are in agreement with our findings. Previous work on the Iowa gambling task in HD(482, 483) has shown deficits compared with controls, but this deficit did not correlate with the disinhibition measure used (the FLOPS – the precursor to the frontal systems behaviour scale). This measure does include some questions which indicate impulsive behaviour (e.g. "acts impulsively"), but others which do not (e.g. "neglects personal hygiene"), and hence may not be the best measure of impulsivity. It is much more difficult to assess impulsivity than some of the other neuropsychiatric symptoms, given the heterogeneity of cognitive processes underlying the behaviour, and consequent lack of a gold standard measure. Nonetheless I have shown progression of impulsivity on some questionnaire measures and tasks in association with disease progression. Furthermore, I found some association between questionnaire measures and task performance suggesting at least some degree of overlap of the cognitive processes involved. The absence of impairment on the inter-temporal choice task is explicable in terms of the structures affected by HD, as this task predominantly activates ventral striatum and orbito-frontal cortex(508, 509), which remain relatively preserved until the later stages of HD(81, 142).

7.7 Depression and Suicidality Findings

The most striking finding from our study in mood disorders and suicidal ideation in HD was the effect of executive function and estimate of performance on suicidal ideation. Impairments in cognition are noted by HD patients(619), and an awareness of decline could make suicide and suicidal ideation more likely in HD patients(620). Often suicidal ideation is perceived as a rational choice in the face of advancing disease(25) by HD patients. Anecdotally many patients report

a plan for suicide when the disease advances, which they describe as a 'comfort' knowing they 'have a way out if things get too bad'. The association between suicidal ideation and increased estimate of performance is unexpected, but a possible explanation mediating this effect is hypomania, which has been seen as part of HD psychopathology(197) Hypomania and agitation is also associated with increased estimate of performance and increased suicidal ideation(621, 622) when seen as part of bipolar disorder, which may mediate the association seen in our cohort. Our measures of reward and effort did not predict mood disorders, or suicidal ideation in HD. Given the early appearance of depression in HD(211, 212, 566), and the fact that deterioration in reward related structures occurs relatively late in HD, this is not an unexpected finding. I did not include an assessment of negative salience or affective bias in our test battery, and future studies should test this aspect of mood disorder in an HD cohort. However, in light of our findings relating to insensitivity to aversive stimuli in HD patients, depressed mood may not be related to negative salience in this cohort. The cognitive process of rumination has been related to depressed mood and changes in the default mode network(322); this network has been found to be abnormal in HD(623–625). Future studies could include an assessment of rumination as a predictor of depression in HD.

7.8 Irritability and Aggression Findings

Our data show that aggression and irritability in HD is primarily driven by anticipatory emotional reactions to real world tasks or irritating situations and is not related to impaired frontal control, measures of fairness or impulsivity. Previous work in presymptomatic cohorts found irritability in HD was associated with altered functional connectivity between the amygdala and medial orbito-frontal cortex(130) and in separate work with alterations in a network involving the cingulate cortex, thalamus and amygdala(555). The experience of excessive anger has been strongly linked with amygdala activation in other disorders, and may represent a heightened response to threat, particularly in impulsive aggression(626, 627). Alterations in emotional interpretation and experience may also play a role in irritability and aggression in HD. I did not include the emotional faces task in our task battery, but the deficits in emotion recognition (particularly of negative emotion) are well-described(439). Furthermore, HD patients have altered emotional responses, with reduced fear and increased anger compared with controls(553). Both of these deficits could precipitate some of the aggression and irritability seen in HD. A further intriguing hypothesis was suggested to the author by Hugh Rickards (Reader in Neuropsychia-

try, Cinical Neurosciences, University of Birmingham); irritability is often provoked in healthy controls by cognitive overload (too many tasks at once), given the known impairments in dual tasking caused by HD, cognitive overload may occur much more easily and lead to the increased irritability seen in HD.

7.9 Future Research Plans

There are a number of different future directions this work could extend to. Firstly validation of the Persistence task in a larger cohort, with longitudinal assessment could provide a reliable, objective measure of apathy in HD for use in future clinical trials. There is also translational potential: a task showing differing sensitivity to aversive and rewarding stimuli could provide the first valid assessment for apathy in HD animal models. There is clear potential to study fMRI changes during punishment and reward in HD and controls to delineate the underlying neurobiology of this deficit. Finally there is the potential to extend the test battery across disease states.

Appendix A

Publications and presentations arising from this thesis.

Publications

1. McLauchlan DJ, Lancaster T, Craufurd D, Linden D and Rosser AE (2018): Spare the Rod? Insensitivity to Punishment Predicts Apathy in Huntington's disease. Brain (in submission).

Presentations and published abstracts

1. McLauchlan DJ and Rosser AE. A Systematic Review Of The Behavioural Symptoms In Huntington's Disease: A Cross-Sectional And Longitudinal Approach. MDS Congress June 2013.

2. McLauchlan DJ, Craufurd D, Linden D and Rosser AE. Huntington's disease patients are 'stuck in a rut': objective testing of apathy in Huntington's disease. EHDN Congress September 2016.

3. McLauchlan DJ, Craufurd D, Linden D and Rosser AE.Limited Insight? Objective Testing Of Irritability In Huntington's Disease. EHDN Congress September 2016. Limited insight? Objective testing of irritability in Huntington's disease. EHDN Congress September 2016.

4. McLauchlan DJ, Craufurd D, Linden D and Rosser AE. Depressed Mood And Suicidal Ideation In Huntington's Disease: Contribution Of Reward, Effort, Executive Function And Depressive Cognition. EHDN Congress September 2018.

5. McLauchlan DJ, Linden D and Rosser AE. Impulsivity In Huntington's Disease: Impaired Decision-Making And Motor Disinhibition. ECNP Barcelona October 2018.

Appendix B

Scenarios for the Maze Task.

Open Scenarios

1. "You are alone next to a red house."
2. "You are in a forest."
3. "You are at some cliffs."
4. "You are at a sandy shoreline."
5. "You are beside a path."
6. "You are in a cave."
7. "You are in a crowd next to a skyscraper."
8. "You are adrift in a boat at sea."
9. "You are in a castle. "
10. "You are in a farmyard."
11. "You are at a railway station."
12. "You are in a school."
13. "You are in a garden."
14. "You are at the top of a mountain."
15. "You are in an empty shop."

Chapter 8

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