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Evaluating Eye Movements as Potential Biomarkers for Monitoring the Progress of Huntington's Disease

SCHOOL OF OPTOMETRY & VISION SCIENCES CARDIFF UNIVERSITY

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Summary

The purpose of the studies documented within this thesis was to identify if eye movements can be used a biomarker for the progress of Huntington's Disease. There are no cures, or disease modifying treatments available, with the disease ultimately eventually proving fatal.

With therapeutic trials in the immediate future, it is crucial that reliable biomarkers of disease progress be observed, and quantitative assessment of eye movements potentially offer such a biomarker.

Abnormal optokinetic nystagmus is present in asymptomatic HD gene carriers, with some demonstrating a loss of the classic sawtooth waveform usually seen in healthy controls. This finding is found in the majority of HD participants, and is repeatable. HD gene carriers also show deficiency during the self-paced saccade task. These abnormalities are present in asymptomatic gene carriers, and could potentially be the first manifest motor symptom of Huntington's Disease. An incidental finding from the abnormal OKN is the presence of elevated motion sensitivity thresholds in HD. This non-oculomotor finding is also present in asymptomatic gene carriers, and could potentially be the first manifest sensory symptom.

Future investigation of these findings is crucial to determine their clinical viability as biomarkers. Both of the oculomotor findings were substantial and may be gross enough to transfer into the clinical environment without the need for specialist equipment.

Chapter 1: Background

Huntington's Disease (HD) is a genetic, neurodegenerative disorder characterised by cognitive decline, psychological problems, and abnormalities in movement; in particular chorea – irregular involuntary dance like movements. HD is associated with a mutated IT15 gene (Huntingtin gene) in chromosome 4p16.3. This gene contains a polymorphic trinucleotide (CAG) repeat that is expanded and unstable in HD (The Huntington's Disease Collaborative Research Group 1993). The normal range of CAG repeats is 7-35; repeats in excess of this are indicative of Huntington's Disease.

Kremer et al. (1994) conducted a worldwide study into the use of CAG expansion as a predictor of HD. In 995 patients from a total cohort of 1007 (98.8%), expanded CAG repeats were present (range 36-121, median 44). In addition the CAG repeats in 599 of 600 control subjects (99.83%) were fewer than 29. In this study the CAG repeats in neuropsychiatric conditions including Alzheimer's, Schizophrenia, Senile Chorea and Benign hereditary chorea were determined to be normal. Therefore the presence of a CAG expansion in excess of 35 repeats is a highly sensitive marker for the diagnosis of HD.

Increased size of the CAG expansion does correlate with age of clinical onset (larger expansion results in earlier onset), however age of onset cannot accurately be predicted by CAG expansion (Golding et al. 2006).

1.1 A Brief History of Huntington's Disease (HD)

Although not profiled until the 19th century, it is suspected that Huntington's Disease (HD) may have been one of the conditions responsible for the dancing mania plagues that occurred between the 10th and 17th centuries in central Europe (Walker 2007). A plague characterised by involuntary movements and tremors, which could eventually cause death (Waller 2009). It has been suggested that this plague may in fact have been a mass psychological phenomena, and should be dismissed as being a neurological condition (Donaldson, Cavanagh and Rankin 1997). However, a dancing mania epidemic known as *el mal* which devastated small towns along Lake Maracaibo, Venezuela as recently as the 1950's was identified as Huntington's Disease (HD) has thrown this into doubt (Okun and Thommi 2004)

The first recorded mention of HD in the literature is by Charles Oscar Waters, documenting his observation of 'magrums' (the name of which HD was known at that time) which was later published in *Practise of Medicine* (Dunglison 1842). Waters was the first to determine the genealogical nature of HD describing the disease as '*markedly hereditary*' remarking '*I have never known a case of it to occur in a patient, one or both of whose ancestors were not, within the third generation at farthest, the subject of this distressing malady*'. Waters described the manifestation of HD as '*a spasmodic twitching of the extremities generally of the fingers which gradually extend and involve all the voluntary muscles. This derangement of the muscular action is by no means uniform; in some it exists to a greater, and in others a less extent, but in all cases it gradually induces a state of more or less perfect dementia*. Further to this Waters also recorded the age of onset, and the prognosis; '*The singular*

disease rarely, very rarely indeed makes it's appearance before adult life, and attacks after 45 years of age are also very rare. When once it has appeared however, it clings to its suffering victim with unrelenting tenacity until death comes to his relief. It very rarely or never ceases while life lasts' (Bates, Tabrizi and Jones 2014).

Despite being the earliest known clinically based description for HD, the observations made by Waters even to this day remain remarkably relevant and thorough. In 1872, George Huntington published 'On Chorea', a paper describing the disease in a vivid and comprehensive manner, based on 79 years of observations made by three generations of family doctors. It was this paper that first brought HD to worldwide attention, a full transcript of this paper is included in the appendix. The description given by Huntington (1872) is considered to be one of the most exceptional in medical history (Chiu 1994).

Although the hereditary nature of HD was detailed in Huntington (1872), it was not until the early 20th century that it was suggested HD followed mendelian dominant inheritance (Wexler 2010). This led to the first large scale study of HD which was carried out involving 962 individuals with HD in New York and New England (Davenport and Muncey 1916). Along with establishing mendelian dominated inheritance; age of onset and inter-family variability in symptoms and disease severity were recorded. For the first time HD onset could be anticipated.

1.2 Epidemiology of Huntington's Disease

Harper (1992) reviewed epidemiological studies from 14 European nations and concluded the prevalence of HD as being 4-8 per 100000. Later studies in Northern Ireland (Morrison, Johnston and Nevin 1995) and Slovenia (Peterlin et al. 2009) confirmed this value. This prevalence value is cited in the literature as being representational of the European population (Frank and Jankovic 2010; Arran, Craufurd and Simpson 2014).

A notable exception to this is the prevalence of HD in Finland, which appears to be 0.5 per 100000 (Palo et al. 1987). It has been suggested that this significant variation is due to the Finnish being genetically distinct from other European populations (Harper 1992). Prevalence values among non-European populations appear to be significantly lower. HD among the black population in South Carolina, USA is 0.97 per 100000 (Wright, Still and Abramson 1981). In Japan, the population is also less likely to have HD at 0.65 per 100000 (Nakashima et al. 1996). It is suspected that this is due to a lower frequency of CAG repeated alleles within the Japanese population compared to Caucasians (Takano et al. 1998).

Aside from normal regional variation, there are examples of large families who are descended from a HD sufferer that have significant numbers of individuals identified as having HD. In Tasmania, Australia, 196 (16.6%) of the 1179 living descendants of the Robert Brothers were found to have HD (Pridmore 1990), increasing the HD prevalence for Tasmania in excess of 40 per 100000. Furthermore, 128 (25.2%) of the 508 living

descendants of a single woman from a village on Lake Maracaibo, Venezuela, have been identified as having HD (Penney et al. 1990).

More recently Evans et al. (2013) carried out a detailed study into the HD prevalence within the United Kingdom, based upon GP records between 1990 and 2010; data for geographical regions were also studied. The UK wide prevalence increased from 5.4 to 12.3 per 100000 with significant increases seen in subjects aged 60-69 (12.6 to 24.2) and 70+ (7.2 to 15.6), with an increase of at least 20% observed for all age ranges.

Evans, et al. (2013) further observed a geographic variation in HD. The lowest prevalence in the UK was observed in London (5.4 per 100000), it is suspected that this is due to the effect of migration into London. This would account for the areas with the largest HD prevalence (North East England [18.3] and Scotland [16.1]) where net migration is significantly lower.

1.3 Assessment of Disease Stage in HD, Unified Huntington's Disease Rating Scale

The Unified Huntington's Disease Rating Scale (UHDRS) was developed by the Huntington Study Group to be a 'comprehensive and reliable instrument to assess the clinical features of HD' (Huntington Study Group 1996). At this time there were several scales already available to assess various features of HD; the Quantitated Neurological Exam (QNE), Huntington's Disease Motor Rating Scale, Physical Disability and Independence scale, Marsden and Quinn's chorea severity scale and Huntington's Disease Activities of Daily Living Scale. However none of these scales provided a comprehensive coverage of the clinical manifestations of HD.

The UHDRS is a hybrid scale that assesses four areas of clinical performance:

- Motor function – both voluntary (i.e. oculomotor, tongue protrusion) and involuntary (i.e. chorea, dystonia).
- Cognitive function – verbal fluency, Stroop Interference Test and Symbol Digit Modalities Test (SDMT).
- Behavioural abnormalities – emotion/mood (i.e. suicidality, irritability, aggression) and psychological conditions including, anxiety, delusion, obsession, and hallucination.
- Functional capacity – functional assessment using the Huntington's Disease Functional Capacity Scale (HDFCS), an independence scale and a checklist of daily tasks.

For each motor task (15 total), the clinician explains the procedure to the patient and demonstrates the task if necessary. A numerical score (integer) is awarded to reflect the patients' ability to perform this task. For normal responses, a score of 0 is awarded. A score of 1, 2 and 3 is awarded for a mild, moderate and severe impairment respectively, and if a patient is unable to perform the task, a score of 4 is awarded. The total score shall be between 0-60, higher scores indicate more severe impairment. A video demonstrating the motor examination, including examples of grading for each abnormality are available to practitioners.

Scoring for the cognitive function assessment differs from the methodology used for the motor tasks. For all three tests, the verbal fluency test (tasking the patient to name related words for a certain topic within a time period), the SDMT (tasking the patient to match symbols to letters in 90 seconds) and Stroop Interference Test (tasking the patient to verbalise the colour of words as opposed to reading them aloud), correct responses are collated as a raw score. Converse to the motor assessment, a higher score indicates less impairment.

The behavioural assessment is measured in both severity of the symptom, and the frequency of this symptom occurring (normal time scale 1 month). As with the motor scores, the minimum and maximum are 0 and 4 respectively, hence a higher raw total score indicates more severe impairment. However, in addition to scoring responses for the ten questions, the clinician is required to express if they believe the patient to be confused, demented or depressed. Should the clinician believe the patient is depressed, they are also required to record if they believe that pharmacological intervention for the depression is

required. The decisions made by the clinician in regards to these psychological issues do not impact on the behavioural score.

Functional capacity is a combination of the scores given for the HDFCS, an independence scale, and yes/no responses to a checklist of daily tasks. The HDFCS consists of scores given to 5 areas of functional capacity; occupation (0-3), finances (0-3), domestic chores (0-2), Activities of Daily Living (0-3) and care level (0-2). As with the cognitive function assessment, a lower score indicates severe impairment. The raw score is collated with the total number of positive responses to the checklist (25 total questions), and an independence score (increments of 10, maximum 100) where a lower score also indicates severe impairment.

Despite the relative ambiguity with the UHDRS, inter-practitioner consistency has been reported to be high, with strong correlation for the motor, cognitive and functional scores (Huntington Study Group 1996). The small cohort size (n=24) and number of practitioners involved (n=3, who were experienced in evaluating patients with HD) may have influenced this strong correlation. There was also a strong correlation between the scores for each area assessed.

Although UHDRS is commonly used in monitoring the progression of HD, later studies have indicated that the scale may require modification (Siesling et al. 1997; Vaccarino et al. 2011). Siesling et al (1997) obtained UHDRS data from 69 patients with HD and calculated a new total motor score (TMS) for 4 reduced sets of motor tests. It was concluded that the number of items included within the TMS could be reduced to nearly half, without loss of reliability, validity or relationship to other parts of the UHDRS. During this study, removal of eye movements from the TMS appeared to result in a small loss in correlation.

Vaccarino et al (2011) analysed the motor and behavioural assessments for 737 pre-HD patients (PREDICT-HD cohort) and 686 HD patients (REGISTRY cohort) and concluded that although certain items (i.e. smooth pursuit, saccade initiation and finger tapping) are sensitive to subtle signs of HD, items such as dystonia and arm rigidity *'did not discriminate individual differences over the full range of severity and contain options that do not track with changes in overall motor severity'*.

Despite its shortcomings, the UHDRS is the standard assessment tool for monitoring the progression of HD (Toh et al. 2014).

1.4 Existing Treatments and Management in HD

At this time, there are no disease modifying treatments, hence the disease is managed through the use of a combination of pharmacological agents to address the primary symptoms in HD.

Tetrabenazine (dopamine depleter) is the sole treatment shown to significantly reduce chorea in HD, however patients often exhibit impairment of voluntary movements, and experience side effects including depression and anxiety. These side effects may be treated using selective serotonin uptake inhibitors (anti-depressants). High potency neuroleptics (Haloperidol, Olanzipine or similar) are the standard treatment for HD, due to the primary action (anti-psychosis) addressing psychiatric symptoms, with the secondary action markedly reducing the severity of the chorea.

To manage cognitive impairment, psychostimulants (Methylphenidate) or cholinergic agents (Rivastigmine) are prescribed to enhance executive functioning. Pharmacological management may be supplemented using physical therapy to improve gait and balance, occupational therapy to reduce the risks within the home which may be caused by involuntary movements, speech therapy and exercise. Patients with advancing HD may also require assistive devices. Modification of diet to increase intake of Omega-3 fatty acids is also recommended.

Potential disease modifying treatments aiming to slow or stop the progression of HD need to overcome several substantial obstacles. In addition to identifying plausible targets for intervention, challenges include timing for effective initiation, a lack of reliable biomarkers, the relatively small pool of eligible study participants and their variable presentation (Venuto et al. 2012). Despite these obstacles, there have been several trials for emerging therapies: neuro-protective treatments, novel drugs, surgical intervention and gene therapy.

Neuro-protective treatments aim to reduce the neuronal loss over time. In a study using Memantine, a drug used to treat dementia, 9 patients with HD demonstrated a significant improvement in the UHDRS motor score with no negative effect on cognitive, behavioural or functional measures (Ondo, Mejia and Hunter 2007). Mcgarry et al. (2016) trialled coenzyme Q10 (ubiquinone) with a large cohort (N=609) over a 5 year period. There was no significant difference between the placebo and coenzyme groups for the outcome

measures. It was concluded that this study did not justify the use of coenzyme Q10 to slow functional decline in HD.

Creatine has demonstrated neuroprotective effects in animal HD models (Hersch et al. 2006), however the 'CREST-E' study, a multicentre placebo-controlled study, was terminated early as interim analysis had indicated with high confidence that Creatine would show no beneficial effect (Hersch et al. 2017). De Yebenes et al. (2011) trialled Pridopidine, an experimental drug, in a 6 month placebo-controlled study. The efficacy of the drug was not ascertained despite being well tolerated. Recent results from the PRIDE-HD study, Pridopidine was found to have no significant effect (Reilmann et al. 2016). At this time there are no effective pharmacological treatments.

Surgical options are also being explored. Deep brain stimulation, previously approved for use in Parkinson's disease and dystonia has been used on an individual basis. Zeef et al. (2011) summarised the case reports, which reported an improvement in UHDRS chorea score up to 77%. Neural transplantation is yet to provide robust benefits to those with HD (Rosser and Bachoud-Lévi 2012). Although previous studies have shown transient improvements, patients have experienced severe complications (Reuter et al. 2008).

Whereas the previously mentioned treatments for HD have focused on alleviating the symptoms of the condition, RNAi gene therapy aims to prevent the pathological process altogether by silencing the mutant gene. Currently this therapy is in the pre-clinical stage, however use in mouse models has provided positive results (Kolli et al. 2017; Stanek et al. 2014).

1.5 Why is it important to find a biomarker for the disease?

As the population of developed countries continues to age, the prevalence of neurodegenerative disorders is set to increase substantially. Predominantly chronic and incurable, these disorders may continue for years or even decades. As such, these disorders represent an enormous disease burden, in terms of mortality, morbidity and economic cost (Fineberg et al. 2013). Recognised as the 'coming crisis' (Ray Dorsey et al. 2013), investment in research that leads to more effective diagnosis, treatment and management of these conditions will be crucial in reducing this burden (Luengo-Fernandez, Leal and Gray 2015)

Unlike other conditions with significant disease burden (i.e. HIV/AIDS, cardiovascular conditions and cancer), there is a lack of quantitative methods in the diagnosis and management of neurodegenerative disorders (Menéndez-González 2014). Genetic testing may indicate the presence of the defective gene and brain scans may indicate the presence of neuro-degeneration. However these tests lack the specificity and sensitivity to determine disease progression and the associated impairment.

To overcome the lack of quantitative methods, rating scales have been developed for use with Parkinson's Disease (Siderowf et al. 2002) and Huntington's Disease (Huntington Disease Study Group 1996) to quantify disease, and are extensively used in both the clinical & research environments. However, due to using a combination of subjective assessments, there is significant intra-practitioner and inter-practitioner variability. The relative unreliability of these subjective measures demonstrates the requirement for a quantitative objective measure, a biomarker in neurodegenerative disease.

Identifying effective biomarkers is of particular importance to neurodegenerative disorders with disease modifying treatment therapies likely to be used in clinical trials in the near future (Menéndez-González 2014). Different approaches are being taken to identify such a biomarker including neuroimaging, cognitive testing, biochemical profiling and physical tasks. Each of these approaches has their own advantages and disadvantages. Neuroimaging may provide objective and precise measures of change, however the equipment available is prohibitively expensive and relatively inaccessible in clinical practice. Cognitive testing can be readily available in clinical practice, however they lack objective precision. Biochemical profiling can provide an objective measure but is physically invasive. Physical tasks can provide a simple objective measure but can be affected by co-morbid factors.

The ideal biomarker for neurodegenerative diseases must possess certain characteristics (Henley, Bates and Tabrizi 2005):

- Easy to quantify in accessible tissue or biofluid
- Not subject to wide variation in the general population if used as a diagnostic biomarker
- Unaffected by unrelated conditions and co-morbid factors
- Measurement is reliable and quick
- Measurements are reproducible at a different time or in a different centre
- The biomarker changes linearly (either negatively or positively) with disease progression
- The biomarker changes in response to a disease modifying therapeutic intervention that closely correlates with established clinic-pathological parameters of the disease.

Eye movements could be utilised as a potential biomarker in neurodegenerative conditions. Currently, eye movements are used as a biomarker for conditions including concussion (Heitger et al. 2009) and schizophrenia (Morita et al. 2016). The effects of pharmaceuticals and intoxicants have been documented (Reilly et al. 2008) in addition to the characteristics found in the 'normal' population. Eye movement studies have been of particular interest as a diagnostic tool in the field of psychiatry (Kennard, Crawford and Henderson 1994).

Eye movements are potentially a powerful biomarker and meet most of the criteria set out by Henley, Bates and Tabrizi (2005). Eye movements can be measured quickly, accurately and non-invasively using eye trackers and can be compared directly to the metrics established within the general population. The measurements are also reproducible within and across groups. There is also literature on the neural structures involved in executing ocular movements.

Eye movements are the most common form of voluntary behaviour, with several of these movements being made every second to attend to objects in our environment. All forms of eye movements are subject to disruption in various neurodegenerative disorders, both due to the impaired motor processes and cognitive impairment, one of which is usually present in the early stages of the disorders. For example, patients in the early stages of Parkinson's Disease manifest predominantly motor abnormalities, whereas patients with early Huntington's Disease will predominantly manifest cognitive changes. As these neurodegenerative disorders advance, they frequently exhibit both motor changes as main symptoms (MacAskill and Anderson 2016). Due to this, rudimentary eye movement

assessments are used in the clinical environment for monitoring disease progression (Termsarasab et al. 2015).

1.6 Eye Movements

As discussed previously, subjective assessment of eye movements (EMs) are currently used in the UHDRS to assess the status of HD. It is important that we understand the anatomical mechanisms involved, and define the different types of eye movement (EM).

1.6.1 Why do we move our eyes?

The principal functions of EMs is to direct gaze to move an object of interest into the centre of the visual field, and to maintain stable fixation on this object (Land 2012). Unlike fellow vertebrates such as birds that will choose to move perform these tasks by moving their heads, humans (and other primates) choose to move their eyes, namely as it is more economical to move the eyes than the entire head (Walls 1962).

1.6.2 Saccades

Saccades are fast ballistic EM, characterised by a classic temporal profile; the eye rapidly accelerates from stable fixation to a peak velocity, before decelerating to a new stable fixation. The peak velocity is dependent on the amplitude of the saccade. This tight linear relationship is termed the saccadic main sequence (Bahill, Clark and Stark 1975), and demonstrates a system that optimally balances accuracy and duration (Harris and Wolpert 2006).

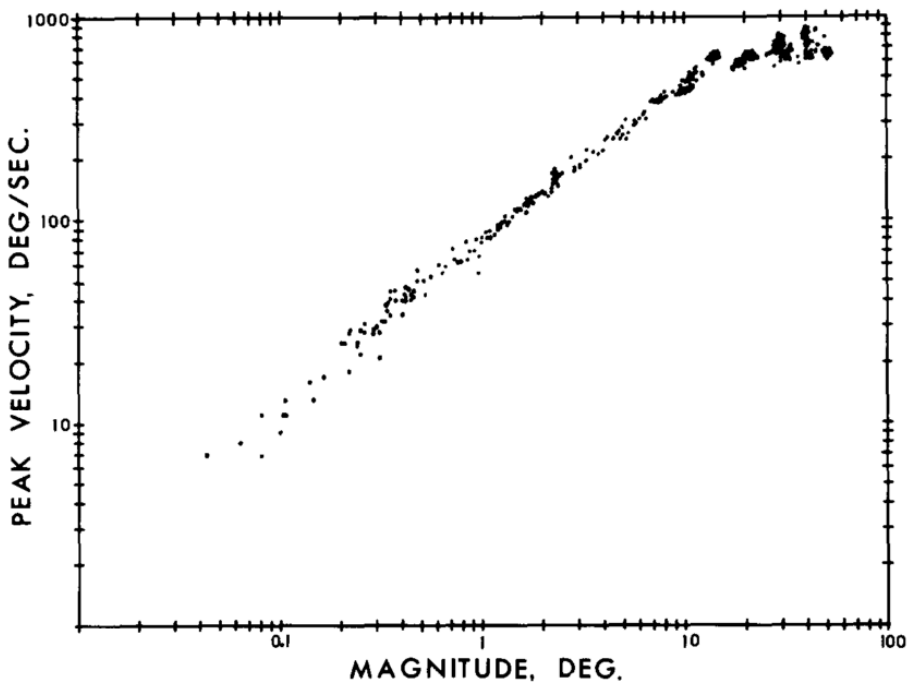


Figure 1 - Saccadic Main Sequence (Bahill, Clark and Stark 1975)

A main sequence plotted (Figure 1) as Peak Velocity x Duration (degrees) versus Amplitude (degrees) gives the ratio of peak velocity to mean velocity, known as a Q-ratio (Harwood, Mezey and Harris 1999).

During a saccade there is suppression of the magnocellular pathways of the visual system (Burr, Morrone and Ross 1994). This is necessary to prevent the perception of image motion during the saccade as the human visual system is sensitive to image motion up to 800˚/second (Motter and Mountcastle 1981).

1.6.2.1 Saccadic Velocity

Saccades are the fastest type of EM and may reach velocities in excess of 700^0/second (Carpenter 1988). Decreased saccadic velocity may be observed in those with alcohol

intoxication (Wilkinson and Kime 1974), fatigue (Bahill and Stark 1975) and clinical pathology (Gorges, Pinkhardt and Kassubek 2014).

1.6.2.2 Saccadic Amplitude

Under normal conditions, 85% of saccades have an amplitude of 15° or less. For amplitudes greater than 15°, head movement is involved with redirecting the eye (Bahill, Adler and Stark 1975). In the absence of head movements, saccades larger than 15° will consist of two steps; the first is a saccade that moves the eye approximately 90% of the distance towards the target, followed by a small corrective saccade that accounts for the undershoot (Becker and Fuchs 1969).

1.6.2.3 Saccadic Duration

Saccadic duration increases with amplitude, which is also described in the saccadic main sequence (Figure 1). For 5° amplitude, the duration is 20-30ms, increasing by 2ms per degree (Robinson 1964)

1.6.2.4 Saccadic Latency

Saccadic Latency is the time taken for the saccade to be initiated and ranges between 100ms and 1000ms; generally, latency increases with more complex tasks. In experimental studies saccadic latency is defined as the duration between stimulus presentation and the onset of the saccade.

1.6.3 Smooth Pursuit

Smooth pursuit describes the foveal tracking of a small slow moving object. There is no suppression of the retinal image, and OKN is suppressed. The velocity of a smooth pursuit eye movement is closely related to that of the target (Carpenter 1988). At an early age,

predictive gaze tracking and corrective 'catch-up' saccades develop to enhance pursuit accuracy (von Hofsten and Rosander 1997).

Gain (eye velocity/target velocity) is used to assess the accuracy of the pursuit system. During ideal pursuit, gain is close to 1.0, hence there is not lag between the eye and the target. There is no significant deterioration of pursuit gain until the target velocity exceeds 100°/second (Meyer, Lasker and Robinson 1985).

1.6.4 Optokinetic Nystagmus

Optokinetic Nystagmus (OKN) is a compensatory EM evoked in response to retinal slip when tracking a large moving visual stimulus. OKN consists of a smooth tracking-like movement until the eyes reach maximum rotational eccentricity (slow phase), and an anti-compensatory saccade to re-fixate the background and continue tracking (fast phase) (Carpenter 1988). OKN was first observed in the eyes of a crowd watching a column of galloping cavalry (Punkinje 1825, cited in Carpenter 1988), however normally, OKN is described as the being evoked whilst viewing the countryside whilst inside a moving train.

The slow phase is not the same as smooth pursuit; OKN is evoked when a large image moves uniformly over the retina to stabilise the entire retinal image; whereas smooth pursuit is the tracking of a small foveated target. Hence OKN is suppressed during smooth pursuit to allow tracking of objects moving relative to the visual scene (Leigh and Zee 2006). A linear velocity slow phrase followed by a quick phase in OKN produces a 'sawtooth' waveform, which differs from the waveforms seen in other types of nystagmus (Abadi 2002). This classic 'sawtooth' waveform is shown in Figure 2.

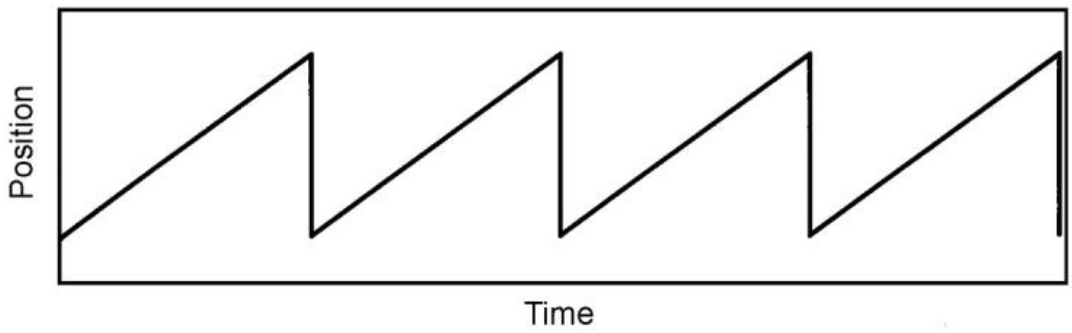


Figure 2 - 'Sawtooth waveform seen in OKN (Abadi, 2002)

Clinically OKN is used to test vision in very young children using a rotating drum with a line grating. Although the visual acuity of young children is poor, the child will fixate upon a line and follow until it goes out of view, and repeat (Rosner 1982).

1.6.5 Vestibulo-Ocular Reflex

Vestibulo-Ocular reflex (VOR) is a compensatory EM driven by the vestibular system. VOR stabilises gaze to ensure clear vision during head movements, particularly during locomotion by moving the eyes in an equal and opposite direction to the head (Leigh and Zee 2006). The vestibular system responds to the movement of fluid within the three semi-circular canals of the inner ear (Angelaki 2004). Maas et al. (1989) observed EMs attributed to VOR to have a latency ranging between 6-15ms, significantly less than in saccades.

1.7 Methods of Eye Movement Recording

Ideally, any EM recording system would need to detect the full range of ocular rotation at a high spatial and temporal resolution with no noise, and to differentiate between EMs and head movements. This system would also need to be non-invasive, comfortable for the subject and to be user friendly (Collewijn 1998).

From around 1950, a number of technologies have been utilised for recording EMs (Holmqvist et al. 2011):

- Lens system with mirrors
- Electromagnetic coil
- Electrooculography (EOG)
- Video Oculography

1.7.1 Lens system with mirrors

This system was developed in the early 20th century and used during 1950-1970, it consisted of the subject wearing a mirrored contact lens, and measuring the angle of reflection. Alternately a small lamp was placed atop a stalk attached to the contact lens and the angle that the light passed through a slit was measured (Byford 1962). This system was highly precise, albeit very uncomfortable for the subject.

1.7.2 Electromagnetic coil

More commonly known as the scleral search coil, measures the electromagnetic induction in a silicon contact lens placed onto an anaesthetised eye. Although long considered to be the most precise technique (Collewijn 1998) and the 'gold standard' for EM measurement

(Irving et al. 2003), it has been demonstrated that it can underestimate the peak velocity of saccadic EMs, due to slipping of the coil annulus on the ocular surface (Träisk, Bolzani and Ygge 2005). An image of a scleral search coil is shown below (Chronos Vision 2015).

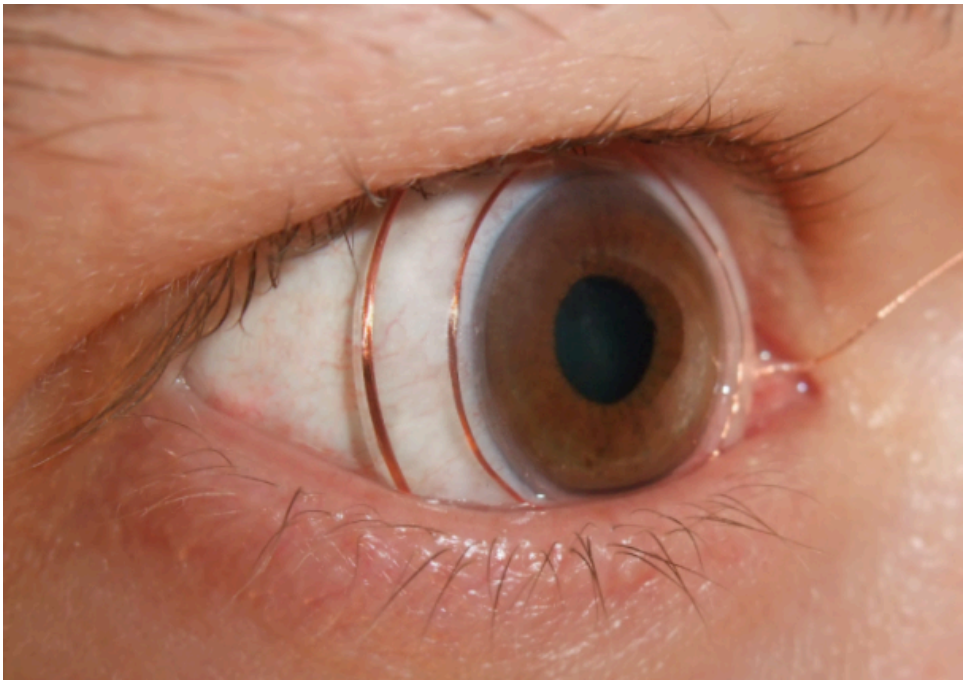


Figure 3 - 3D scleral search coil (adapted from Chronos Vision 2015)

The silicon contact lens is custom manufactured for each subject. Despite this, the contact lens is uncomfortable to wear, and hence prolonged experiments are difficult as repeated topical anaesthetic use is toxic for the corneal epithelium (Boljka, Kolar and Videnšek 1994).

1.7.3 Electrooculography

Electrooculography systems (EOG) measure the corneo-retinal potential, the potential difference in voltage between the front and back for the eye. An electrode is placed at the outer canthus that detect changes in voltage during EMs. Traditionally however, EOG systems only measure horizontal EMs, and are susceptible to noise caused by the

extraocular muscles and changes in retinal luminance (Holmqvist et al. 2011), hence are inaccurate due to this drift.

1.7.4 Video Oculography

Video-oculographic (VOG) recording is a highly effective technology for measuring EMs. VOG is non-invasive with precision comparable to coil systems, and provides a suitable alternate, particularly for testing over 30 minutes (Houben, Goumans and van der Steen 2006). VOG uses infrared (IR) cameras to measure the eyes position. A camera tracks the centre of the pupil using the first and fourth Purkinje reflections (Clark 1975) to locate the centre of the eye. The camera may be mounted in goggles with dichotic filters, or be freestanding (Gans 2001).

Although there is a range of commercially available VOG eye trackers, there are two VOG eye trackers that are available at the School of Optometry and Vision Sciences, Cardiff University. The Tobii X300 (Tobii Technology) and the EyeLink1000+ (SR Research).

1.7.4.1 Tobii X300

The Tobii X300 Eye Tracker model is an IR-based VOG capable of binocular tracking at a temporal resolution of 300Hz, with a precision of ~0.4° up to a 35° gaze angle (Tobii Technology 2015). This model allows for freedom of head movement within a 37x17x30cm (horizontal x vertical x depth) area, 50cm from the tracker (Tobii Technology 2015).

Figure 4 - Tobii X300 Eye Tracker

Reduced setup time and the non-invasive nature are of significant advantage of the Tobii X300. Currently this model is used for clinical research at Cardiff University.

1.7.4.2 SR Research – EyeLink 1000+

The EyeLink 1000+ is an IR-based VOG system. The EyeLink 1000 is capable of tracking at a temporal resolution of 1000Hz monocularly, and 500Hz binocularly (2000Hz and 1000Hz respectively with an optional camera upgrade) (SR Research 2015a). The tracking range is 32°x25° with an optimal test distance between 40cm and 70cm. With the remote camera upgrade, the EyeLink 1000 can record EM data without the requirement for head restraint within a 40x40cm area at 70cm (SR Research 2015b).

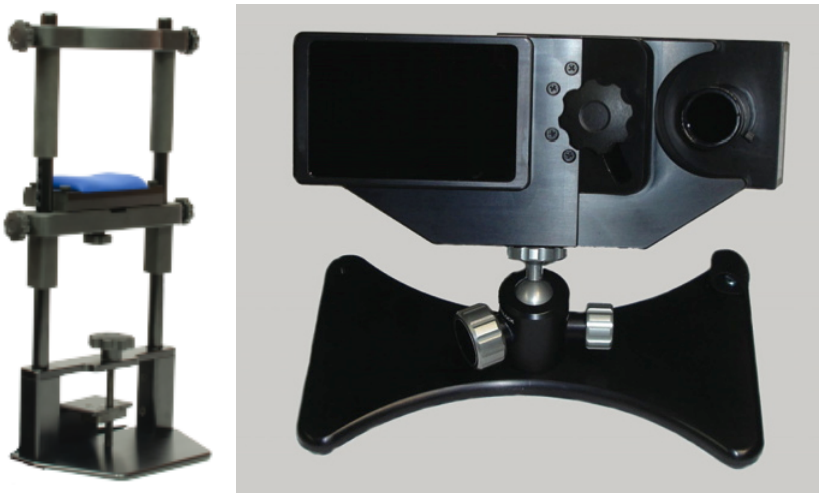


Figure 5 - EyeLink 1000+ head mount and EyeLink 1000+ in desktop configuration

SR Research also manufacture a range of accessories for the Eyelink 1000+ including a headrest and three mounts; desktop – a free standing option, LCD arm – an integrated LCD monitor and EyeLink 1000+ attached to an articulating arm, and tower – EyeLink 1000+ attached to the top of a headrest with integrated IR hot mirror (SR Research 2015c).

1.8 Eye Movements in Huntington's Disease

1.8.1 Saccades

Oculomotor abnormalities have been associated with HD since the late 19th century (Lasker and Zee 1997). It was not until a study by Starr (1967) that abnormalities among specific categories of eye movements were recorded. Starr observed a slowing of saccades within 3 of his 6 subjects and severe difficulties in initiating saccades.

Abnormal saccades have been measured using eye trackers in several studies; increased saccade latency is consistently recorded across the literature (Blekher et al. 2004; Ali et al. 2006; Golding et al. 2006; Peltsch et al. 2008; Antoniades et al. 2010; Patel et al. 2012; Winograd-Gurvich et al. 2003) with Antoniades et al. (2010) reporting an increase of 24ms per year in patients with HD, compared to the 1ms increase per year seen with aging in controls. This study, however, did not account for medication, and it is unclear what proportion of the latency is present due to pharmacological intervention.

Ali et al. (2006) observed that the median latency of saccades is 36ms longer in patients with HD (n=24) than age matched controls (n=20). Duration and variability of the duration in the saccades were also observed to increase. Only pro-saccades were measured, and despite the medication being listed for each subject, the pharmacological impact is not accounted for. There appeared to be a strong correlation between the latency of saccades and the UHDRS motor score (excluding the ocular movement scores), which suggests objective measurement of saccades using eye tracking software could replace the crude oculomotor

assessment performed during the UHDRS.

Further to this, Ali et al. (2006) applied an individual Bayesian test to each subject and could correctly diagnose 75% HD and 95% non-HD patients based on the latencies of their saccades. With an adjustment to the criterion applied, 96% HD were correctly diagnosed, but the false positive rate among controls increased substantially.

Blekher et al (2004) observed a significant increase in latency and decreased velocity for pro-saccades and anti-saccades with disease progression. Increased latency was particularly significant in anti-saccades (296ms for controls, 348ms for pre-clinical HD and 384 for HD), and memory guided saccades (281ms, 319ms and 375ms). A negative correlation between the saccade velocity and number of CAG repeats was observed. Although it may be possible to estimate CAG expansion through saccade latency, CAG repeat length cannot accurately predict clinical onset of HD, so for this reason saccades cannot accurately predict HD.

Golding et al. (2006) identified that, although increased latency is not present for horizontal pro-saccades in pre-clinical HD, it is present in vertical saccades. Increased latency with disease progression is also observed for voluntary saccades (289ms in controls, 344ms in pre-clinical HD, 436-487ms in HD). A reduced saccade velocity was also observed (253°/sec, 232°/sec, 209-192°/sec). Golding et al. (2006) used a cohort of HD (n=12), pre-HD (n=12) and age matched controls (n=24). CAG expansions between 40-51 repeats were present in the HD subjects.

Peltsch et al. (2008) observed the saccadic eye movements of HD patients (n=9) and age matched controls (n=9) and, as with previous studies, recorded deficiencies in latency for

pro-saccade and anti-saccade tasks. Significant directional errors were observed (particularly in pro-saccades), and the ability to suppress reflexive eye movement appears to progressively worsen with disease progression suggesting an attention deficit.

In a study by Winograd-Gurvich et al. (2003), the latencies of pro-saccades within the HD group (n=11) and age matched controls (n=11) were not significantly different for amplitudes of 10° and 20°. However, significantly increased latencies were observed in the HD group when the amplitude was modified to 30° and 40°. More corrective saccades were initiated by the HD group (1.58) than the control group (0.98) due to directional errors. All subjects performed a self-paced voluntary saccade task, 500ms alternating fixation rapidly between two targets with 20° separation. The HD group completed significantly fewer saccades (mean 40.64) than controls (mean 72.64), and demonstrated significant variability in the duration of the saccades.

Patel et al (2012) observed an increased latency for both pro-saccades and anti-saccades in both the horizontal and vertical meridians. Contrary to the previous study by Ali et al. (2006), the correlation between UHDRS motor score and latency for pro-saccades and anti-saccades appears to absent when age is taken into account. Patel et al. (2012), however, concluded that the latency for pro-saccades and the error rate for anti-saccades correlate strongly with both the UHDRS motor score and total chorea score. They suggest that this correlation may allow pro-saccades and anti-saccades to serve ‘as quantative biomarkers of disease severity and progression in HD’.

In comparison to finger tapping, another potential biomarker in HD, saccades appear to be superior in distinguishing changes in pre-clinical HD (Antoniades et al 2010). Increased saccadic latency has been observed for both pro-saccades (Antoniades et al. 2010) and anti-saccades using either the traditional paradigm (Turner et al. 2011) or the interleaved paradigm (Peltsch et al. 2008). Vertical saccades are affected more than horizontal (Lasker and Zee 1997). Latency has also been found to increase with disease progression (Blekher et al. 2004). The increased saccadic latency correlates with the UHDRS motor score used in clinical practice (Patel et al. 2012). A significant increase of error rate is seen in the anti-saccade task (Peltsch et al. 2008) and increased latency is also present in memory guided saccades (Blekher et al. 2004) and self-paced saccades (Winograd-Gurvich et al. 2003). Saccadic dysmetria has also been documented in pro-saccade and anti-saccade tasks (Antoniades et al. 2010).

1.8.2 Smooth Pursuit

There appears to be no deficiency present in smooth pursuit eye movements for patients with HD. The pursuit gain for both vertical and horizontal tracking show no significant difference between controls, pre-HD, and HD (Blekher et al. 2004; Collewijn et al. 1988; Henderson et al. 2011). Collewijn et al. (1988) did observe that 'smooth pursuit was often heavily contaminated by square wave jerks' with HD. A significant proportion of the controls also showed equally deficient pursuit.

Deficient inhibitory control is present in HD (Henderson et al 2011), HD patients are less likely to suppress saccade initiation in response to distractor stimuli than controls. In this study, the gross percentage of erroneous pro-saccades made during this task positively correlated to disease progression.

1.8.3 Optokinetic Nystagmus

Reduced OKN gain is present in clinical HD for a drum velocity at 60°/s, whereas OKN gain appears normal in pre-HD or controls. OKN gain is also normal in clinical HD at slower velocities (Blekher et al 2004). Reduced gain has also been observed by Oepen, Clarenbach and Thoden (1981). As with Blekher et al. (2004) the stimuli presented were moving at 60°/s. Abnormal OKN has been reported in three further studies (Beenen, Buttner and Lange 1986; Young et al. 1986; Kirkwood et al. 2000), however the nature of the abnormality present in these studies, and the number of participants within the studies who presented with abnormal OKN are not discussed.

1.9 The Anti-Saccade Task

1.9.1 What is the anti-saccade task?

Introduced by Hallett (1978), the anti-saccade task is a measure of control of behaviour sensitive to fronto-striatal dysfunction (Hutton and Ettinger 2006). In this task, the participant is presented with a fixation target in the centre of the screen, and then presented with a stimulus in the periphery. The participant is instructed to look at a location in the equal and opposite location to the stimulus, and therefore must inhibit the reflexive pro-saccade, and instead initiate a voluntary saccade. As such, it is a well characterized measure of impulse control (Mirsky et al. 2011).

The characteristic participant responses are:

- Correct response – participant looks at a point equal and opposite to the presentation of the stimulus
- Incorrect response – participant looks at the stimulus, i.e makes a pro-saccade. This is known as an anti-saccade error.
- Incorrect response followed by a correction – participant initially looks at the stimulus before making a saccade towards the correct direction
- No response – participant does not respond to stimulus

The relevant metrics for this task are; saccadic latency, peak velocity, anti-saccade error rate and anti-saccade cost, the difference between pro-saccade latency and anti-saccade latency measured under identical conditions (Godijn and Kramer 2008).

1.9.2 An appropriate measure of inhibitory control

Despite its relative simplicity, the anti-saccade task has been adopted in psychiatry, psychology and neurology due to its sensitivity to changes in the neuroanatomical function, and its performance as a motor proxy to changes in cognitive function. The exact cognitive processes which underlie anti-saccade performance are not known, however previous studies have proposed several theories.

Crawford et al. (2002) argued that incorrect responses (errors) during the anti-saccade task reflect a failure of frontally mediated inhibitory control. Quintessentially, that impaired inhibitory control would result in a greater number of errors during the anti-saccade task. Miller and Cohen (2001) suggested that the correct inhibition of incorrect responses would

occur as a direct result of the initiation of the correct response (see 1.9.3 for theories of anti-saccade modelling).

Later studies proposed that performance during the anti-saccade task is not purely a measure of inhibitory control, but rather potentially a combination of working memory, goal orientation and attention (Reuter and Kathmann 2004; Mitchell, Macrae and Gilchrist 2002). The perseverance, or lack there-of, of task instruction could result in variable responses, or no attempt to inhibit an erroneous response. Increased attentional focus improves anti-saccade performance (Wang et al. 2013), whilst increasing working memory load will result in poorer performance (Lee et al. 2010).

Although by no means a perfect measure of pure impulse control, the anti-saccade task is a reliable measure for changes in cognitive performance.

1.9.3 Theories of Anti-Saccade Modelling

Principally during the anti-saccade task, two opposing processes are initiated in parallel: a reflexive response, and a voluntary response. Ultimately to execute a response, one of these two process activated in the neural system will have to reach threshold. At stimulus presentation, a competition between these two systems will ensue.

If activation in the neural systems supporting the anti-saccade reaches threshold prior to that of the reflexive pro-saccade, the correct response (i.e. the anti-saccade) is initiated and activation of the reflexive pro-saccade is cancelled. Conversely, if activation in the neural systems supporting the reflexive pro-saccade reaches threshold first, an erroneous saccade towards the target is made (i.e. an anti-saccade error). Unlike during the ‘correct response’,

successful activation of the 'error' does not necessarily terminate the activation of the anti-saccade. Instead, this process may continue, manifesting in a corrective pro-saccade. Dependent on the relative time to complete the initiation of the anti-saccade activation, and time to complete initiation for the pro-saccade, it is also possible that the anti-saccade activation interrupts the pro-saccade before the eye movement is complete; therefore correcting the error before it has completed.

Pro-saccade latencies are shorter than anti-saccade latencies. This would suggest that a larger number of neural systems must be involved with the process to initiate an anti-saccade, than a pro-saccade.

1.9.4 The anti-saccade task in normal and clinical groups

Within the normal population, an increased latency is observed relative to that found in pro-saccades (Rupp et al. 2012; Evdokimidis et al. 2002). A range of normative values for error rate have been published (Evdokimidis et al. 2002; Mirsky et al. 2011; Taylor and Hutton 2011), which do not exceed 30%. The anti-saccade task has been used in numerous clinical groups, with the relevant metrics reported in the literature.

Previous studies involving participants with ADHD (Rothlind, J. C., Posner, M. I., & Schaughency 1991), HIV (Johnston, Miller and Nath 1996), OCD (Tein et al. 1992), Schizophrenia (Clementz, McDowell and Zisook 1994), dementia (Currie et al. 1991), Parkinson's disease (Gorges et al. 2016) and Alzheimer's disease (Crawford et al. 2015) have all demonstrated an increased error rate and increased latency in the presence of pathology.

These metrics may be heavily influenced by the instruction given to the participant (Taylor and Hutton 2011). Latency will decrease with a corresponding increase in error rate if the participant is explicitly told to react quickly. If they are told to react accurately, error rate diminishes with a corresponding increase in latency. Reduced error rate is also observed in those with a higher IQ (Evdokimidis et al. 2002).

Chapter 2: Pilot Study

2.1 Review of oculomotor paradigms used in previous studies involving HD

In Chapter 1, multiple studies were referenced which had reported their findings for eye movements in HD. These studies however, each used different paradigms, therefore across the studies, participants did not undertake identical testing. With this in mind, I wish to review the paradigms utilised in the aforementioned studies.

2.1.1 Pro-Saccades

Study	Orientations	Amplitudes	Stimuli (Total)
Ali et al. (2006)	Horizontal	±10°	300
Antoniades et al. (2007)	Horizontal	±10°	300
Antoniades et al. (2010)	Horizontal	±10°	300
Blekher et al. (2004)	Horizontal	±5° ±10° ±15°	30
Golding et al. (2006)	Horizontal Vertical	±7° ±14° 11.5°	42
Patel et al. (2012)	Horizontal Vertical	±7° ±7°	48
Peltsch et al. (2008)	Horizontal	±5°	120
Turner et al. (2011)	Horizontal Vertical	±10° ±10°	288
Winograd-Gurvich et al. (2003)	Horizontal	±10° ±20° ±30° ±40°	100

Table 1 - Pro-Saccade Paradigms Undertaken by HD Participants

The paradigms used in the studies discussed in chapter 1 are shown in table 1. The majority of studies collected data for horizontal pro-saccades only, and the most used amplitude is 10°. Three studies collected data for multiple amplitudes. The total number of stimuli presented in the studies varied, with four studies presenting around 300, three studies presented fewer than 50. The other two studies presented around 100 stimuli.

2.1.2 Anti-Saccades

Study	Orientations	Amplitudes	Stimuli (Total)
Blekher et al. (2004)	Horizontal	±5° ±10° ±15°	30
Patel et al. (2012)	Horizontal Vertical	±7° ±7°	48
Peltsch et al. (2008)	Horizontal	±5°	240

Table 2 - Pro-Saccade Paradigms Undertaken by HD Participants

Of the studies discussed in chapter 1, three involved anti-saccades. The paradigms used are shown in table 2. Two of the studies presented fewer than 50 stimuli, the other presented 240. The amplitudes presented are different between each study, but are identical to that presented in the pro-saccade task during the same study. Only one study presented vertical anti-saccades.

2.1.3 Smooth Pursuit

Study	Stimuli Velocity
Beenen et al. (1985)	Sinusoidal – up to 55°/s
Blekher et al. (2004)	Not stated
Collewijn et al. (1988)	Not stated
Henderson et al. (2011)	15°/s

Table 3 - Smooth Pursuit Paradigms Undertaken by HD Participants

Four studies recorded smooth pursuit in HD, as shown in Table 3. Two of these studies did not state the velocity of the stimuli used, or its nature (i.e. sinusoidal or constant velocity). One study used a constant velocity of 15°/s, the other used a varying velocity up to 55°/s.

2.1.4 Optokinetic Nystagmus

Study	Stimuli Velocity
Beenen et al. (1985)	30-100°/s
Blekher et al. (2004)	23-60°/s
Kirkwood et al. (2000)	Not stated
Oepen et al. (1981)	60°/s
Young et al. (1986)	Not stated

Table 4 – OKN Paradigms Undertaken by HD Participants

The five studies which recorded OKN in HD are shown in Table 4. Two of these studies did not include any methodology of stimulus presentation. The other studies presented stimuli at velocities between 30°/s and 100°/s.

2.1.5 Paradigms included within studies

Study	PS	AS	SP	OKN	Vertical	Control Cohort
Ali et al. (2006)	*					*
Antoniades et al. (2007)	*					*
Antoniades et al. (2010)	*					*
Beenen et al. (1985)			*	*		
Blekher et al. (2004)	*	*	*	*	*	
Collewijn et al. (1988)			*			*
Golding et al. (2006)	*				*	*
Henderson et al. (2011)						
Kirkwood et al. (2000)				*		*
Oepen et al. (1981)				*		*
Patel et al. (2012)	*	*			*	*
Peltsch et al. (2008)	*	*				*
Turner et al. (2011)	*				*	*
Winograd-Gurvich et al. (2003)	*					*
Young et al. (1986)				*		

Table 5 - Paradigms included within studies. PS - Pro-Saccade, AS - Anti-Saccade, SP – Smooth Pursuit, Vertical - Vertical Tests Included

The above table shows the paradigms included within each study. There is no individual comprehensive study that includes all four tasks (pro-saccade, anti-saccade tasks, smooth pursuit and OKN), procedures testing vertical eye movements, and a control group. The most comprehensive study is Blekher et al. (2004), but this study only includes vertical testing for the smooth pursuit paradigm, and does not have a control cohort.

2.2 Aims

2.2.1 Verification of set-up

The primary aim of this pilot study is to produce an oculomotor testing set-up which can procure accurate reliable data in normal participants, with a view to moving towards potential use with a HD cohort.

2.2.2 Replication of previous studies

The secondary aim of this pilot study is to replicate previous studies measuring eye movements in the normal population. Such replication would verify the set up for use with a HD cohort.

2.2.3 Trialling paradigms for use in HD

Based on the paradigms previously used in the literature to measure eye movements in HD, a potential test battery for use with the HD group will be trialled during this study.

2.3 Study Design

In this pilot study, a small cohort of students (n=20) shall be recruited to participate in the study. These students will be recruited from the undergraduate and postgraduate student bodies at the School of Optometry & Vision Sciences, Cardiff University.

2.3.1 Recruitment of student cohort

Potential students will be approached both directly, and via email, and provided with a participant information sheet. In both cases, it will be made clear to the students that there is no obligation to participate, and all participation is voluntary.

2.3.2 Ethical Approval

An application for ethical approval was submitted to the School Research Ethics Audit Committee on 24th February 2015. The application was accepted with amendments on 21st April 2015. Copies of the ethical approval and accompanying documents are available in the Appendix.

2.3.3 Exclusion Criteria

For this pilot study, the exclusion criteria are as follows:

- Previous diagnosis of HD
- Participant not currently enrolled as a student at Cardiff University

2.4 Proposed protocol for measurement of eye movements in HD

2.4.1 Set-up and materials

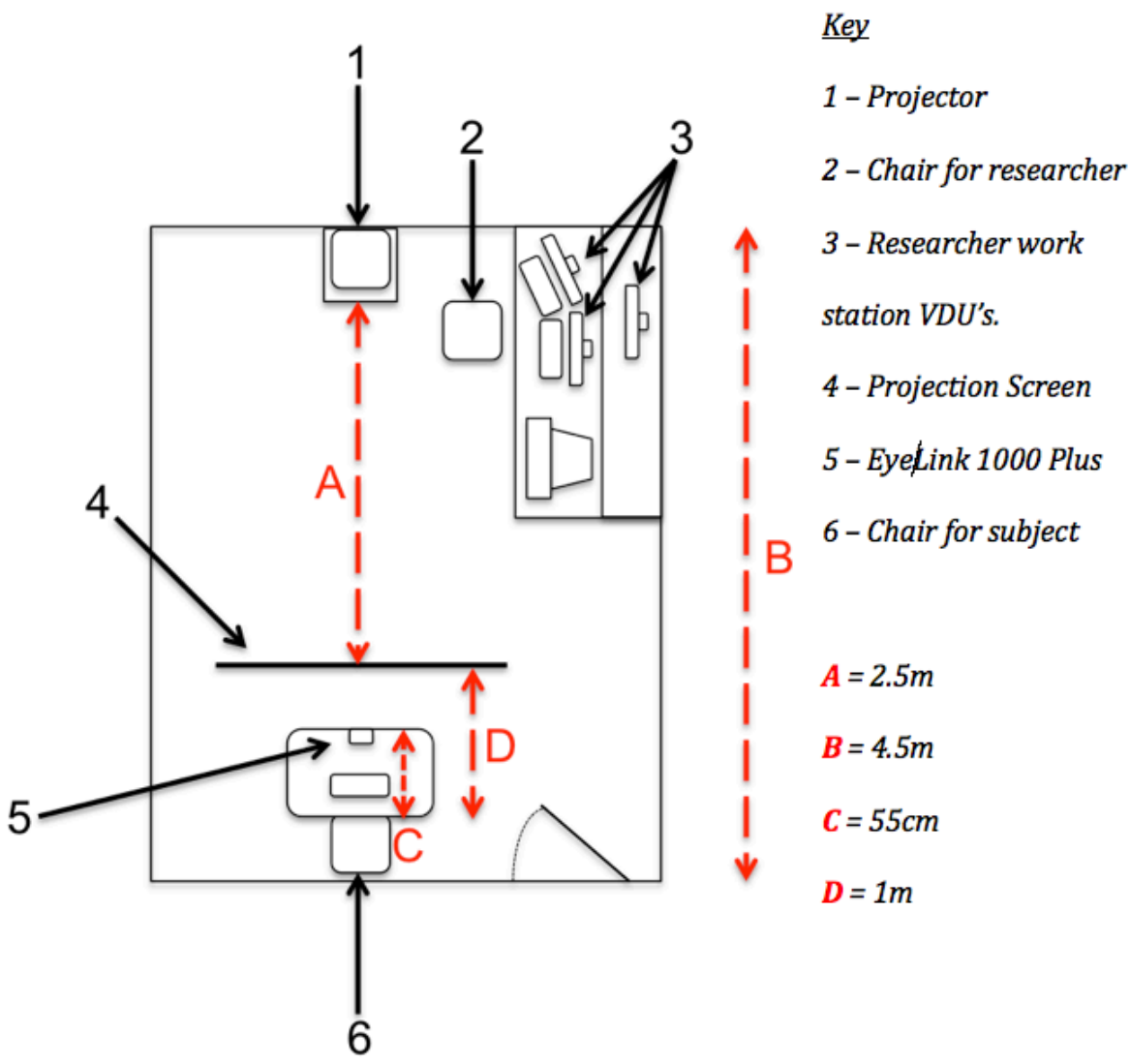


Figure 6 - Diagram of the lab

2.4.1.1 Eye Tracker

Due to saccadic latency being of particular interest in this study, the EyeLink 1000 Plus was chosen for use due to the excellent temporal frequency, and also the ability to program the device using MATLAB with Psych-Toolbox installed.

2.4.1.2 Projector

The projector that will be used is a Christie DS+26 DLP® manufactured by Christie Digital (*Figure 2.5*). The projector has a vertical scan rate of 50-110Hz and projects at a 4:3 aspect ratio for throw distances between 1.5-10m (Christie Digital Systems 2006)

Figure 7 - Christie DS+26 projector (Christie Digital Systems Inc, 2006)

2.4.1.3 Stimulus Generation

Stimuli are programmed using the 'Tools made for James' HD work' package programmed by Dr Matt Dunn. This suite was written for use on MATLAB with Psychtoolbox installed.

2.4.1.4 Fixation Target

The fixation target programmed into OMS is one designed by Thaler et al. (2013) as the result of a study into the optimal fixation target to be used in eye tracking studies. The 'ABC' target shape is a combination of bulls eye and cross hair with a total diameter 0.6° (Figure 8) with a central circle diameter of 0.2°. Stability of fixational eye movements are improved compared to other target shapes and as such is "*appropriate for experimental paradigms that require precise and/or prolonged fixation*'.

Figure 8 - 'ABC' Target shape (adapted from Thaler et al. 2003)

2.4.2 Paradigms

2.4.2.1 Saccades

Test	Eccentricities (°)	Return to Centre	Total Presentation	Duration
PS Horizontal	±5, ±10 & ±15	Yes	96	~270 seconds
AS Horizontal	±5, ±10 & ±15	Yes	96	~240 seconds
PS Vertical	±5 & ±10	Yes	64	~190 seconds
AS Vertical	±5 & ±10	Yes	64	~170 seconds

Table 6 - Design of Saccadic Tasks

Based on previous studies from the literature, it was decided to test both pro-saccades, and anti-saccades. Additionally it was decided that targets would be presented at multiple amplitudes, both vertically and horizontally.

To further inform the design of the study, it was decided to adhere to the 'gold standard' design recommended by Antoniades et al. (2013), which is as follows.

Recommended Protocol:

- Maximum duration of eye movement testing should not exceed 20 minutes to avoid fatigue
- Use of single stimulus throughout is preferred
- Task difficultly must not result in a saturation of errors or a lack thereof
- Conventional Pro-Saccade data should be gathered alongside anti-saccade Data
- Tasks should be divided into blocks of comfortable size
- No use of stimulus gap/overlap
- Single amplitude of 8-10° (note, as there is an interest to determine the appropriate amplitude to use with HD participants, for the purpose of the pilot study, multiple amplitudes are to be used).

Recommended Outcome Measures:

- Latency of the first response
- Latency of corrective saccade (Anti-Saccade task)
- Peak velocity
- Positional accuracy

2.4.2.2 Smooth Pursuit

The smooth pursuit target shall move at a constant velocity of 30°/s. Although this is greater than the peak velocity used in previous study, it is the velocity described as a smooth

pursuit EMs by Holmqvist et al. (2011). A frequency of 0.25Hz will be used with amplitude of 30^0. Pursuit will be tested vertically and horizontally.

2.4.2.3 OKN

Although abnormalities are present at a velocity of 60°/s, target velocities greater than 40°/s are likely to be saccadic in nature, therefore the protocol will test at 30°/s, the velocity used for smooth pursuit EM's. Gratings will be presented moving both vertically and horizontally.

2.4.3 Test procedures

1. Subject is provided with a participant information form, written consent is to be provided for participation in the study
2. Subject is seated on the chair in front of the projection screen, and is asked to place their head onto the head rest.
3. Room lights are extinguished and the EyeLink is focused and calibrated.
4. The protocol is run in three phases:

   Phase 1 – Saccadic testing (pro-saccade & anti-saccade)

   Phase 2 – Smooth pursuit testing

   Phase 3 – OKN testing

   For each phase, the order of the tests is randomised
5. Between each test, there is a brief resting period whilst the next test is being prepared.

2.4.4 Subject Instructions

For each test, the subject is given standardised verbal instructions that are repeated twice. Before the test begins, the subject will be required to confirm that they understand the instructions.

2.4.4.1 Instructions for Pro-Saccade Paradigm

'In this test you will be shown a sequence of lights on the screen in front of you. Each light will be presented for a moment, before instantly moving to another location. I would like you to follow the light when it moves as quickly as you can.'

2.4.4.2 Instructions for Anti-Saccade Paradigm

'In this test you will be shown a sequence of lights on the screen in front of you. You will be presented with a light at the centre of the screen for a moment, before it moves instantly to another location. The light will then return instantly to the middle again, and the process is repeated. I do not want you to follow the light when it moves from the middle; instead I would like you to look in the equal and opposite direction to where it has moved to.'

2.4.4.3 Instructions for Smooth Pursuit Paradigm

'In this test you will be shown a light moving back and forth across the screen in front of you. I would like you to follow this light to the best of your ability'

2.4.4.4 Instructions for OKN Paradigm

'In this test you will be shown a grating moving across the screen. I would like you to stare at the middle of the screen, and try not to follow the grating'.

2.5 Results

2.5.1 Pro-Saccades

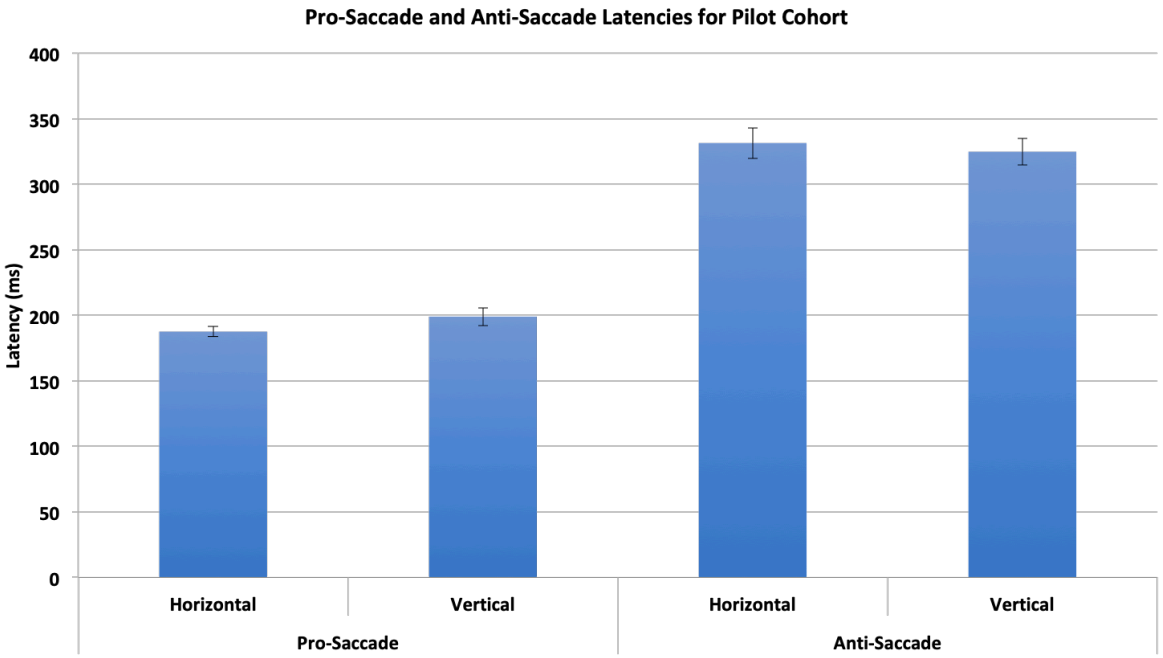


Figure 9 - Latencies recorded in the Pro-Saccade and Anti-Saccade tasks for both the vertical and horizontal tasks

To verify our set-up we analysed the latencies for the pro-saccade and anti-saccade task. The mean latencies above (187ms and 199ms for the pro-saccade tasks, 331ms and 324ms for the anti-saccade task) are comparable to those in Evdokimidis et al. (2002).

2.5.2 Anti-Saccades

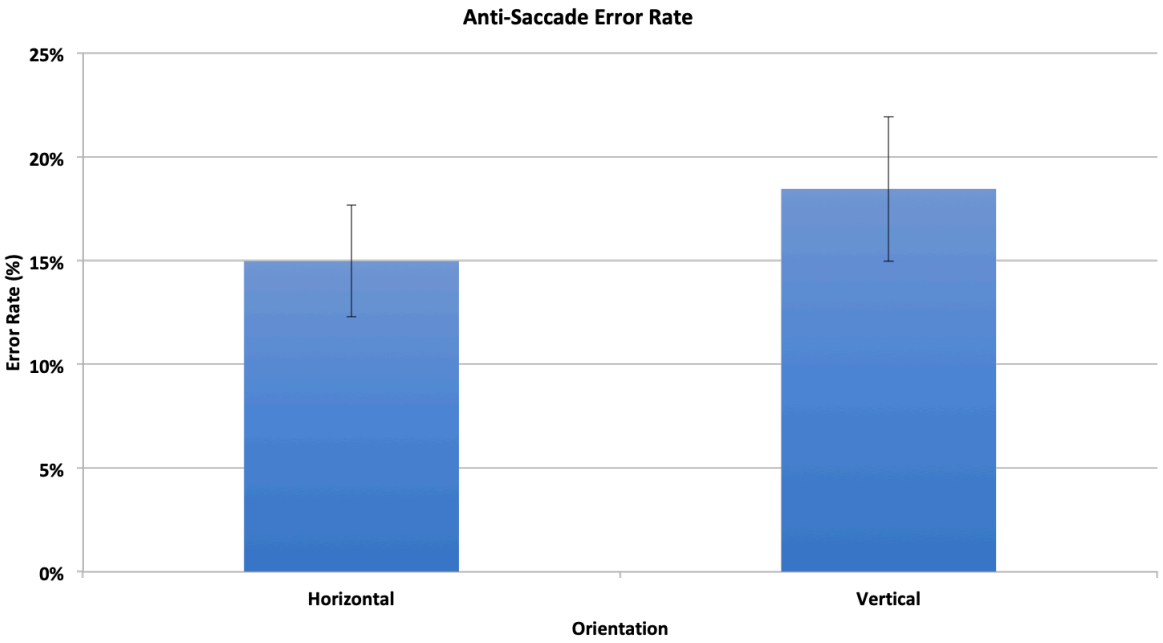
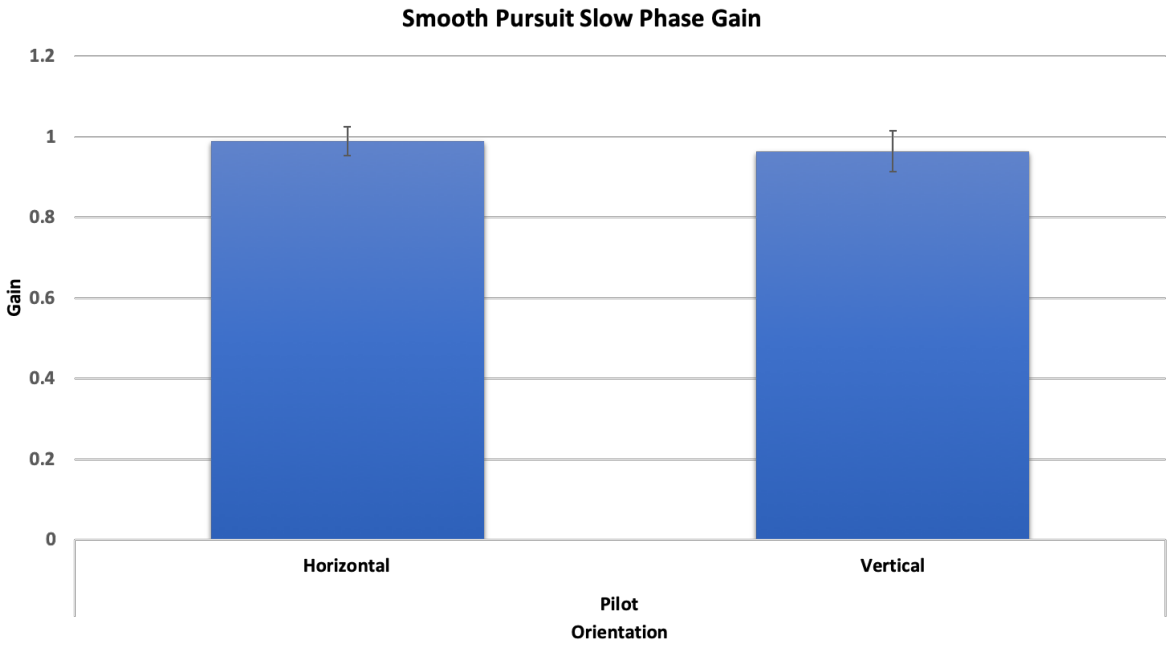


Figure 10 - Anti-Saccade error rate for the horizontal and vertical tasks

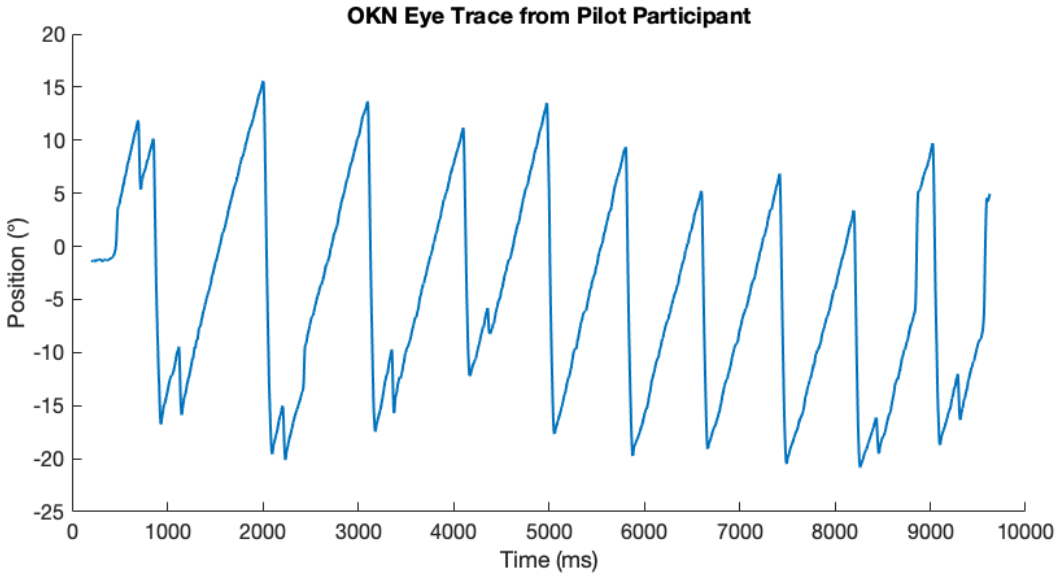
Anti-saccade error rates within the pilot group as comparable to that reported in Evdokimidis et al. (2002).

2.5.3 Smooth Pursuit



Smooth pursuit gain within the pilot group is within normal limits (Meyer, Lasker and Robinson 1985).

2.5.4 Optokinetic Nystagmus



Due to systematic error in participant instruction, virtually all participants performed look OKN as opposed to stare OKN. This is shown in the eye trace above.

2.6 Discussion

2.6.1 Verification of protocol

As outlined in section 2.5, the protocol used in the pilot study produced analysable and reliable data which produced values consistent to that presented in previous studies. Of the participants recruited, all bar one were successfully able to complete all tasks with relative ease. The one exception to this was a participant whom was wearing a large amount of mascara, which prevented the calibration of the eye tracker as the reflection of the make-up appeared to mimic the pupil. Verbal feedback provided by the participants expressed that all tasks were generally straight forward, but they did however find the anti-saccade task challenging.

Feedback was generally positive in regards to the amount of time required to undertake testing, and the set-up of the lab. The only issue raised was of the explanation of the OKN task. One participant did explain after completing the OKN task that they were confused as to if they were to follow the grating, or to look at the centre of the screen.

2.6.2 Feasibility of use with clinical population

The duration of the visit, inclusive of the consent procedures, explanation of the tasks, and the time to undertake the tasks themselves did not exceed 30 minutes. The timings of each individual visit were not recorded, however 2 visits were timed to durations of 27 minutes 12 seconds and 24 minutes 53 seconds.

Following consultation with members of the HD team at the Cardiff Huntington's Disease Clinic, and with Professor Anne Rosser our collaborator, it was felt that the protocol would be feasible for use with participants affected by Huntington's Disease.

2.6.3 Recommendations for studying involving HD participants

As previously discussed, individuals with HD exhibit symptoms including the loss of fine muscle co-ordination, abnormalities in gait, and difficulty in balance. These symptoms increase the risk of falling or tripping. Cognitive changes can also lead to a greater likelihood of confusion and anxiety. Therefore the following guidance is to be put into action:

- All participants with HD are to be accompanied at all times, with the investigator walking by the side of the participant in case they trip/fall
- Prior to each visit, all potential trip hazards in the lab shall be removed
- The investigator shall ensure that the lighting in the laboratory and adjoining corridor is to be left on.
- When applicable, the participant is to use one of the lifts to move to the first floor, and not the stairs.
- All investigators collecting data from the participants should either hold existing certification, or undergo training for Good Clinical Practice (GCP) and Valid Informed Consent in Research.

The aim of the above guidance is to ensure that all participants are able to undertake the future study in a safe environment meeting their physical needs.

Chapter 3: First HD Experiment

3.1 Review of pilot study

In the pilot study, an oculomotor battery was designed for potential future use in a cohort of HD participants. Using the set-up described in section 2.4, data was successfully recorded from 20 students. Using the purpose built software, this data was subsequently analysed, with metrics (i.e. saccadic latency) values closely matching that which has been reported in the literature in control studies. This confirmation of normative data using the set-up and software is sufficient to verify the protocol.

3.1.1 Inclusion of HD participants

In the previous chapter, a cohort of students were recruited to undertake a protocol designed to be used with individuals with HD. The set-up was able to produce reliable data which is consistent with that found in previous studies. With the feedback from the pilot cohort, and the recommendations made in section 2.6, it is felt that the current set-up, and protocol will be suitable for those with HD. Additionally, steps will also be taken in accordance with the guidance in section 2.6.3 to ensure safety for those with HD.

3.2 Aims

3.2.1 Tolerability of set-up with HD participants

It is likely that some participants with HD, in particular at a later disease stage are likely to experience changes to their temperament. This can be exhibited with a participant being particularly irritable, quickly becoming annoyed or impatient. A participant with HD may become frustrated with prolonged or difficult tasks. It is important to ensure that each participant is provided encouragement throughout testing, and additionally that each participant is encouraged to ask questions so that they may further engage with each task during the protocol.

Regarding participant set-up, each participant will be sat on a chair with their chin placed on a chin rest. This will be especially crucial as it is expected that those with HD will exhibit chorea, through which involuntary head movements would also be anticipated. The chin rest should be comfortable for the participant to use, and allow them to undertake all testing in a reasonably comfortable setting.

3.2.2 Testing a comprehensive battery of oculomotor tasks

As covered in Chapter one, there already exists a literature pertaining to oculomotor studies in HD. As covered in 2.1.5, there has been no comprehensive battery of oculomotor tests in the literature for testing EM's in HD. It is our aim, using the existing set-up (which has been verified through the pilot study), to produce data which will replicate the findings of previous studies, and to determine the best EM to be used as a biomarker.

3.2.3 Paradigms for use in HD

As used previously in the pilot study, we will be using an identical protocol, consisting of:

- Pro-saccades
- Anti-saccades
- Smooth pursuit
- OKN

3.3 Study Design

This study will be a case control study between two cohorts (n=20). The HD cohort will consist of 20 individuals recruited through the HD clinic at Cardiff University. The controls will be recruited through the Cardiff University Eye Clinic.

3.3.1 Recruiting and identification of HD cohort

The HD cohort will be identified by Professor Anne Rosser at the HD clinic, who will discuss the study with potential participants. Once a suitable participant has been identified, Professor Anne Rosser will introduce them to James Brawn, who will provide them with a Participant Information Sheet, and will discuss the study with them. If the participant is happy to participate, they will be provided with a consent form to complete.

3.3.2 Ethical Approval

Ethical approval for the study has been provided by the North Wales Research Ethics Committee REC – 13/WA/0162. The ethics covered the recruitment and testing of participants with HD. For the recruitment of control participants, ethical approval has been provided by the School of Optometry and Vision Sciences Human Science Ethical Committee, project number – 1390.

3.3.3 Inclusion & Exclusion Criteria

To be recruited into the study, all of the following inclusion criteria must be met:

- Participant age must be 18 years or over
- Gene positive status must be known
- Participant must be capable of providing informed consent
- Participant must be consented to the ENROL-HD study (in accordance with the ethical approval)

The following exclusion criteria are also applied to ensure eligibility to participate in the study:

- Those with an unknown gene status will not be included
- Potential participants with significantly impaired cognitive ability.
- Those with any co-morbid ocular pathology which may impact upon the measurements of eye movements.

3.3.4 Recruitment of age matched control cohort

The age matched control cohort will be recruited from patients registered at the Cardiff University Eye Clinic who have previously indicated that they wish to be contacted as potential participants in future research studies. Ethical approval for the recruitment of these controls has been provided by the School of Optometry REC.

3.3.5 Study aims and novelty

The aims of this study are:

- To create a feasible battery of tasks to identify eye movements as a potential biomarker in HD
- To replicate findings reported in the current literature to further verify the set-up

In regards to this study, the novel aspects are:

- Investigating pro-saccades, anti-saccades, smooth pursuit and OKN in a cohort of HD participants with age matched controls, in both the horizontal and vertical meridians.
- Investigating both vertical and horizontal saccadic and pursuit eye movements in HD. Former studies have primarily focused on horizontal eye movements only, whereas in the UHDRS, both horizontal and vertical eye movements are measured.
- Assessing the accuracy of subjective eye movement scoring in the UHDRS.
- Investigating the impact of amplitude for pro-saccade and anti-saccade testing in HD. Previous studies have used single amplitudes of various size. It is unknown if changes in amplitude will impact the responses found in HD during EM testing.

3.4 Proposed protocol

3.4.1 Set-up and materials

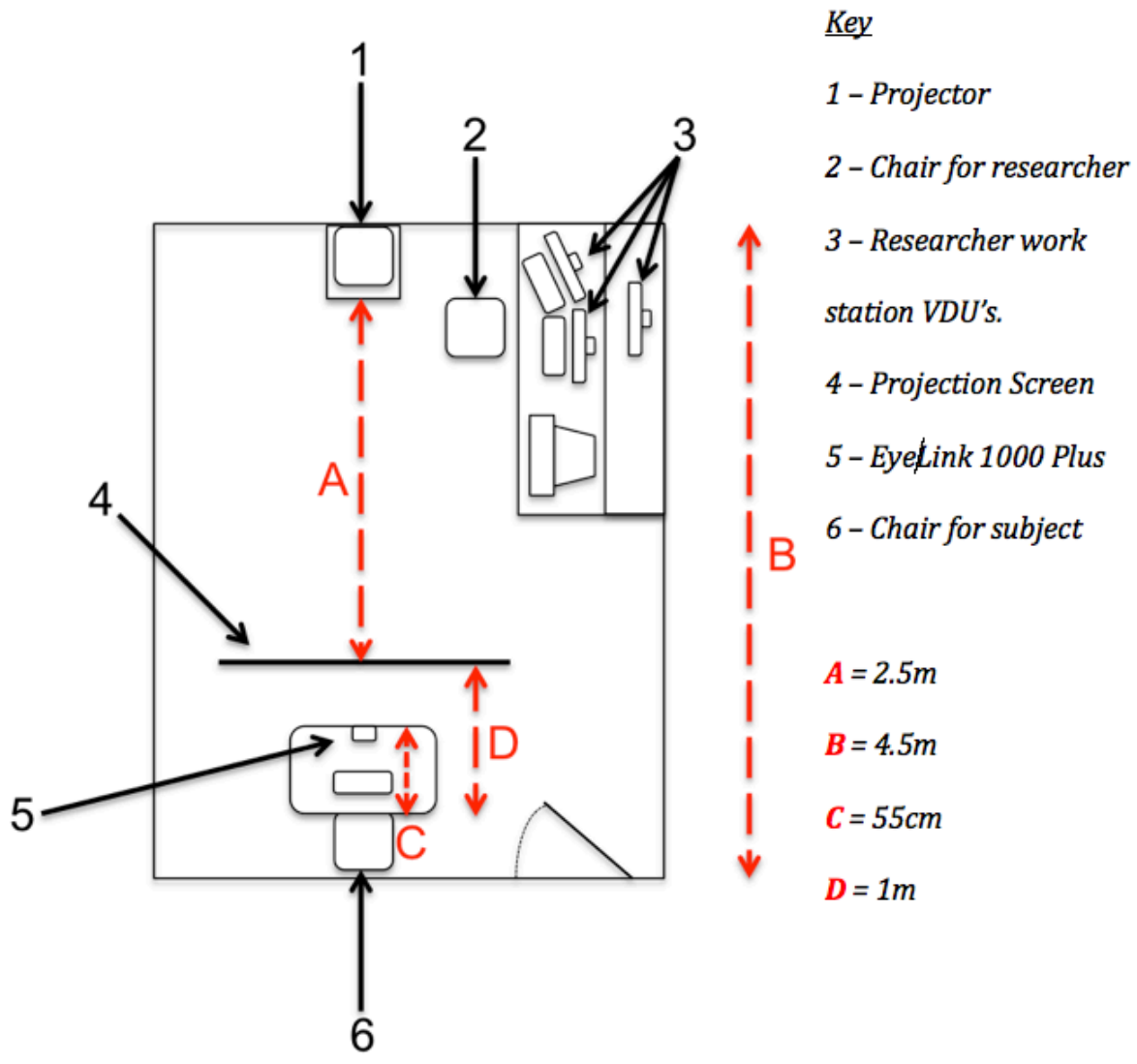


Figure 11 - Diagram of the lab

The room set-up and equipment used in this study shall be identical to those used in the Pilot experiment as described in 2.4.1. The only amendment to the set-up will be to change the EyeLink in the tower mount configuration from the desktop mount configuration. This change has primarily been made due to practical considerations; the table mount could be

tricky to set-up initially with the participant. The tower mount configuration also has a larger trackable range (60° x 40°) to the desktop mount (32° x 25°). Additionally the tower mount should facilitate quicker set-up.

As with the plot study the Christie DS+26 DLP® projector shall be used with a rear projection screen. Stimulus generation shall be programmed using the same package detailed in 2.4.1.3, with no significant amendments. The participants will undertake the same protocol as used in the pilot study. This protocol is detailed in 2.4.2.

3.4.2 Procedures

The test procedures shall be the same as those used in the pilot study, as detailed in 2.4.3. However, there will be changes to the instructions given to the subject. As the HD participants may struggle with some mild cognitive difficulties, a less wordy, more concise set of instructions shall be given. These changes are listed below.

3.4.2.1 Instructions for Pro-Saccade Paradigm

For the pro-saccade task, as this is a simple task, the explanation shall be shortened.

Original instruction:

'In this test you will be shown a sequence of lights on the screen in front of you. Each light will be presented for a moment, before instantly moving to another location. I would like you to follow the light when it moves as quickly as you can.'

New instruction:

'In this test you will see a red dot on the screen, and it will move from the middle to different locations. All that you are needed to do is to follow it as it moves.'

3.4.2.2 Instructions for Anti-Saccade Paradigm

For the anti-saccade task, as it is cognitively more difficult, it is essential to ensure that the participant understands the test. It is also important that the participant is encouraged to try their best as they may feel discouraged through 'performing badly'.

Original instruction:

'In this test you will be shown a sequence of lights on the screen in front of you. You will be presented with a light at the centre of the screen for a moment, before it moves instantly to another location. The light will then return instantly to the middle again, and the process is repeated. I do not want you to follow the light when it moves from the middle; instead I would like you to look in the equal and opposite direction to where it has moved to.'

New instruction:

'In this test you will see a red dot on the screen, and it will move from the middle to different locations. When this dot is at the centre, I would like you to look at it. When it moves away from the centre, do not follow it. You must instead try to look in the equal and opposite direction like a mirror image. Do not worry if you don't get it right every time, you will make mistakes. But it is important that you try your best'.

3.4.2.3 Instructions for Smooth Pursuit

The instructions for the smooth pursuit task shall remain the same as those listed in 2.4.4.3.

3.4.2.4 Instructions for OKN paradigm

In the pilot study, despite the instruction, with exception to a small minority of participants, there was confusion was to what they were required to do in the task. This resulted in most participants using the voluntary look OKN, as opposed to the involuntary stare OKN response. Therefore, the instruction will be changed. It shall also be made clear that it is

normal for the eyes to be moving in response to the stimuli, something which may be seen as a failure to carry out the instructions by the participant.

Original instruction:

‘In this test you will be shown a grating moving across the screen. I would like you to stare at the middle of the screen, and try not to follow the grating’.

New Instruction:

‘In this test we will be testing optokinetic nystagmus. This is the sort of eye movement you may have experienced looking out of the train window, that wiggle that you feel your eyes do. To produce this movement, you will be shown a set of stripes moving across the screen. I would like you to try to keep looking at the middle. If you feel your eyes moving, that is fine. Please do not try to follow the stripes. Try to stare at the middle of the screen.’

3.5 Results

A total of 24 HD participants were recruited into the study, of which three were unable to undergo testing due to excessive chorea preventing calibration of the EyeLink. One further participant withdrew consent during assessment. Full datasets were collected for 20 HD participants. Full datasets were also recorded from 20 control participants, who were age matched to within $\pm$ 2 years. A table listing the participants recruited for both studies and their age at time of visit is shown on the next page. Also included is the total motor score (TMS) from the UHDRS for the HD participants.

Table 7 - Participant Information

HD:			Control:	
Participant:	Age	TMS	Participant	Age
HD1	54	8	CON1	55
HD2	60	78	CON2	60
HD3	41	2	CON3	42
HD4	62	26	CON4	62
HD5	51	1	CON5	52
HD6	34	0	CON6	34
HD7	38	10	CON7	39
HD8	51	15	CON8	49
HD9	58	31	CON9	57
HD10	48	27	CON10	48
HD11	47	27	CON11	48
HD12	52	32	CON12	54
HD13	41	0	CON13	41
HD14	50	37	CON14	49
HD15	35	2	CON15	35
HD16	68	82	CON16	70
HD17	41	7	CON17	40
HD18	53	34	CON18	53
HD19	36	0	CON19	36
HD20	64	42	CON20	62
Mean	49.2	23.05	Mean	49.3
SD	9.81	23.49	SD	9.83

3.5.1 Pro-saccade and Anti-saccade latency

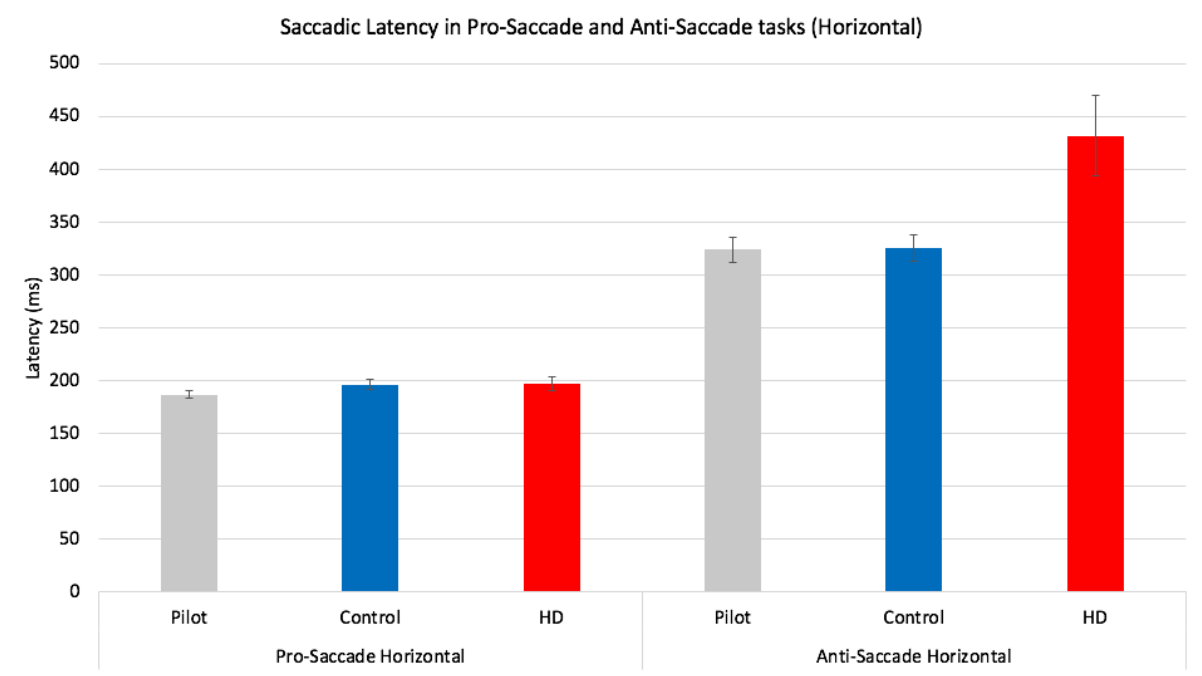


Figure 12 - Saccadic Latency in Pro-Saccade and Anti-Saccade tasks (Horizontal)

Figure 12 above shows the latency values for the horizontal pro-saccade and anti-saccade tasks. There is no significant difference between the control cohort (196ms) and HD cohort (197ms) in the pro-saccade task. Also included are the latency values from the pilot data. There is no significant difference between the three groups in the pro-saccade task, and there is no significant difference between the pilot and control group in the anti-saccade task (323ms and 325ms). However the latency in the HD group is significantly longer than in the control group ($P<0.01$) in the anti-saccade task.

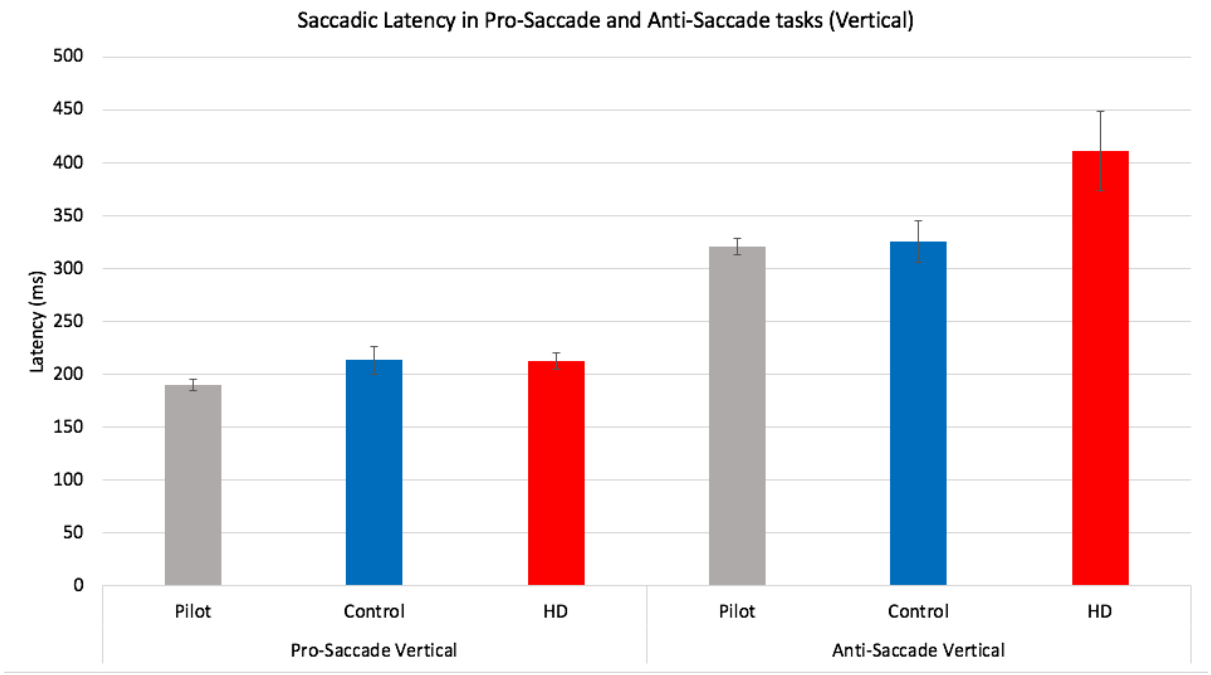


Figure 13 - Saccadic Latency in Pro-Saccade and Anti-Saccade tasks (Vertical)

Figure 13 shows the latency in the vertical pro-saccade and anti-saccade tasks. As with the previous figure, pilot data has been included for reference. There is no significant change in latency for the vertical pro-saccade task between the three cohorts. The latency in the vertical anti-saccade task is again greater in the HD group than in the control and pilot groups, this different is significant ($P<0.01$).

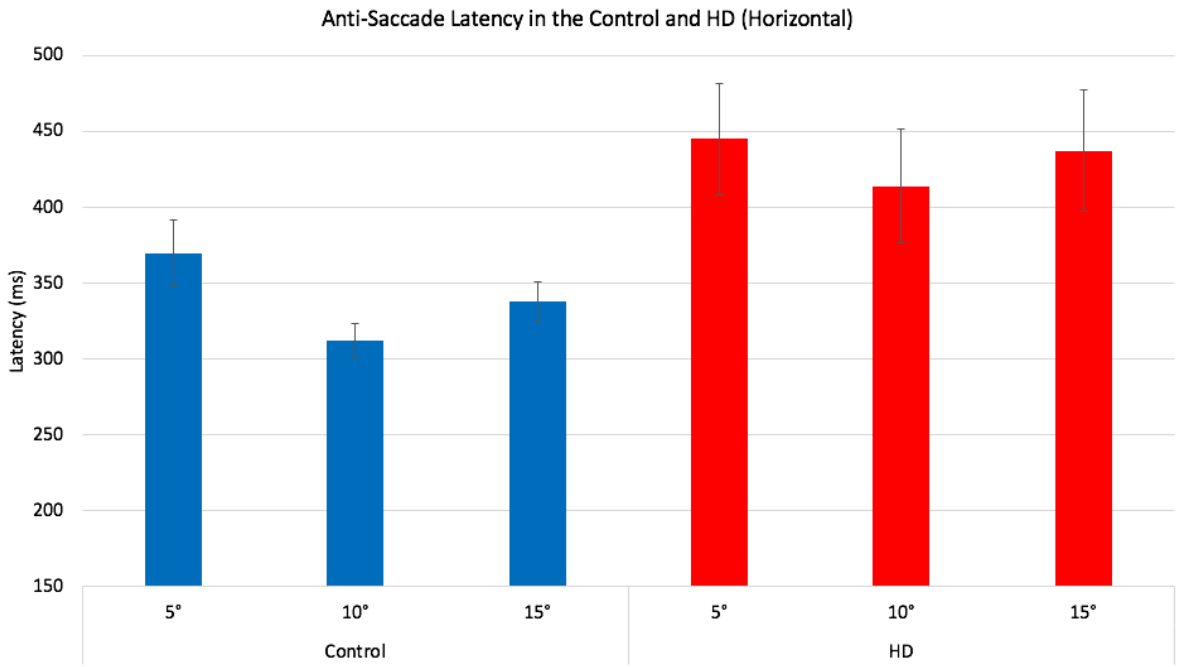


Figure 14 - Anti-Saccade Latency in Control and HD (Horizontal Tasks) by Amplitude

In both the pro-saccade and anti-saccade task there is no effect of amplitude on the latency in control HD. This is shown in Figure 14. This is also observed to a lesser degree in the vertical task, where the latency for the 10° amplitude is quicker than the 5° saccade in controls. As per horizontal pro-saccades and anti-saccades, there is once again no change in latency due amplitude.

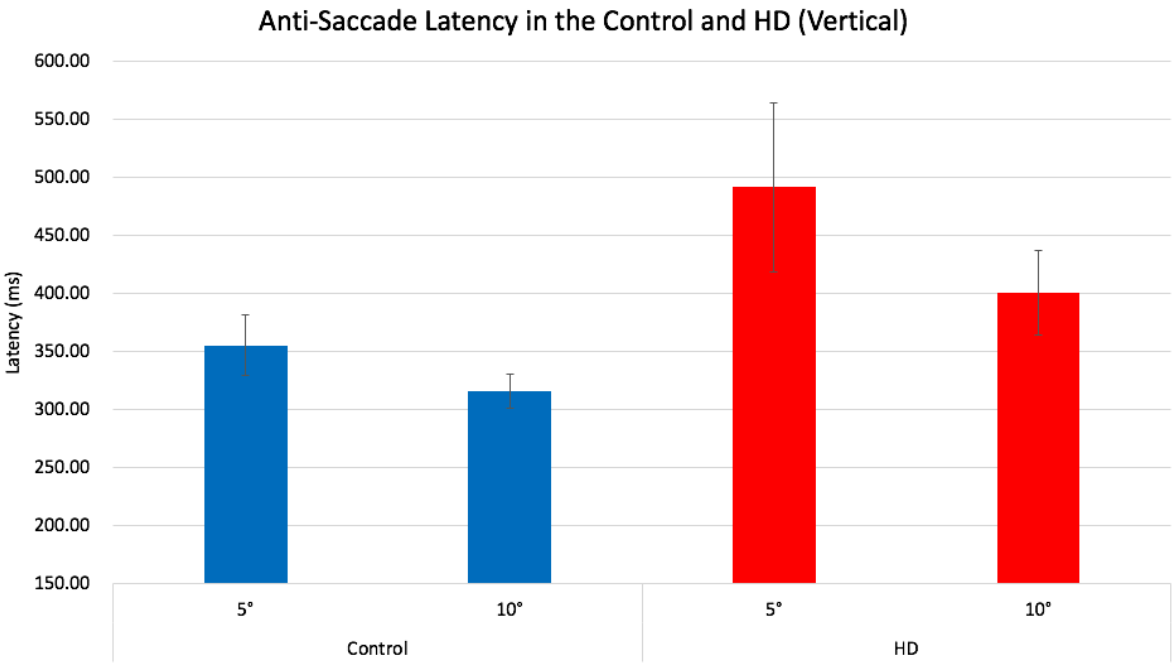


Figure 15 - Anti-Saccade Latency in Control and HD (Vertical) by Amplitude

3.5.2 Anti-Saccade Cost

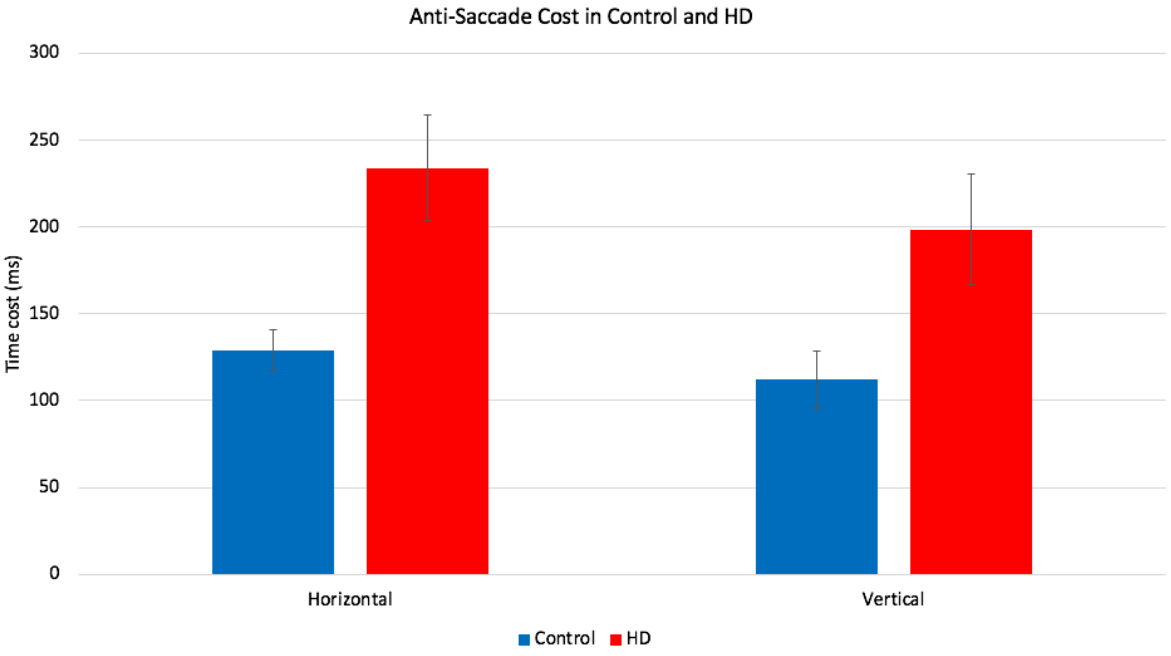


Figure 16 - Anti-Saccade Cost in Control and HD

Figure 16 shows the mean anti-saccade cost for the participants in the control and HD group. This is an average of the individual anti-saccade costs for each participant. In both

the horizontal and vertical meridians, the cost of performing the anti-saccade is greater in HD than in control (P<0.001).

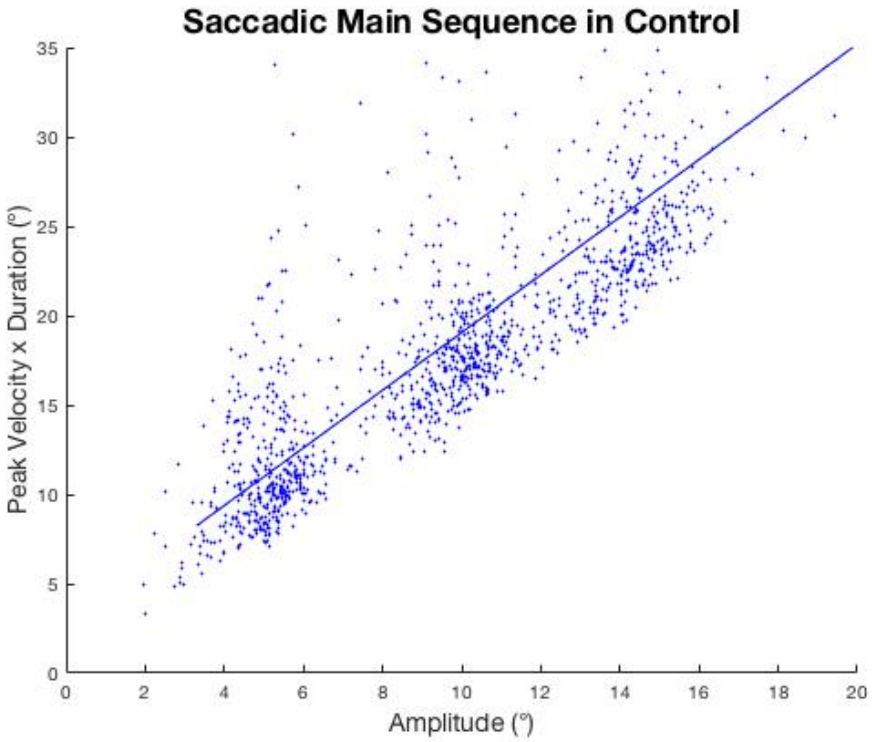


Figure 17 - Grouped Main Sequence in Controls

As discussed in 1.6.2, saccadic eye movements are characterised by a classic temporal profile, a tight linear relationship termed the main sequence (Bahill, Clark and Stark 1975). A main sequence plotted as Peak Velocity x Duration (degrees) versus Amplitude (degrees) gives the ratio of peak velocity to mean velocity, known as a Q-ratio (Harwood, Mezey and Harris 1999). In controls the Q-ratio, the slope of the regression is 1.87, as plotted above in Figure 17. The range of values reported in Harwood, et al. (1999) are 1.54 to 1.80 with a mean of 1.72. The Q-ratio in the HD group is 1.94, which again is greater than the previously reported values. This can be seen in the Figure 18.

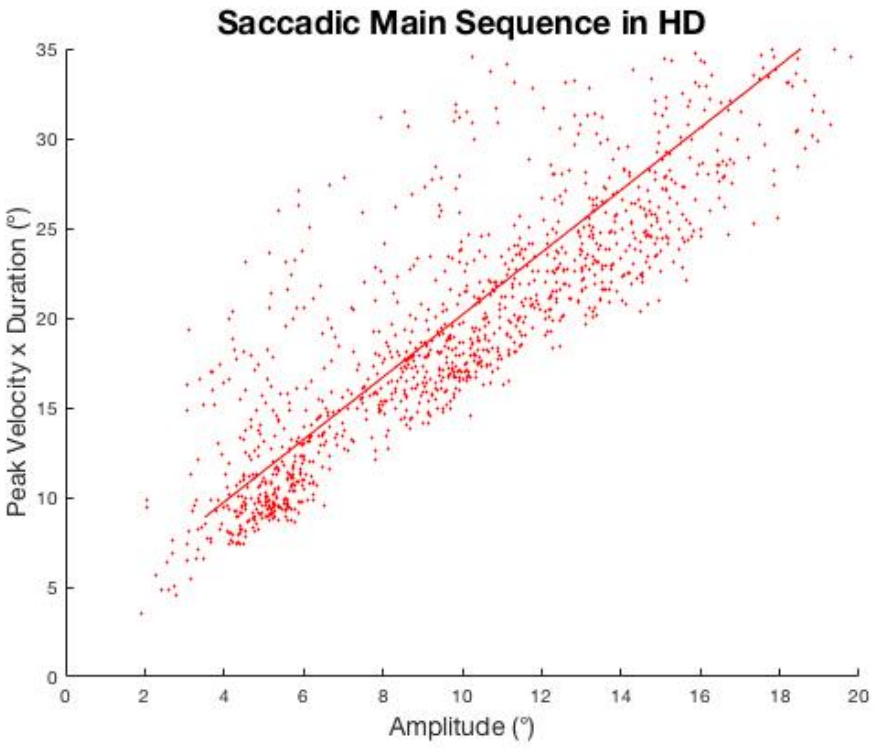


Figure 18 - Grouped Main Sequence in HD

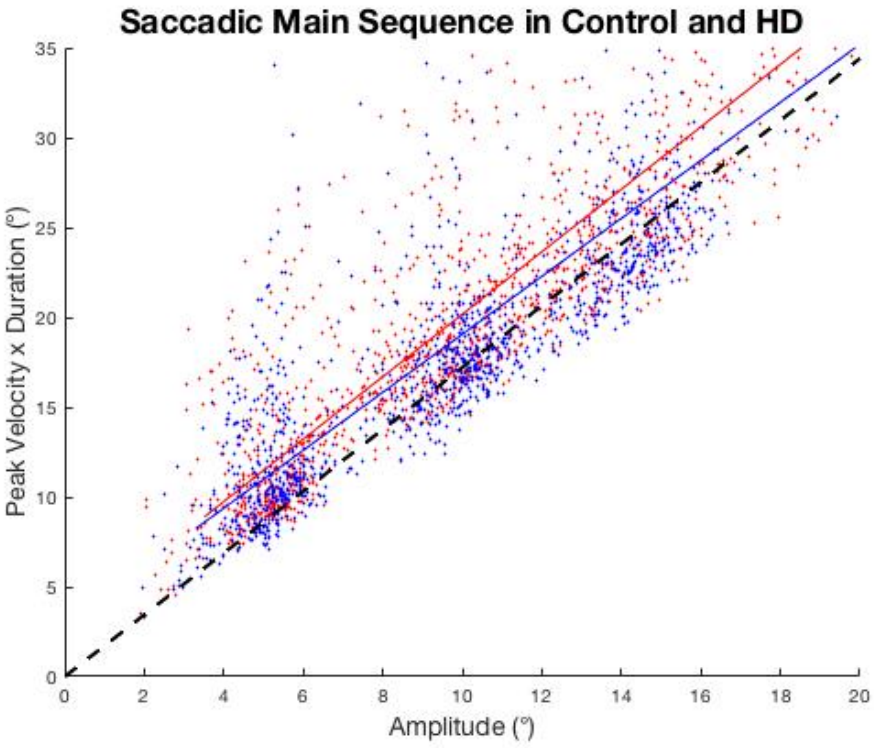


Figure 19 - Pooled data from both cohorts. Included are regression lines for HD (red), control (blue), and normative values from Harwood et al . (1999)

3.5.3 Anti-Saccade Error Rate

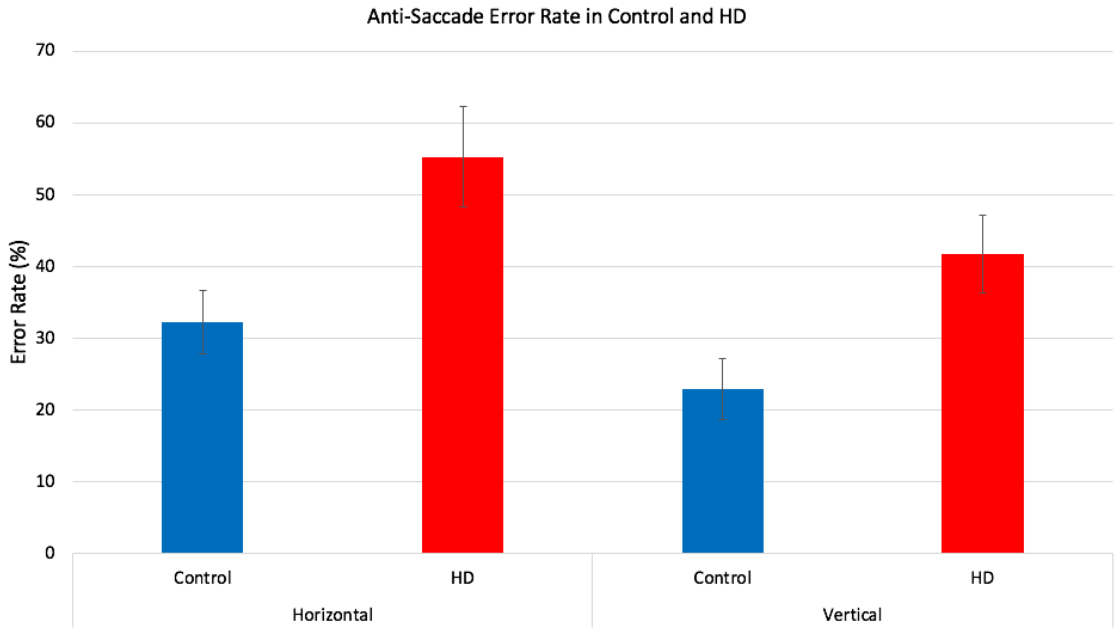


Figure 20 - Anti-Saccade Error Rate in Control & HD

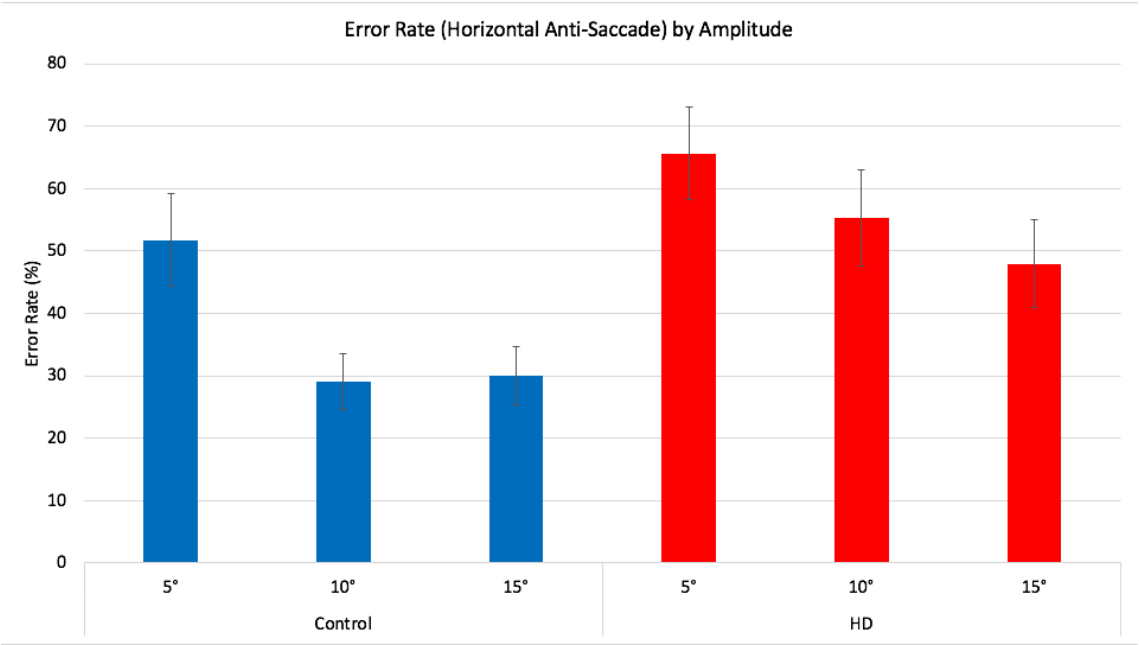


Figure 21 – Horizontal Anti-Saccade Error Rate by Amplitude

In both the horizontal and vertical anti-saccade tasks, the error rate is significantly higher in HD than in controls (P<0.001), as shown in Figure 20. In both groups, the error rate is lower in the vertical task than in the horizontal (Figure 21 and Figure 22). The mean error rates reported in the HD group (55% and 41%) correspond to those previously observed in the studies listed in 2.1.1. In the vertical anti-saccade task there is no significant difference between amplitudes, however in the horizontal task, the error rate at the 5° amplitude is greater than that observed at 10° and 15° in controls. Error rate decreases with increased amplitude in HD.

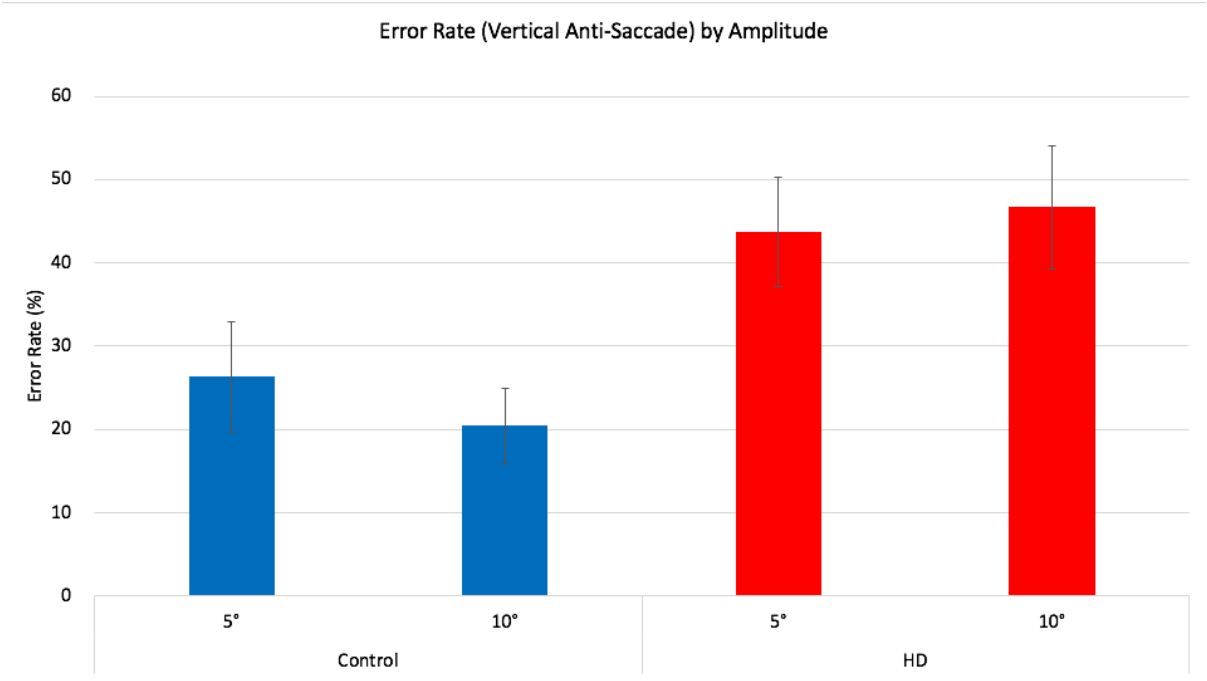


Figure 22 –Vertical Anti-Saccade Error Rate by Amplitude

3.5.4 Performance against subjective measures

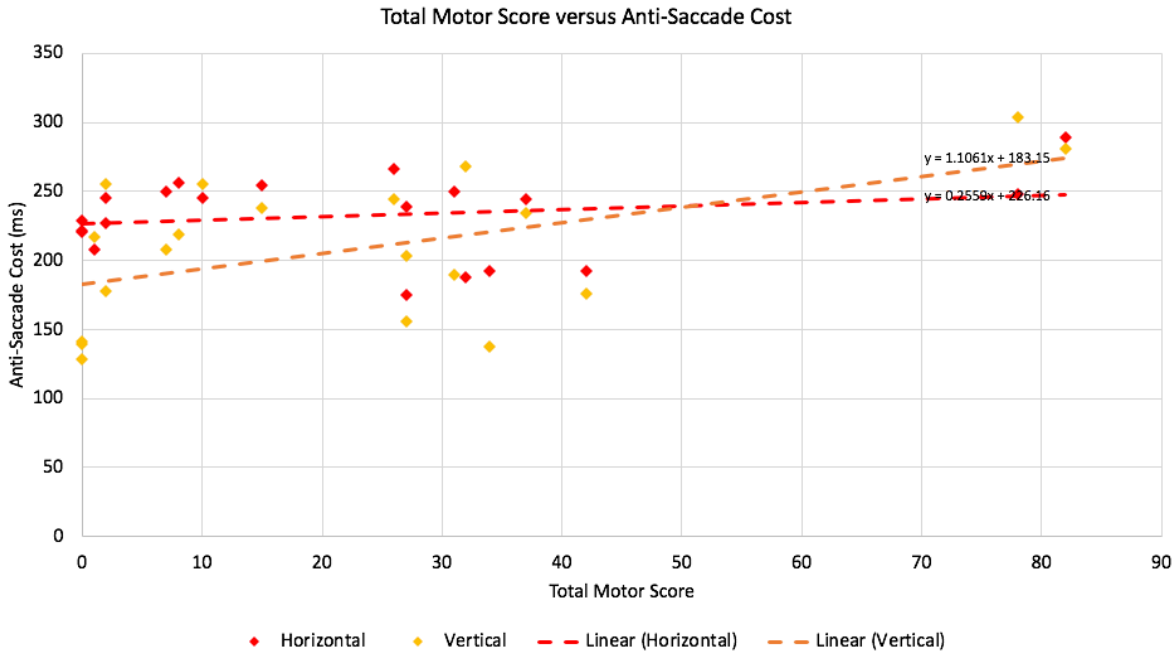


Figure 23 - Total Motor Score versus Anti-Saccade Cost

Each HD participant prior to undertaking the study had recently been assessed using the UHDRS scale, which assesses motor function, cognitive function, functional capacity and behavioural abnormalities. The assessment of motor function produces a composite total motor score which indicates the physical manifestations of the disease. A higher score indicates great impairment, a lower score indicates less impairment. Anti-saccade cost has been plotted against the total motor score (Figure 23). The relationship between anti-saccade cost and total motor score are weak. However it does appear that anti-saccade cost increases with disease stage.

A similarly weak relationship is also observed between the anti-saccade error rate and total motor score. As with the anti-saccade cost, the error rate increases with disease stage. The error rate for the HD participants with low total motor scores are greater than those in the control group.

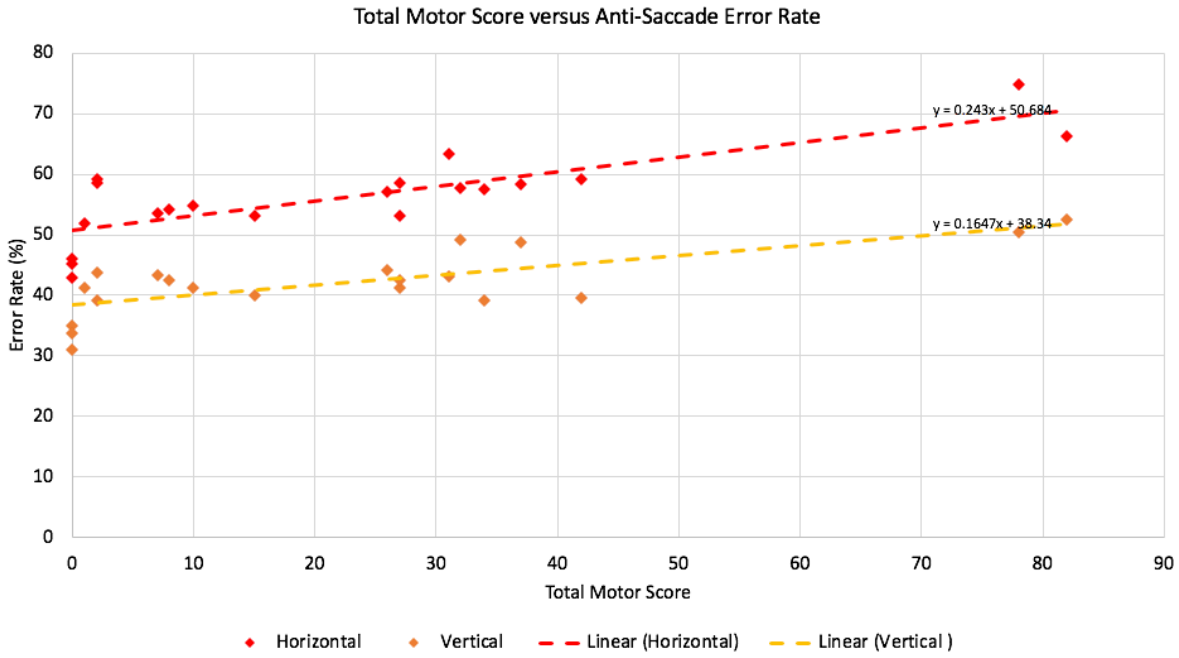


Figure 24 - Total Motor Score Versus Error Rate

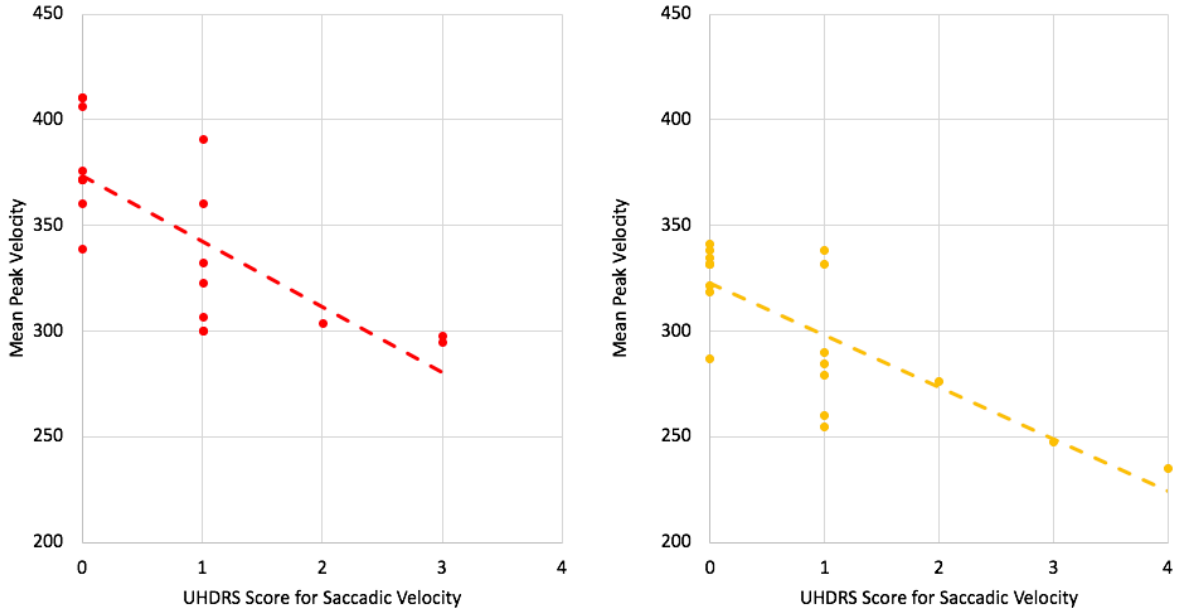


Figure 25 - Subjective Saccade Velocity compared to Objective Saccade Velocity (Horizontal on Left, Vertical on Right)

During the UHDRS motor testing, there is a subjective assessment of saccadic eye movements, and the velocity of pro-saccades is recorded as a score between 0 and 4, the former indicating no deficit, the latter indicating severely slowed saccades. The UHDRS

oculomotor scores for saccadic velocity are plotted against the corresponding recorded mean saccadic latencies from the pro-saccade task. There negative correlation between the subjective and objective measures, mean peak velocity reducing with an increased score.

3.5.5 Smooth Pursuit

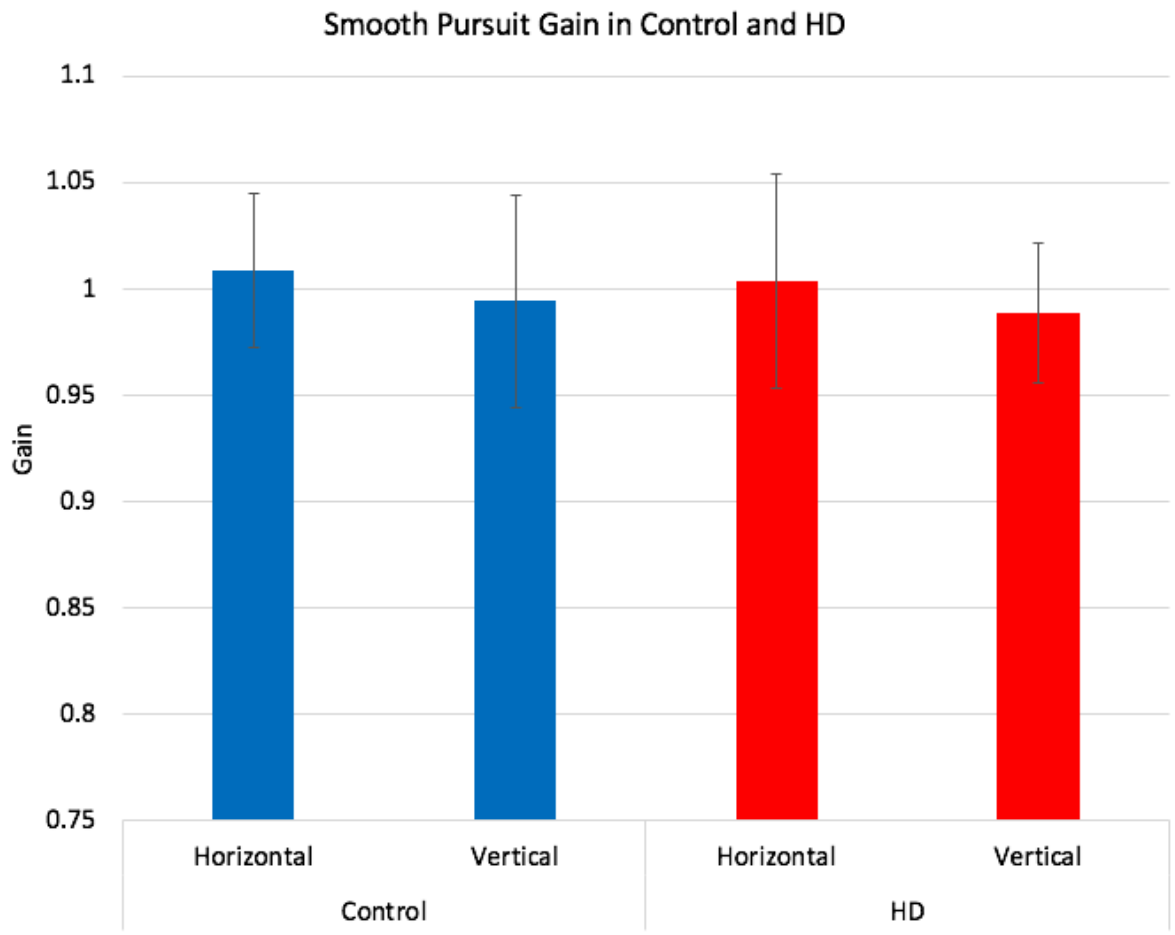


Figure 26 - Smooth Pursuit Gain in Control & HD

The above figure shows the smooth pursuit gain for the control and HD groups. There is no significant difference between the groups, and therefore there is no obvious deficiency in the HD group.

3.5.6 Optokinetic Nystagmus

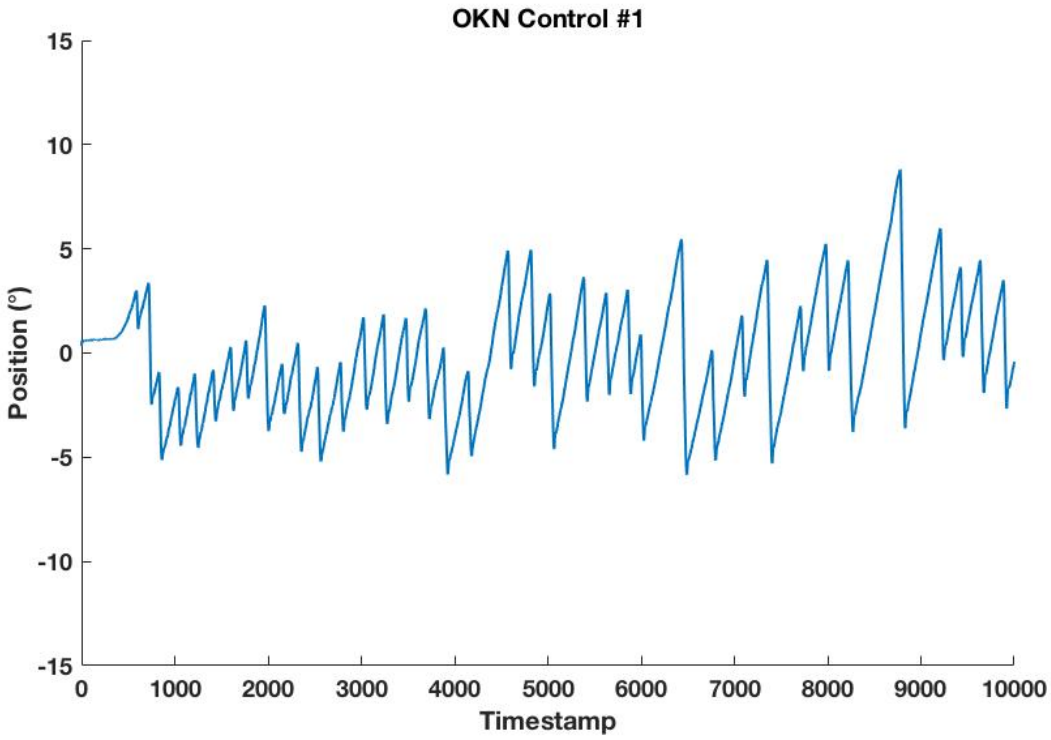


Figure 27 - Example raw eye trace from Control Participant

Prior to analysis, the OKN waveform was viewed to ensure that the participant was undertaking stare OKN, as opposed to look OKN. An example of this is shown in Figure 27. The eye trace shows a characteristic sawtooth waveform of alternative saccades and slow phase eye movements. Prior to analysis, all controls have produced 'normal' eye traces. This however is not true of the HD cohort.

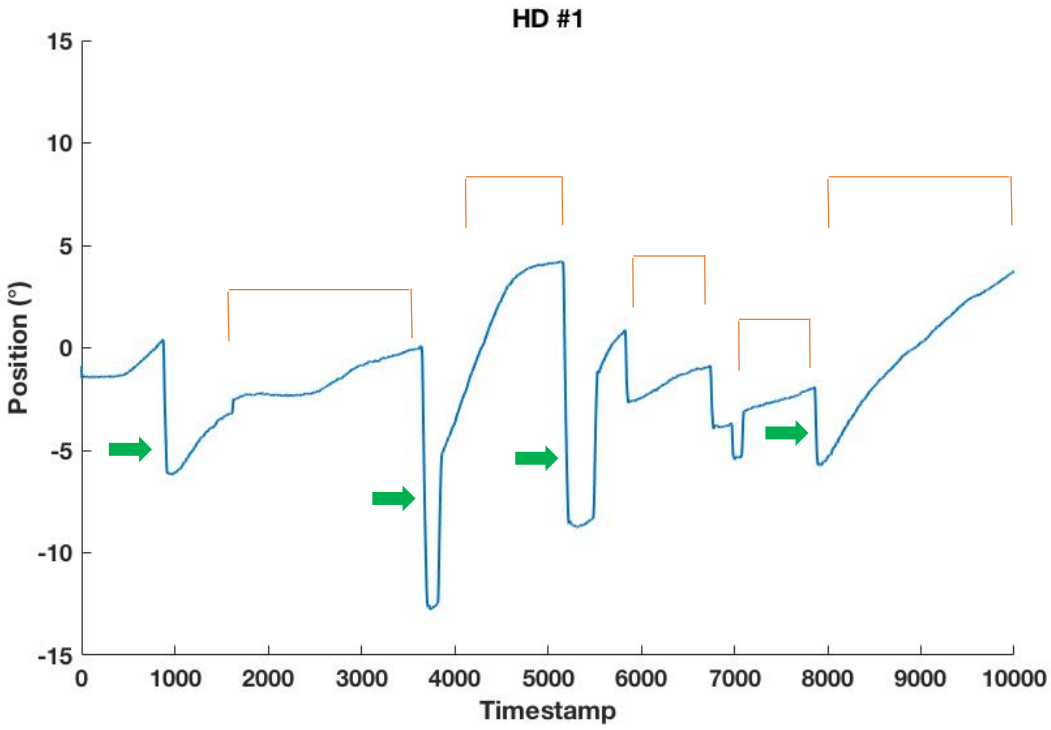


Figure 28 - Example raw eye trace from HD Participant

In this participant (Figure 28), the classic OKN waveform is absent. There appears to be low gain slow phases (orange brackets) and saccades (indicated by the green arrows). Abnormal waveforms are prevalent within the HD cohort, exhibiting different characteristics.

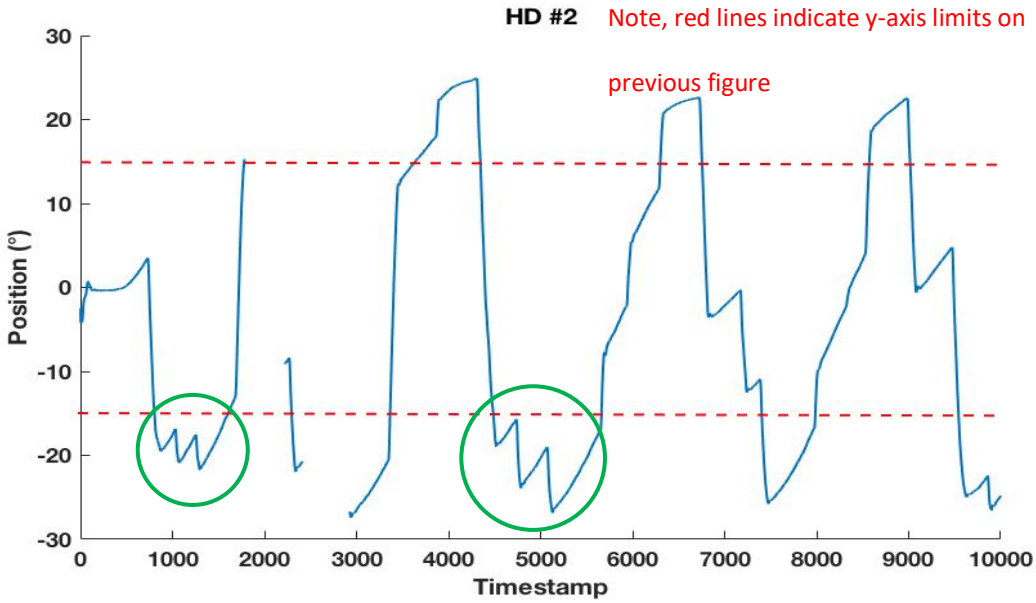


Figure 29 - Example raw eye trace from HD Participant

The waveform is not necessarily absent for the duration of the testing. In this example (Figure 29), the classic sawtooth pattern is present (indicated by the green circles), however is intermittent, and is being performed to the far leftwards of the screen. The red dotted lines indicate the limits of the y-axis on the previous example. That participant is executing large saccades of up to 20° across the screen.

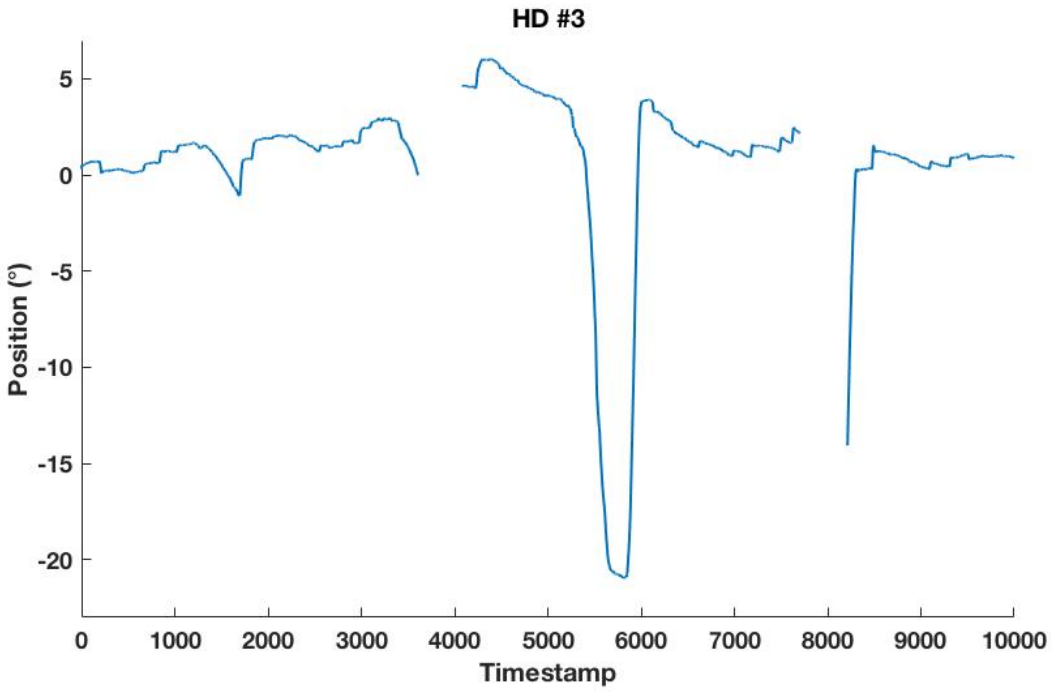


Figure 30 - Example raw eye trace from HD Participant

In the third example (Figure 30), the participant appears to be keeping their fixation near the centre of the screen throughout the task, aside from a large leftward slow phases and subsequent reset at 5250ms. The waveform (if present) has a very small amplitude.

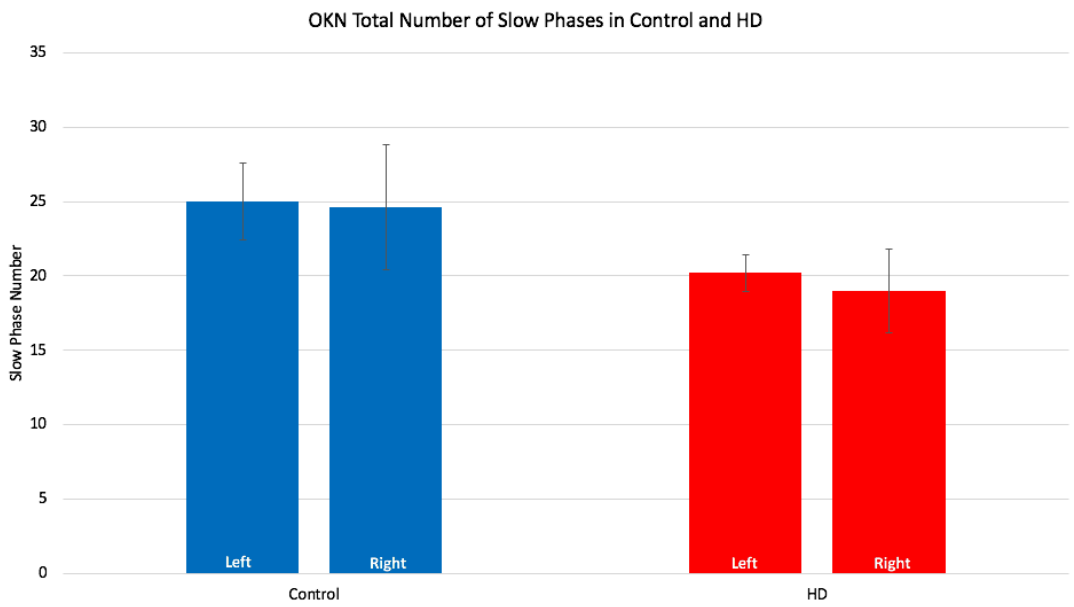


Figure 31 - Total Number of Slow Phases Performed in Control & HD

Participants with HD initiate fewer slow phases than the control group during OKN both rightwards and leftwards (Figure 31). There is no asymmetry between the response in either direction. The same participants upon undertaking the slow phases exhibit a significantly larger amplitude ($P<0.05$, Figure 32). These amplitudes are also significantly more variable within group, and within the individual participant.

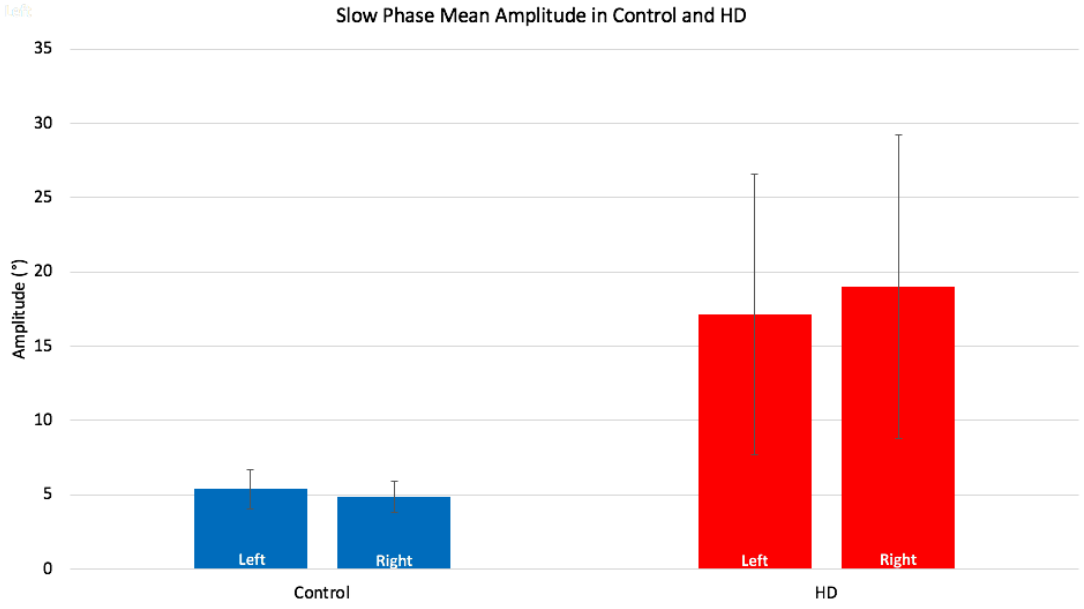


Figure 32 - Mean Amplitude for Slow Phases in Control & HD

3.6 Discussion

In the pro-saccade task, no significant difference between the control and HD groups was observed for saccadic latency in both the vertical and horizontal tasks. When split by amplitude there is no significant difference between the 5°, 10° and 15° amplitudes in HD. This is consistent with Golding et al. (2006) who also observed no significant latency change with HD. However, this finding was only present in the horizontal task, increased latency was observed in the vertical task. Blekher et al. (2004) and Ali et al. (2006) both observed increased pro-saccade latency in HD, however conversely Winograd-Gurvich et al. (2003) and Patel et al. (2012) have no observed changes in pro-saccade latency in either the horizontal and vertical meridians.

In the anti-saccade task, the latency was significantly longer in HD. When this is split by amplitude, there does not appear to be an amplitude effect in HD. As with the pro-saccade task there is a moderate reduction in latency in the controls at the 10° amplitude compared to 5° and 15°. Elongated anti-saccade latencies have been reported in all studies involving HD and control participants.

The anti-saccade cost, which has not explicitly been reported in previous HD studies, however can be ascertained from results presented, is greater in the HD group than in the control group ($P<0.001$). There are no significant differences in regards to orientation.

The error rates in the anti-saccade task are greater in the HD group than in controls ($P<0.001$). In both groups the error rate is lower in the vertical task, however this difference

is not significant. Separated by amplitude, the error rate does not differ significantly with a change to amplitude in the vertical task, however in the horizontal task error rate does appear to reduce with increased amplitude in HD. Previous studies involving anti-saccades in HD have not used multiple amplitudes. The error rates for the pooled data from all amplitudes is consistent with those reported in Blekher et al. (2004) and Patel et al. (2012).

The effect of disease stage on anti-saccade cost and error rate were also investigated. It is clear from the data, that the deficiencies present in HD (the increased anti-saccade latency and error rate) are present at the earliest stages of the disease, and are in themselves, potentially biomarkers that precede other motor symptoms. There is a weak correlation between disease stage and performance in then anti-saccade task.
Comparison of the objective pro-saccade measures recorded during the participant visit, and the oculomotor scoring applied during the UHDRS testing has been performed. The reduced saccadic velocity observed during the subjective testing persists in the objective testing. This confirms the accuracy of the practitioners in identifying subtle changes in eye movements in early stage HD.

Smooth pursuit gain is normal in both the control and HD groups. Previously Collewijn et al. (1988) and Henderson et al. (2011) have reported no deficiency in HD. Although some participants with HD can produce 'erroneous pursuit' which could be perceived as abnormal, Collewijn et al. (1988) reported that such errors were also present in a large portion of controls.

Few previous studies have investigated OKN in HD (these are covered in 1.8.3), and in these studies abnormalities have been reported. Blekher et al. (2004) reported a reduced velocity gain at higher stimulus velocities, Oepen, Clarenbach and Thoden (1981) reported a reduced saccadic velocity in OKN. Beenen, Buttner and Lange (1986) reported non-specific disturbances in OKN.

In this study, we have found the optokinetic response to be abnormal, and largely absent in HD. The classic OKN waveform was only produced in a small minority of participants. Failure to initiated OKN has not been reported in a clinical group. Starr (1969) reported a case of two patients with advanced HD who could not produce a response to optokinetic stimulation. In both cases, it should be noted that the patients were unable to initiate voluntary saccades, one patient lapsed into a coma and died within 18 months.

The observation of a loss, be it transient or prolonged, of the optokinetic response in HD is a novel finding, in particular in participants who are otherwise healthy.

3.6.1 Tolerability of protocol in HD

One of the main concerns with use of an experimental protocol is the tolerability of it in a clinical group. As discussed in 3.2.1, participants with HD may not be as tolerable of undergoing clinical testing as someone without the disease. As data has been successfully recording from 20 individuals, it is felt that the protocol used was appropriate for use with this clinical group.

During each visit, participants from the HD cohort were invited to share their thoughts on their experience undertaking the protocol. The general consensus was that the testing was that it wasn't particularly exerting, and a time duration of 30 minutes 'felt about right'. The anti-saccade task was most frequently discussed due to it being much more challenging than the other tasks.

One participant withdrew consent after attempting the anti-saccade task, and removed himself from the room before any feedback could be provided.

3.6.2 Failure of Optokinetic Nystagmus in the HD cohort

In the literature, abnormal OKN has previously reported, however this abnormality is either not defined (as discussed in 1.8.3), or has been reported as producing a reduced gain in response to stimuli. There is a single case reported where an individual with pronounced HD failed to initiate OKN. This individual however was unable to initiate any kind of eye movement, and died shortly after examination.

Therefore, the abnormal OKN observed in this study, in particular the failure to elicit an appropriate response (i.e. the classic sawtooth pattern) is a novel finding. This is particularly notable as this abnormality is present in those whom are either asymptomatic, or exhibiting a very mild physical symptoms. This novel finding, may potentially be the earliest presenting non-invasive and quantifiable biomarker for HD.

3.6.3 Effect of Medication

Retrospective to data collection, information pertaining to the medication currently being taken by the participants has been provided by the clinic, these are shown in the table below

Table 8 - Medication Data for HD Cohort

Participant	Medication #1	Medication #2	Medication #3
HD1	Naproxen	Diclofenac	Corticosteroids
HD2	Aspirin	Fluoxetine	Simvastatin
HD3	Amitriptyline	Naproxen	Omeprazole
HD4	Nil		
HD5	Nil		
HD6	Symbicort inhaler		
HD7	Amitriptyline	Omeprazole	Co-codamol
HD8	Nil		
HD9	Chlorphenamine	Doxycycline	Mycophenolic Acid
HD10	Not known		
HD11	Citalopram	Ventolin	Steroid inhaler
HD12	Ibuprofen	Paracetamol	
HD13	Nil		
HD14	Nil		
HD15	Omeprazole	Mefanamic Acid	Tranexamic Acid
HD16	Citalopram	Losartan	Mirtazapine
HD17	Tamoxifen	Venlafaxine	Migraleve
HD18	Citalopram	Bendroflumethiazide	Lansoprazole
HD19	Nil		
HD20	Fluoxetine	Oxybutynin	Fluticasone

Of the 20 participants, six are not currently taking any medication. All of these medications are commonly prescribed amongst medical practice. These medications fall under the following areas:

- Depression (Amitriptyline, Citalopram and Fluoxetine)
- Stomach complaints (Omeprazole and Lansoprazole)
- Hypertension (Bendroflumethiazide, Aspirin and Losartan)
- Asthma (Ventolin, Symbicort)
- Pain relief (Co-codamol and Paracetomol)
- Hyperlipidaemia (Simvastatin)
- Anti-Inflammation (Ibuprofen and Naproxen)

There is no reference in the British National Formulary of oculomotor deficits as a side effect, or adverse reaction to any of these medications. It is unlikely that the medication being taken has resulted in the abnormal OKN.

3.6.4 Impairment of Motion Perception

As demonstrated in the pro-saccade and smooth pursuit tasks, the motor system for producing OKN is intact, therefore suggesting that the inability to appropriately initiate the optokinetic response may be due to deficient motion perception. If those with HD have impaired sensitivity to motion, the stimulus to drive OKN would be abnormal or absent. Impaired motion perception has been reported in HD in response to global motion (Filoteo et al. 1995), trajectory discrimination tests (O'Donnell et al. 2003), and with moving gratings (O'Donnell et al. 2008). More recently biological motion has been shown to be deficient in HD (Muratori, Evinger and Reilmann 2016).

3.6.5 Reviewing the aims of the study and novel aspects

The primary aims of the study were to create a feasible battery of tasks to identify eye movements as a potential biomarker in HD, and to replicate findings reported in the previous literature to further verify the set-up. The major finding of this study is that of impaired OKN in early stage/asymptomatic HD. The gross level of this impairment, the intermitted or constant failure to provide an appropriate response to optokinetic stimulus, has not been previously reported. Other findings within the study were consistent with that found in the present literature which verifies the reliability and accuracy of the protocol.

A novel aspect of this study, is testing saccades (pro and anti), pursuit and OKN in both the horizontal and vertical meridians using a HD group with age matched controls. No previous study has performed a comprehensive battery without the absence of a control group, or vertical testing. This protocol is the most comprehensive battery performed in HD.

Another novel aspect was assessing the accuracy of the subjective eye movement measures in the UHDRS. It has been demonstrated that the subjective rudimentary testing correlates with the objective measures recorded in the laboratory.

Previous studies involving pro-saccades and anti-saccades have presented targets at a single fixed amplitude. Across the studies, this amplitude has varied between 5° and 20°. It was unknown if amplitude had an impact on the reported findings, and if these findings across the literature were directly comparable. There does not appear to be a significant difference between performance in the pro-saccade and anti-saccade tasks in HD. This would suggest that testing at a single amplitude for saccadic tasks in HD is sufficient.

3.6.6 Recommendations for future studies

Subsequent to this study, it is important to ascertain that the primary novel finding, the abnormalities in OKN, are further investigated to demonstrate repeatability, and to test the hypothesis of impaired motion perception being co-incident in these participants.

Therefore the primary recommendations for future studies would be to repeat the testing of OKN in HD, potentially over a prolonged time period (extending from the 10 seconds to 30 seconds for example). In addition to this, the same participants should undergo a test of their motion perception to ascertain if there is a potential link between the abnormal OKN, and motion perception.

The anti-saccade task has been used in this study (as with previous) to perform as a motor proxy for impaired inhibitory control, however it has been suggested that the anti-saccade task is not a pure measure of inhibitory control (Wolohan and Knox 2014). Therefore in future studies, another paradigm i.e. the Minimally Delayed Oculomotor Response paradigm (MDOR), presented in Woolohan and Knox (2014), should be trialled in HD.

Additionally, as any measure of inhibitory control may be impacted by current cognitive ability, some form of cognitive testing should accompany the MDOR paradigm, to investigate if any changes to inhibitory control in HD are present purely down to poor cognition, or disease stage.

Chapter 4: Second HD Experiment

4.1 Review of paradigms used in first HD experiment

4.1.1 Optokinetic Nystagmus

In Chapter 3 we observed abnormal OKN in participants with HD. In some of the participants there was an apparent absence of OKN, the characteristic alternation of pursuit eye movements and saccadic eye movements were absent. In those for which there was an OKN response, a reduced slow phase gain was observed with a non-uniform waveform. These abnormalities were observed in all four cardinal directions, right, left, up and down. There was no particular difference observed between the horizontal and vertical tasks.

Despite our findings, there were some issues in regards to data quality, and primarily this was due to the short duration of the test. Although abnormalities were observed, in some participants, there was a relative lack of data in comparison to controls. Such loss of data was both due to excessive blinking, but also due to the eye not being tracked as the participant had moved (most likely due to chorea). It is also possible that there may be a 'warm up effect', where the participant's OKN response had not been fully stimulated within the short time period.

4.1.2 Anti-Saccades

As discussed previously, the participants in the first study undertook the pro-saccade and anti-saccade tasks. The data collected was reliable, and a greater anti-saccade error rate and

increased latency in the anti-saccade task in HD relative to healthy controls. Our study replicated findings observed in previous studies involving HD, and in the healthy population.

4.1.3 Modifications made to set-up in response to feedback from HD cohort

Following the completion of each visit, the participant was given an informal interview, primarily to understand their experience with the tasks that they had undertaken. Although there was no set structure to the interview, and no set questions, the aim of this informal interview was to assess the general feeling towards the testing. The feedback from the HD participants, can be summarised as follows:

Test procedures and duration:

- The general feeling with the procedures was that the timing was 'about right'. As a full visit usually did not exceed 30 minutes including consent, it was felt that the testing was short enough to not lead to fatigue, boredom or frustration.
- When asked to give feedback regarding the difficulty of the individual tasks, the HD cohort unanimously indicated the anti-saccade task as being particularly difficult. Several members of the cohort explicitly stated that they found the vertical anti-saccade task to be the most difficult.
- No participants raised any problems with the smooth pursuit, and OKN tasks.

Logistical and practical concerns:

- Some of the participants with more advanced disease struggled to keep their heads on the chin rest, either due to chorea, or comorbid neck related issues.
- No participants voiced any displeasure over needing to be tested in a different building outside of their clinic.

Most importantly, the vast majority of the cohort expressed that they would be happy to undertake further oculomotor testing in the future if required. As the majority of the participants are currently engaged in other research studies, it is possible that as a whole, our cohort was particularly enthusiastic about being involved with research, and that this may not be representative of the 'average' person with HD.

4.2 Inclusion of new paradigms

4.2.1 Elongation of Optokinetic Nystagmus task

To ensure that the abnormal OKN observed in Chapter 3 is genuine, it is crucial that the finding is replicated and observed in greater detail. To facilitate this, the duration of any OKN testing will be increased, and will also be repeated under different conditions.

4.2.2 Minimally Delayed Oculomotor Response (MDOR)

Previously in Chapter 2, we discussed the use of the anti-saccade task as a motor proxy for inhibitory control. The task is often used in neuropsychiatry to demonstrate the loss of inhibition in patients with neurodegenerative diseases, or psychiatric abnormalities. The anti-saccade task requires participants to inhibit a reflexive pro-saccade towards a target, and instead execute a voluntary saccade in the opposite direction (Hallett 1978). Failure to inhibit the reflexive pro-saccade (i.e. an error) would potentially indicate a problem with inhibiting the reflexive response. Such processes have been modelled and are further discussed in Chapter 2.

Wolohan and Knox (2014) propose that the anti-saccade task is not a true measure of inhibitory control. To execute an anti-saccade, you require the 'simultaneous inhibition of a

reflexive pro-saccade and the vector transformation, preparation and execution of a voluntary saccade. Thus, it is not only (or perhaps even primarily) an inhibitory control task'. The MDOR task is a modification of the pre-existing delayed oculomotor response (DOR) or memory guided saccade (MGS) tasks. In this task, the participant is required to look at a central fixation point, and is briefly shown a peripheral stimulus whilst the fixation remains present. Once the fixation point is extinguished, the participant makes a saccadic eye movement towards the location where the peripheral stimulus had been presented.

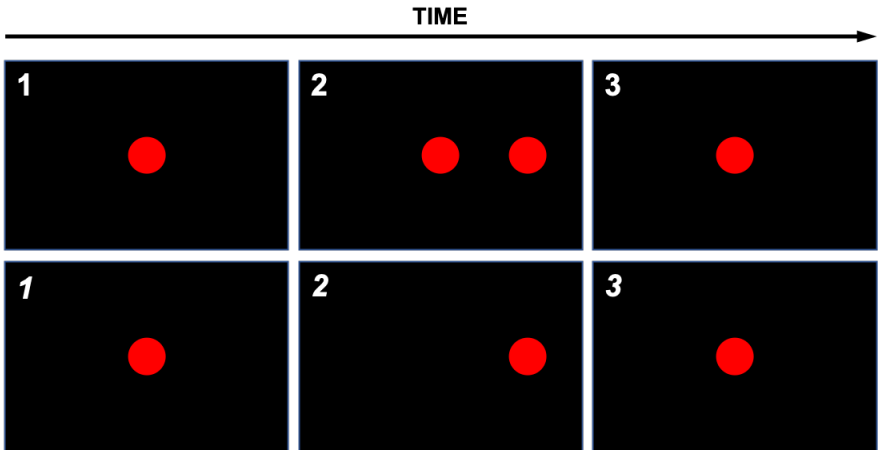


Figure 33 - Stimuli presentation in Pro-Saccade Task. Top row indicates presentation with fixation constant. Lower row with extinguishing of fixation

Order of presentation in Pro-Saccade task with fixation:

1. Fixation target presented in middle of screen
2. Peripheral stimulus presented, participant is required to look at the new stimulus
3. Peripheral stimulus is extinguished, participant returns gaze to fixation

Order of presentation in Pro-Saccade task with extinguishing of fixation:

1. Fixation target presented in middle of screen
2. Fixation target extinguished simultaneous to generation of peripheral stimulus. Participant looks at new stimulus.
3. Peripheral stimulus extinguished simultaneous to generation of fixation target.

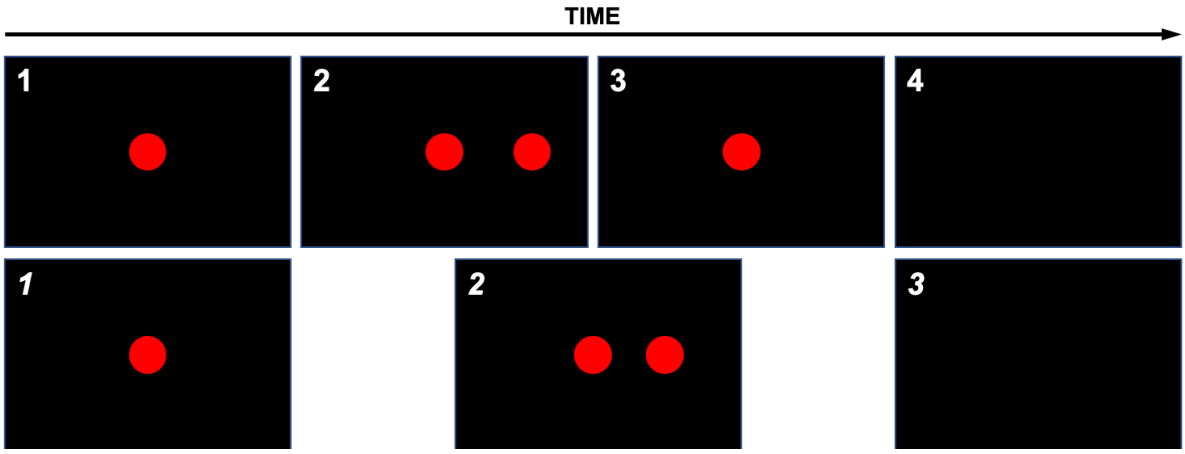


Figure 34 - Stimuli presentation in DOR/MGS and MDOR tasks. Top row indicated presentation order of DOR/MGS. Lower row indicates presentation order of MDOR

Order of presentation in DOR/MGS task:

1. Fixation target is presented in middle of screen
2. Peripheral stimulus is presented in addition to central fixation. Participant to maintain fixation and not to look at peripheral stimulus, but rather to remember the location
3. Peripheral stimulus extinguished. Participant continues to maintain fixation
4. Fixation target extinguished, participant executes saccadic eye movement towards location where peripheral stimulus was previously presented.

Order of presentation in MDOR task:

1. Fixation target is presented to middle of screen
2. Peripheral stimulus is presented in addition to central fixation. Participant to maintain fixation and not to look at peripheral stimulus.
3. Both fixation target and peripheral stimulus are simultaneously extinguished. Participant to execute saccadic eye movement towards location where peripheral stimulus was previously presented.

4.2.3 Self-paced saccades

A self-paced saccadic task has been used previously in Winograd-Gurvich et al. (2003), and is a task where the participant is required to alternate their fixation between two targets as quickly as possible. Self-paced saccades have also been measured in other neurodegenerative conditions (Winograd-Gurvich et al. 2006). Self-paced tasks are used in the UHDRS, i.e. finger tapping, but assessment of these tasks are subjective. Self-paced saccades could potentially be an objective alternative.

4.2.4 Motion Sensitivity

As both saccadic eye movements and smooth pursuit eye movements appear to be fully intact, the motor component of the OKN response we suspect that there could potentially be an abnormality in motion sensitivity in HD.

4.3 Cohort cross matching, age versus IQ

In the first HD study, each participant recruited into the control cohort was age matched to a participant from the HD cohort. This was to ensure that any differences found between the two groups in regards to their oculomotor testing, was not potentially due to age related decline. As shown in the previous chapter, error rate and saccadic latency were substantially increased in the HD cohort relative to the control cohort. It is suspected that this is purely due to the loss of inhibitory control in participants with HD.

However, as has been shown in previous studies (Evdokimidis et al. 2002) there is a correlation between relative performance in the anti-saccade task, and IQ. Due to this, investigation into the IQ status of both the control group, and the HD group will be required.

Ideally a measure of pre-morbid, and current IQ shall be required. After consulting Professor Robert Snowden (School of Psychology, Cardiff University), the following two IQ tests will be administered during this study. The Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II), and the Test of Pre-morbid Function (TOPF).

4.3.1 WASI-II

The Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II) is an individually administered assessment of the intelligence of examinees aged 6 years to 90 years. The original WASI was developed to provide a quick and robust assessment of intelligence in research and clinical settings. The four subtests were chosen for their association with general cognitive abilities and their relationship to constructs of intelligence (Wechsler 1997). Short forms of the Wechsler intelligence scales have been favoured by clinicians and psychologists as a quick estimate of intellectual functioning (Crawford et al. 2010). Such shortening of the intelligence scales were generally ad-hoc, in response to time restrictions or patient fatigue. This resulted in various, non standardised methods of shortening the Wechsler scales (Alley, Allen and Leverett 2007; Axelrod, Ryan and Ward 2001; Schwean and Saklofske 1998). This lack of a standardised abbreviated form of a Wechsler intelligence scale resulted in the development of the WASI.

The WASI-II provides composite scores which estimate intellectual functioning in two areas, intellectual functioning and general intellectual ability. The WASI-II is comprised of four subtests: Block Design, Similarities, Verbal Reasoning, and Vocabulary. Administration of all four subtests quickly estimates the verbal, non-verbal and general cognitive functioning of

an individual in 30 minutes. Administration of two subtests (vocabulary and matrix reasoning) provide an estimate of general cognitive function in 15 minutes (Wechsler 2011). Compared to other short form IQ measures, the WASI-II holds a number of advantages:

- The test is easy to administer and score, and can be administered with minimal appropriate training
- Both the two and four subset forms are efficient and accurate measures of IQ.
- IQ measures recorded using the WASI-II correlate strongly with those recorded using the Wechsler Adult Intelligence Scale (WAIS) (Wechsler 2011).

The inherent limitation of the WASI-II is that there is a modest sacrifice of clinical accuracy due to being designed to be expeditious. The WASI-II also omits subtests used in the WAIS, and other full scale IQ measures, and therefore does not provide a comprehensive assessment of IQ. Despite the limitations, the WASI-II is appropriate to be used where a full battery of IQ testing is not required, for example obtaining estimated IQ scores for research purposes.

4.3.2 TOPF

The Test of Premorbid Function (TOPF) is a revision of the Wechsler Test of Adult Reading (WTAR). The WTAR was developed to provide clinicians and psychologists to assess premorbid intellectual and memory abilities, and was designed and co-normed with the WAIS-III. This co-development of the WTAR and the WAIS-III enables direct comparison between the estimates of intelligence recorded in the tests, however studies have shown that the WTAR underestimates IQ in those with dementia (Mcfarlane, Welch and Rodgers 2006), traumatic brain injury (Green et al. 2008), and aphasia (Leritz et al. 2010). Underestimations were also observed in the highly educated (Ball et al. 2007). Following an

evaluation of the psychometric properties of the WTAR, amendments were made for the TOPF, most notably an increase in difficulty of the test.

The TOPF utilises words of irregular pronunciation to minimise the current ability of the participant to apply standard pronunciation rules, and instead isolates the previous learning of the word (Grober, Sliwinski and Korey 1991). As with the WASI-II, the TOPF provides a quick and robust estimations, and can be administered with minimal appropriate training.

4.4 Aims

4.4.1 Trialling novel paradigms in HD

In chapter 3, based of observations in the literature we aimed to establish a comprehensive battery of oculomotor tests, and to assess the accuracy of subjective eye movement scoring in the UHDRS without our objective measures. The novelty of this battery is due to new application of oculomotor paradigms to HD as a battery, as opposed to the investigation of EM utilising those individual paradigms.

As previously discussed in 3.6.6, the anti-saccade task may not be a pure measure of impulse control. Therefore an alternative oculomotor assessment which more specifically isolates impulse control should be used. It is believed that the MDOR task is 'less contaminated by additional executive function processes, to investigate oculomotor inhibitory control' (Woolohan and Knox, 2014). The MDOR task is described in 4.2.2. The MDOR task is yet to be utilised in a clinical group, so its use with HD would be novel.

4.4.2 Assess the potential relationship between motion sensitivity and OKN in HD

Impairment of motion sensitivity has been reported in HD (Filoteo et al. 1995; O'Donnell et al. 2003; O'Donnell et al. 2008; Muratori, Evinger and Reilmann 2016; Matheis et al. 2019). We are yet to isolate if this impairment of motion sensitivity is associated with the abnormalities in OKN observed in chapter 3. It is crucial to investigate if there is a link between motion sensitivity and the abnormalities in OKN observed in HD.

4.4.3 Establish the effect of IQ on oculomotor performance in HD

There is evidence in the literature that there is a link between IQ and performance in the anti-saccade task. There is however only a weak link between IQ and inhibitory control. Investigating performance between the IQ and performance in the MDOR task may indicate a potential correlation between these two measures. Although investigation of the relationship between IQ and inhibitory control may not be novel, potentially isolating a correlation through the use of EM is novel.

4.5 Study Design

4.5.1 Recruitment of HD and control cohorts

Participants for the HD cohort will be recruited from those attending the South Wales Huntington's Disease clinics in Cardiff. Most patients will already be recruited to ENROLL-HD, a global observational study of HD. As part of this study, patients are also asked if they would like to consent to be contacted in between visits. For patients who have provided consent to be contacted, a copy of the participant information sheet with an accompanying cover letter are to be sent to their home address. Additionally potential participants with HD may be identified at the South Wales Huntington's Disease clinic by Professor Anne

Rosser, and provided with a participant information sheet during their visit. Should the potential participant be interested in participating in the study, they will be offered the opportunity to complete the testing on the same day should it be convenient, and if they are satisfied that they have had full opportunity to consider the information included within the participant information sheet.

Participants for the control cohort will be recruited either through the community panel at the School of Psychology at Cardiff University, or through the eye clinic at the School of Optometry and Vision Sciences. The community panel holds a database of individuals who have indicated, via online questionnaire on the School of Psychology website, that they are interested to participate in research, and are happy to be contacted for future studies.

The eye clinic is a semi-independent optometric practise within the School of Optometry and Vision Sciences. Volunteers for the 3rd year undergraduate primary care clinic complete a form upon attending their appointment, and may indicate via this documentation if they wish to be contacted for future studies.

4.5.2 Ethical Approval

Ethical approval for the study was submitted via IRAS (project ID 198487), and favourable opinion was provided by the North of Scotland Research Ethics Committee on 26th July 2017. A copy of the approval letter is included within the appendix.

4.5.3 Exclusion Criteria

HD Cohort:

- Under 18 years of age
- Have not undergone genetic testing for HD
- Cognitive impairment or communication impairment that would affect informed consent and/or cooperation
- Visual impairment not correctable with glasses
- Evidence of eye disease that would interfere with quantitative eye movement assessment
- Co-morbidity that would interfere with the quantitative eye movement assessment
- Unstable psychiatric disease

Control Cohort:

- Under 18 years of age
- At risk of HD or known HD positive gene status
- Cognitive impairment or communication impairment that would affect informed consent and/or cooperation
- Visual impairment not correctable with glasses
- Evidence of eye disease that would interfere with quantitative eye movement assessment
- Co-morbidity that would interfere with the quantitative eye movement assessment
- Unstable psychiatric disease

4.6 Proposed protocol for the measurement of eye movements in HD

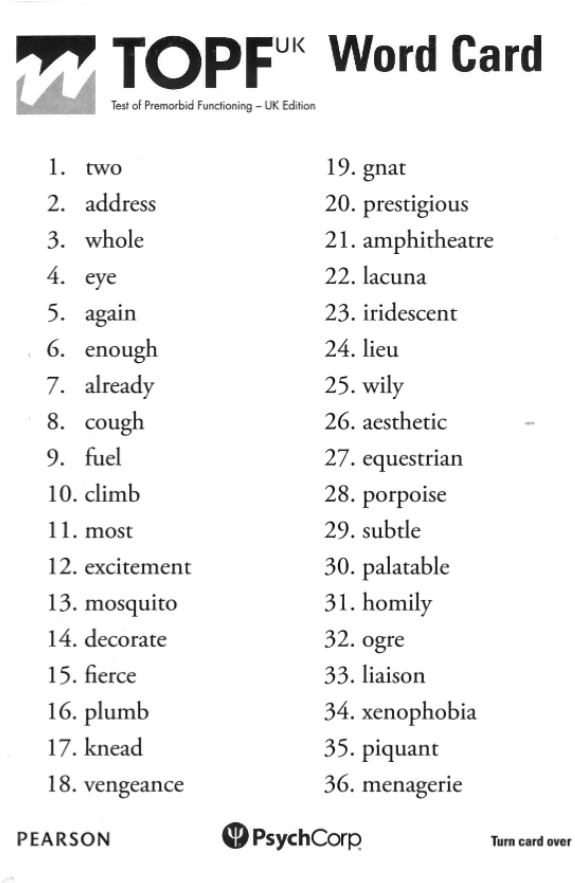
4.6.1 Set-up and materials

4.6.1.1 Visual Acuity

For the assessment of visual acuity an ETDRS chart shall be used, positioned at 4m

4.6.1.2 TOPF

As described in 4.3.2 the TOPF shall be used to assess the premorbid IQ in participants. The edition that shall be used will the TOPF^{UK} (Test of Premorbid Function – UK Edition). This consists of a double-sided word card which shall be presented to the participant. The figure below shows the front of the card.


TOPF^{UK} Word Card

Test of Premorbid Functioning – UK Edition

1. two	19. gnat
2. address	20. prestigious
3. whole	21. amphitheatre
4. eye	22. lacuna
5. again	23. iridescent
6. enough	24. lieu
7. already	25. wily
8. cough	26. aesthetic
9. fuel	27. equestrian
10. climb	28. porpoise
11. most	29. subtle
12. excitement	30. palatable
13. mosquito	31. homily
14. decorate	32. ogre
15. fierce	33. liaison
16. plumb	34. xenophobia
17. knead	35. piquant
18. vengeance	36. menagerie

PEARSON PsychCorp Turn card over

Figure 35 - TOPF Stimulus Card

4.6.1.2 WASI-II

As described in 4.3.1 the WASI-II shall be used to assess the current IQ of the participants. To ensure that the procedure is tolerable for participants with HD, and due to the fact that the estimating of IQ is not the primary area of interest, we shall be using the two-subset configuration of the WASI-II. This shall consist of matrix reasoning, and vocabulary testing. The WASI-II is administered using a stimulus book, presenting the required matrices and vocabulary to the participants.

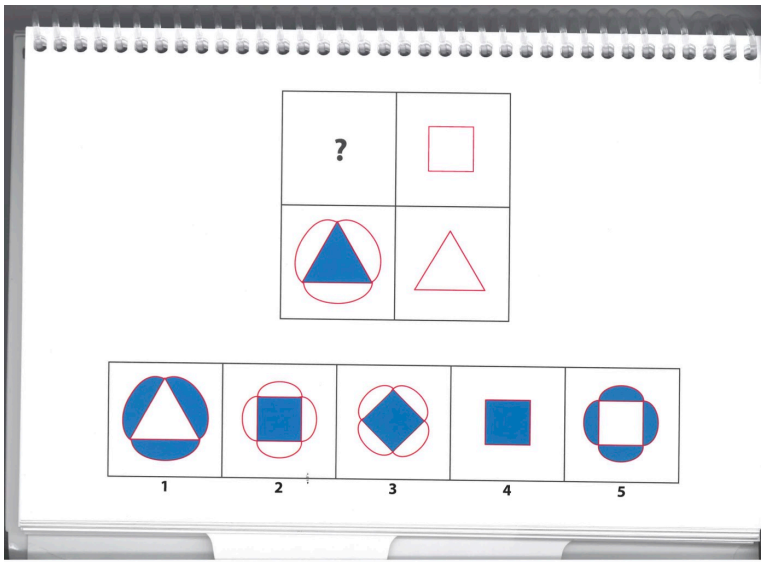


Figure 36 - Matrix Reasoning Page from the WASI-II

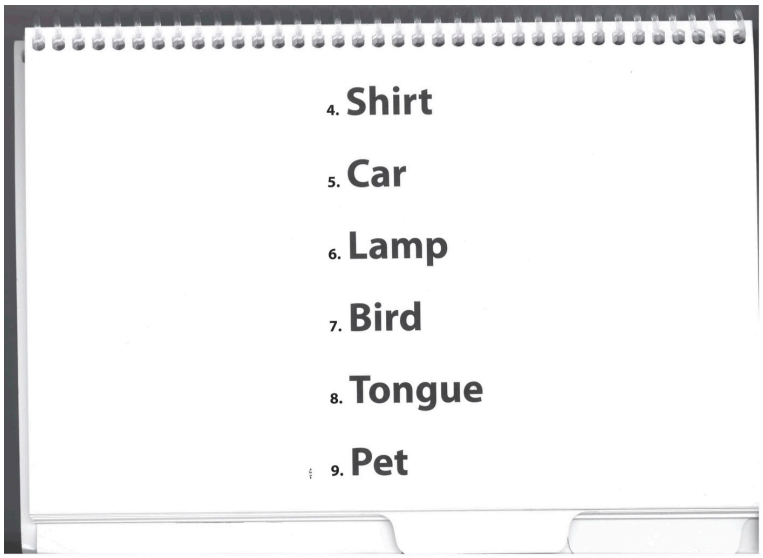


Figure 37 - Vocabulary Page from the WASI-II

4.6.1.3 Oculomotor Testing

In 1.7.4.2, it was discussed that the EyeLink1000+ can be mounted in three different configurations. Previously we have used the desktop mount, and the tower mount to record data from the participants. It was observed however that HD participants with chorea struggled to maintain a stationary position whilst using the chinrest. Movement away from their primary position also appeared to increase the severity of their chorea. This resulted in a somewhat paradoxical situation where using a chinrest reduced the ability of the participants to remain stationary. Therefore, for this experiment we shall be reverting to a 'head free' set up using the arm mount configuration. This should still permit tracking at a high temporaral resolution.

Figure 38 - EyeLink 1000 in the arm mount configuration

4.6.1.4 Motion Coherence

A limited lifetime dots paradigm shall be used to measure motion coherence. The stimuli shall be generated using PsychoPy. Participants shall indicate their responses to the stimuli using a Contour ShuttleXpress shuttle wheel. The shuttle wheel will allow participants to rotate a wheel to modify the coherence of the stimuli shown on the screen. Due to compatibility issues, between the shuttle and the lab computer , the stimuli shall be presented on a MacBook Pro.

Figure 39 - Contour ShuttleXpress

4.6.2 Procedures

1. Having previously been provided with a participant information sheet, and given the opportunity to discuss any concerns regarding the testing, the subject is to provide their consent on the appropriate consent form. Consent shall be received in the School of Optometry and Vision Sciences or the Cardiff Huntington's Disease clinic.
2. Subject is to have their visual acuity measured, and to briefly be questioned regarding potential ocular pathology which may inhibit their ability to undertake oculomotor testing.
3. Subject is to complete the TOPF and WASI-II IQ testing
4. Subject is to be relocated to the eye movement lab
5. Room lights are to be extinguished, and the EyeLink is to be focused and calibrated
6. The oculomotor protocol is to be administered:

   Phase 1 – Self-Paced Saccades

Phase 2 – MDOR

Phase 3 – OKN (Stare, Monocular and Binocular and Look)

7. Subject is to complete the motion coherence experiment
8. Subsequent to the completion of the above tests, or non-completion of the above, be it due to technical, time reasons or otherwise, the subject shall be invited to complete a questionnaire regarding their experience. A copy of this questionnaire is included within the appendix.

4.6.3 Subject Instructions

4.6.3.1 Visual Acuity

'I would like you to read the letters on the chart starting from the top, and going down as far as you can. Don't worry if you get them wrong, just go as far as you can'

4.6.3.2 TOPF

'You will see on the card in front of you that there is a list of words. You may be familiar with most of these, but there will be some which you do not know. What I need you to do here is to read each word out to me. Don't worry if you do not know how to say it, just give it your best attempt'

4.6.3.3 WASI-II

General instruction, adapted from that set out in the WASI-II manual:

'We will be doing a few different things today, which will include looking at some puzzles, and also answering some questions. Generally these start off quite easy, and shall become progressively more difficult. Most people will not get everything correct, and you may find that you don't know the answer to some questions. Try not to worry about this, I would just like you to try your best.'

Vocabulary:

‘For this test I will be showing you a book of words, and will read each one out to yourself. What I would like you to do is to describe what the word means. For example if the word is car, I would like to describe what a car is. For example, a vehicle that you will drive, it has four wheels, tyres and a steering wheel. Do you understand what you need to do?’

Matrix Reasoning:

‘For this test I will be showing you a book of puzzles. What I need you to do is to choose which picture fills the missing piece of the puzzle. We will start off with a few examples to get you into the swing of things, and if you aren’t quite sure I will talk you through it. Do you understand what you need to do?’

4.6.3.4 Self-Paced Saccades

‘You will be shown two spots on the screen in front of you. What I would like you to do is to switch your fixation between the two spots and quickly as you can. You may find this a little fatiguing, but do try your best. I will give you a time check approximately halfway through so that you know how far you are through this test.’

4.6.3.5 MDOR

The below instruction is given whilst a trial stimulus is shown on the screen

‘For this task, you will be shown a spot on the screen. This dot will start off in the middle, then move to one side, and then disappear. What I would like you to do is to look in the middle of the screen, and when the spot moves, keep looking at the same place. When the spot disappears from its second location, I would like you to look at the point it disappeared from. It does seem a bit counter intuitive, but I will talk you through a few examples so that

you get the idea. You will get some wrong, but that is ok, everyone makes mistakes with this, so just try your best. Do you understand what you need to do?'

4.6.3.6 OKN

For stare OKN, the instructions that shall be used are the revised instructions presented in 3.4.2.4.

For look OKN the following instructions shall be used:

'In this test, we will be using the stripes again. When we tested before I wanted you to try to stare at the middle of the screen. This time I would like you to follow the stripes in the way that feels comfortable'

4.6.3.7 Motion coherence

As the below instructions are provided, the stimuli shall be demonstrated on the screen, with the 1.0 coherence (all dots moving in the same direction) and 0 coherence (random movement of dots) both shown to the participant.

'On the screen you can see a set of white dots moving together in one direction, and now when I turn this wheel, you can see that the dots are moving around with no particular pattern. What I would like you to do, is to find the point at which the pattern becomes completely random, and that you cannot see a general trend of the dots. Do you understand what you need to do?'.

4.7 Results

A total of 29 participants were recruited into this study, 18 participants for the HD cohort, 11 participants for the control cohort. All participants completed the tasks successfully.

4.7.1 Optokinetic Nystagmus

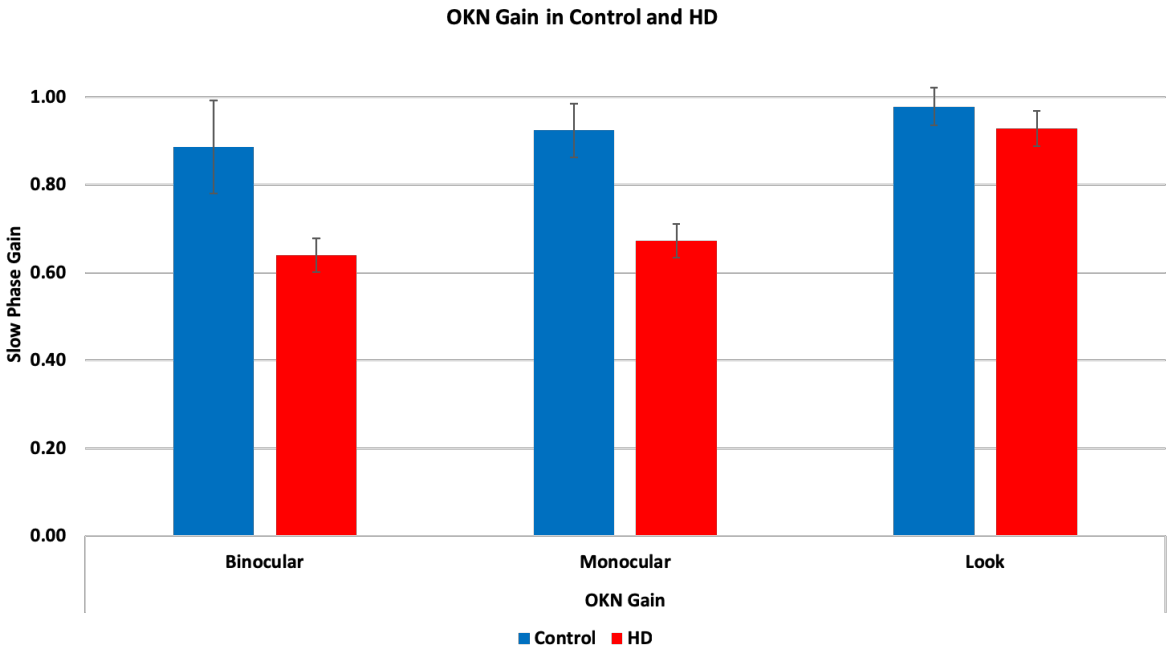


Figure 40 - OKN Gain in Control and HD

In chapter 3, abnormalities in HD were observed, with a reduced OKN gain, and with some participants an absolute absence of OKN. With this study we tested OKN under monocular and binocular conditions for a prolonged period of time, and also tested look OKN. As can be seen from the above results (Figure 40), the mean slow phase gain for the HD cohort is significantly lower than that seen in the control cohort under both monocular (P=0.001) and binocular conditions (P=0.01). There is no significant difference between the two cohorts under the look condition.

4.7.2 MDOR

Virtually all participants from both the control and HD cohort did not undertake the task correctly. It is clear from the raw data prior to analysis that participants were treating the MDOR task as a pro-saccade task, despite being instructed how to complete the MDOR task. Therefore the results from the MDOR task are not appropriate as the participant understanding of the task was insufficient. Below is a latency distribution for this task. Latency is measured from the appearance of the stimuli. The participants are required to initiate a saccade once the stimuli is extinguished. This should produce a bimodal distribution with the greatest frequencies approximately 200ms after the two durations of the stimuli (200ms and 1000ms). As can be seen in the below figure, there are very few saccades made at the 1200ms mark, or thereafter. The majority of the saccades initiated are below 400ms.

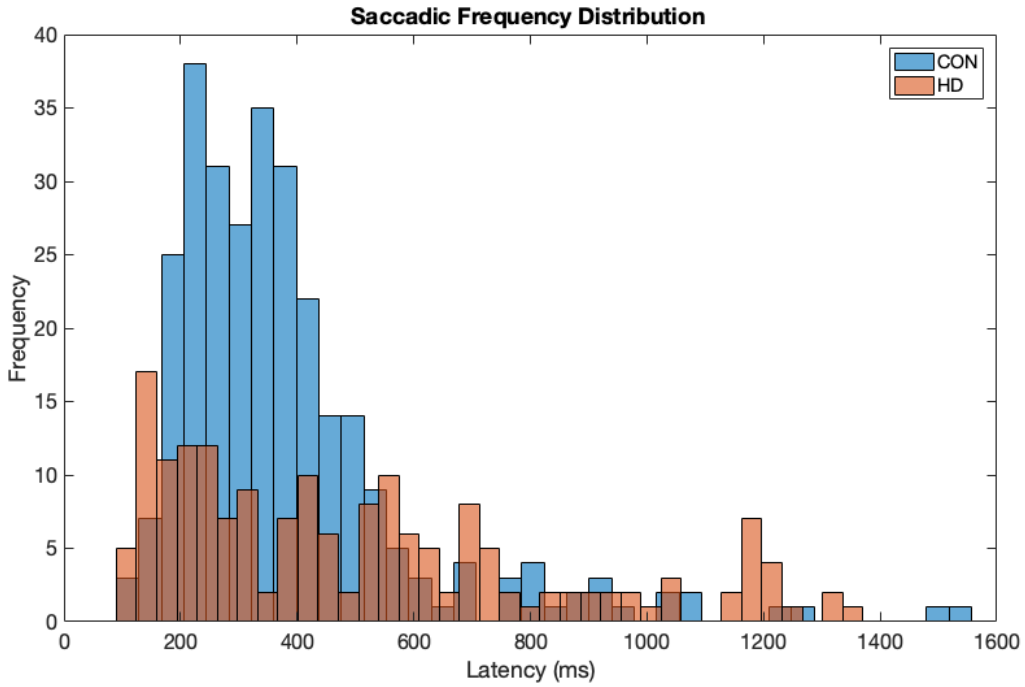


Figure 41 - Distribution of Latencies during the MDOR Task

4.7.3 Self-paced saccades

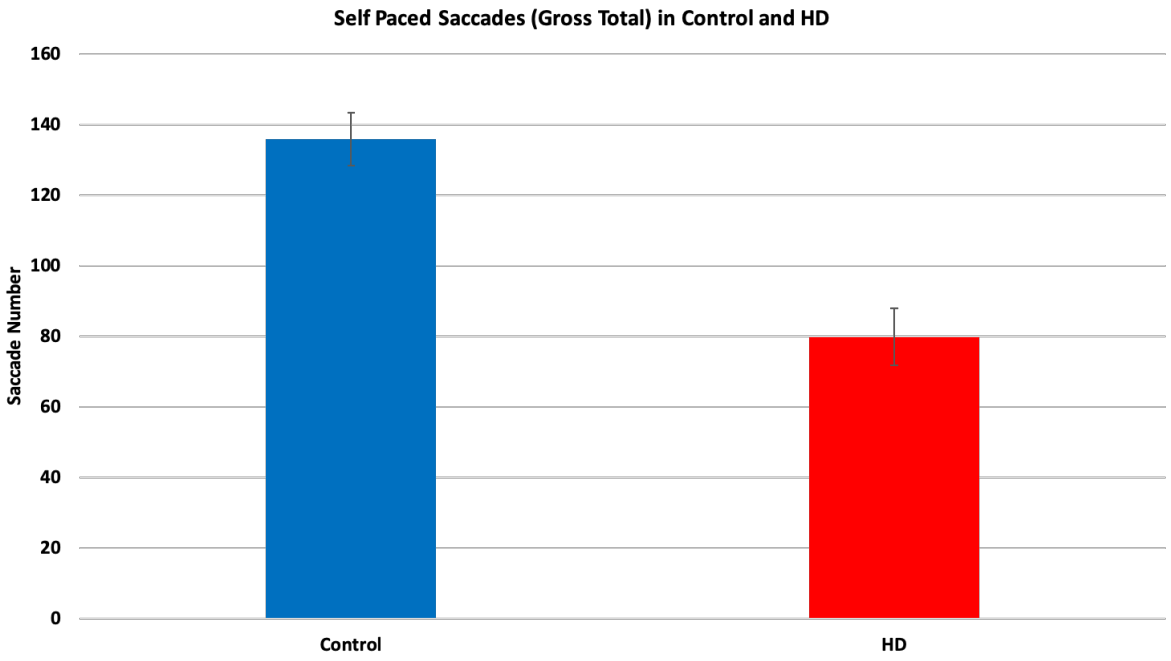


Figure 42 - Mean gross total of saccades completed during the self-paced saccade task for the control and HD cohorts

The above figure shows the gross total number of saccades made during the self-paced saccade paradigm for both cohorts. There is a significant difference between the two groups ($P<0.001$), with the control group making 56 more saccades during the 60 second test period. Winograd-Gurvich et al. 2006 is the only previous paper to use the self-paced task with HD, and also demonstrated a significant difference between control and HD. However, the frequency of saccades reported in the cohorts were substantially lower than those recorded within this study. It is not immediately clear within the paper if the definition of total number of saccades equated to a gross number of all saccades, or if this paper classified a saccade as an alternation. It is also not clear if the instructions requested accuracy, resulting in a speed-accuracy trade off, or just for participants to initiate saccades as quickly as possible.

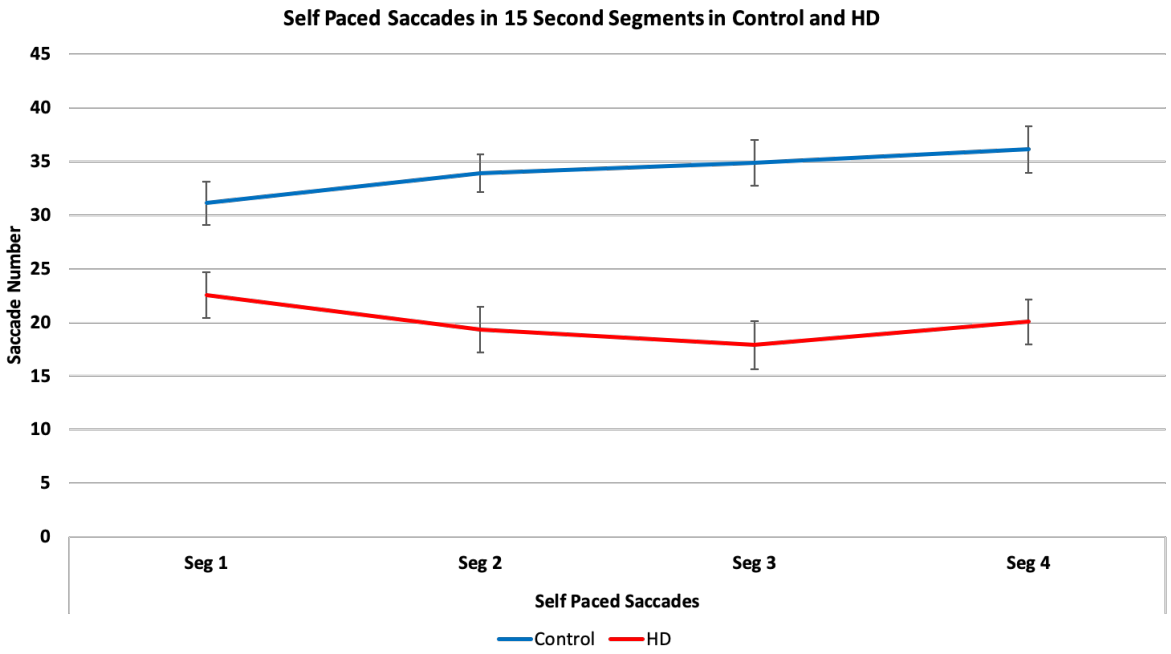


Figure 43 - Mean number of saccades made per 15 second segment in control and HD

The gross number of self-paced saccades are significantly different between the two cohorts, with the HD cohort making approximately 40% fewer saccades than the control group. Figure 42 above demonstrates that when analysing the self-paced saccade paradigm in 15 second segments, participants with HD make fewer saccades than the control group from the start of the paradigm until the end. The difference between the two cohorts is significant for all four segments ($P<0.05$ for the first segment, $P<0.0001$ for the remaining segments). There does not appear to be any significant change in the frequency of the saccades with respect to time.

4.7.4 Motion Sensitivity

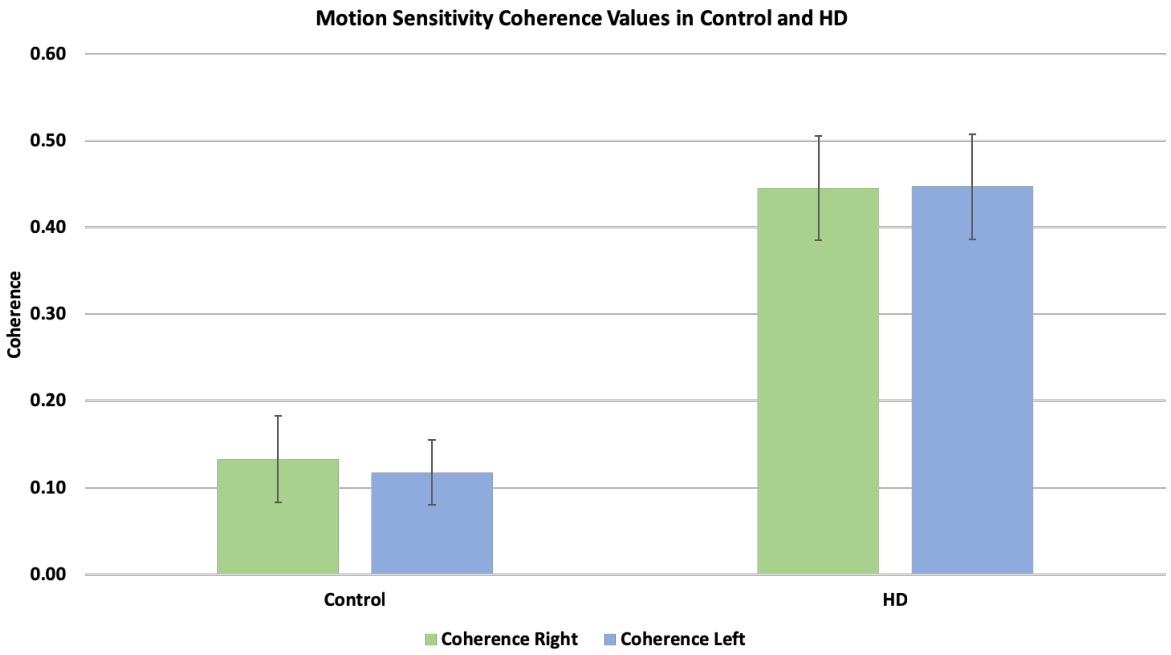


Figure 44 - Motion coherence threshold values for the control and HD group

Motion sensitivity coherence values for the two cohorts are presented in the above figure.

There is a significant difference between the two cohorts ($P<0.01$) for both directions.

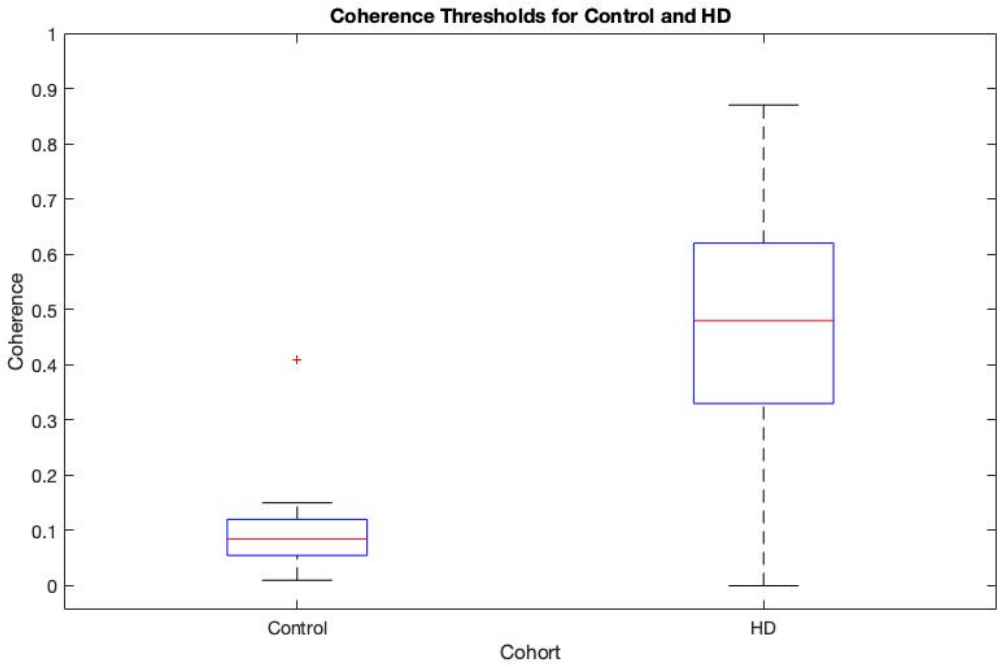


Figure 45 - Motion coherence threshold values for the control and HD group

4.7.5 IQ Testing

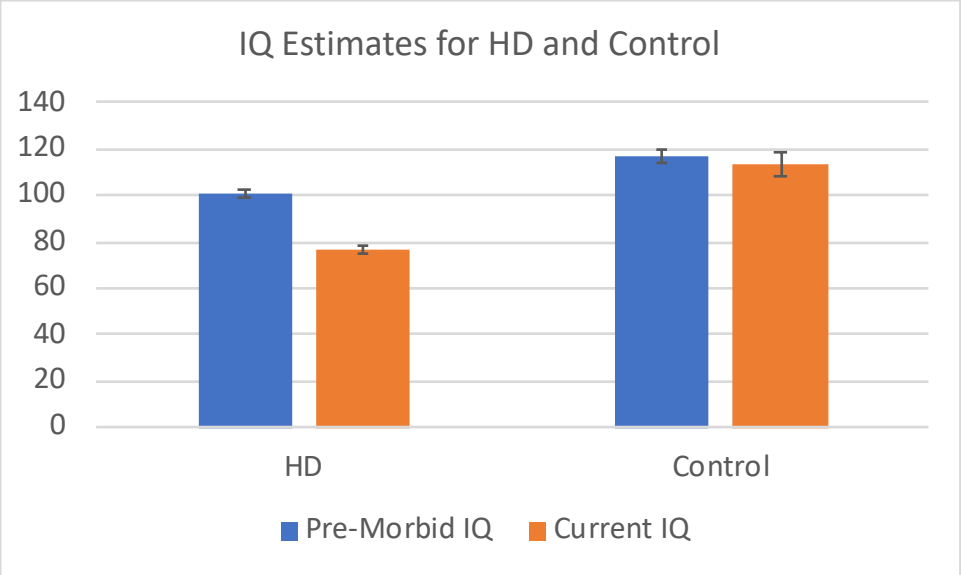


Figure 46 - IQ estimated for the HD and control cohorts. The pre-morbid IQ scores were recorded using the TOPF, and the current scores were recorded using the WASI-II

There is a significant difference between the current IQ, and pre-morbid IQ in the HD group ($P<0.0001$), whereas there is no significant difference between the pre-morbid and current IQ in the control cohort. There is a significant difference between both the premorbid, and current IQ between the two cohorts ($p<0.0001$).

4.8 Discussion

4.8.1 Performance of cohorts in novel tasks

Participants with HD appeared to struggle significantly with the novel tasks. In the self-paced saccade task, there was a significant difference between the two cohorts. Deficient performance in the self-paced task has previously been reported (Winograd-Gurvich et al. 2003), however there is a discrepancy between the numbers obtained in this study relative to that which has been previously reported. The mean number of self-paced saccades completed by a control participant in this study (136) equates to 2.27 per second. The HD group completed 80 per minute, 1.34 per second. In Winograd-Gurvich et al. 2003, control participants completed 72 saccades over 90 seconds (0.8 saccades per second) with the HD group completing 40 saccades in the same time period (0.67 per second).

As demonstrated earlier in this thesis, and in previous studies, pro-saccadic latency is approximately 200ms, and according to the saccadic main sequence (Bahill et al. 1975), the duration of a saccade with an amplitude of 20° is approximately 70ms. Healthy adults make approximately 3 saccades per second (Ibbotson and Krekelberg 2012), and subsequent saccades may be planned during the initiation of an existing saccade resulting in a shorter secondary saccade latency (Araujo, Kowler and Pavel 2001). The likelihood that a healthy adult would not be able to complete a self-paced saccade task at a rate of at least 1 saccade per second is unlikely, therefore the data presented for self-paced saccades in Winograd-Gurvich et al. (2003) may not be accurate. It is notable however, that the ratio of saccades made between the cohorts is relatively consistent. Individuals with HD making fewer saccades than controls is a consistent finding with the previous study.

4.8.2 Assess the potential relationship between motion sensitivity and OKN in HD

In 3.6.4 an impairment of motion perception was suggested as a potential cause for the impairment of OKN. As could be seen from the results presented, there is a significant difference between the two cohorts. During the task 500 limited lifetime dots were presented on the screen to participants in a circular aperture pattern. The dots were moving at 30°/s, the same velocity as the OKN gratings. The mean coherence recorded for the control group is 0.125, with 0.45 recorded for the HD group. In real terms, this equated to the average participant with HD perceiving a pattern with 225 of the 500 dots moving in the same direction as being completely random. Of the 18 HD participants, 7 provided coherence values in excess of 0.50, 3 measurements exceeding 0.70 were recorded in the HD group. Conversely, only one participant from the control group recorded a coherence exceeding 0.15.

Whilst directly observing the participants with HD performing this task, it was abundantly clear that there was deficient motion perception. One participant recorded value of 0.85, in real terms 425 of 500 dots moving together in one direction. Although this is a proof of concept, there is a very clear deficiency in motion sensitivity present.

4.8.3 Establish the effect of IQ on oculomotor performance in HD

The IQ measures recorded for the HD group demonstrated a substantial decline in IQ from their pre-morbid state to their existing IQ. As a group there was a 24 point reducation in IQ, with one participant recording an existing IQ 41 points below that of their pre-morbid status. The percentage of the UK population expected to exhibit a discrepancy of 24 or greater between current and pre-morbid IQ is 0.22%, the percentage of the UK population

expected to exhibit a discrepancy of 30 or more is 0.02% of the population. Of the 18 HD participants, 6 exceeded discrepancies of 30.

4.9 Recommendation for future experiments

The data collected in this chapter demonstrates a significant impairment in motion sensitivity in HD. Whilst administering the task, it became very clear that this impairment is not a subtle change, but a drastic change to the perception of one's environment. The motion sensitivity task performed was included within the protocol as a proof of concept, further investigation with more appropriate and detailed perceptual tasks would be appropriate, where motion sensitivity thresholds could be measured, and quantified more accurately.

Performance during the self-paced saccade task was also significantly impaired in HD relative to the performance of the control group. During the task, participants were required to initiate as many saccades as possible during a 60 second segment. It would appear that the ability to perform the task without signs of impairment is present from the initiation of the task, and there is no significant change in the frequency of saccades during the 60 second time period.

The results of this experiment were substantially different to those presented previously in the literature. It was not clear if this discrepancy could be due to instructional changes, i.e. the previous study encouraging accurate saccades as opposed to initiating as many saccades as possible. Although motion sensitivity may prove to be a potential early biomarker in HD, it will require additional equipment to collect the data, present the stimulus, and potentially

analyse the data. The implementation of self-paced saccades into clinical practise may be more practical, as a gross number of saccades could be recorded subjectively by the practitioner, much in the same was as finger tapping as part of the UHDRS. A comparison between objective and subjective measures of self-paced saccades should be pursued in future.

Chapter 5: CAPIT Study

5.1 Background to study

As established in chapter 1, HD is a complex disorder in which there is a relentless deterioration of motor, cognitive and behavioural functions, usually from midlife onwards. The original Core Assessment Protocol for Intrastriatal Transplantation in Huntington's Disease (CAPIT-HD) battery aimed to capture elements of change in all three domains, but was based predominantly on subjective semi-quantative assessment tools that have poor inter-rater reliability. Moreover, a number of deficits, such as impairments in social cognition, were not recognised when the CAPIT-HD battery was constructed.

Hence, a new clinical assessment battery: Core Assessment Protocol for Intrastriatal Transplantation in Huntingtons's Disease 2 (CAPIT-HD2) has been developed by the REPAIR-HD group, a collaboration between Cardiff University, the University of Manchester, George Huntington Institute Muenster, and Institut national de la sante et de la recherche medical. CAPIT-HD2 represents a substantial revision of the previous CAPIT-HD battery published over 20 years ago, which is in need of updating in order to accommodate knowledge from clinical transplant studies over this time and to take advantage of technological advances in patient assessment.

Beta testing of the CAPIT-HD 2 battery will take place in established clinical centres in Cardiff, Manchester, Paris and Muenster. Patients with early to moderate HD will be

assessed at baseline, with additional visits are one month and one year, to assess the reliability and sensitivity of the battery.

Neurodegenerative diseases are notoriously complex, and clinical studies are often hampered by the difficulties of assessing multiple deficits over a deteriorating baseline. Progress has been made in proving the concept that cell replacement therapy can result in clinical benefit in HD using human primary foetal cells. However, such cells are scarce and ethically problematic. Human Pluripotent Stem cells provide renewable cell sources, but controlling their proliferation and differentiation sufficiently to provide cells suitable for clinical transplantation is key. Co-ordinating the generation of properly specified and safe donor cells with high quality clinical translation is essential for the safety and success of such work, and is also important to secure the future of CNS regenerative medicine by avoiding both serious adverse events and false negative results.

There is increased recognition that HD provides an excellent test-bed for cell replacement therapy. In contrast to Parkinsons disease, where donor cells must be placed ectopically into the striatum, to allow their projection to reach their normal striatal targets, in HD, donor cells are most effective when placed homotopically into their normal position within the striatum. This allows restoration of normal anatomical circuitry, with innervation by host cortical afferents and graft derived innervation of the adjacent globus pallidus. The almost complete gene penetrance and availability of a reliable genetic test allows confident diagnosis of the condition in life, increasing the power and reliability of clinical studies. Additionally the range of excellent animal models of HD greatly facilitates translation between animal and clinical studies.

The REPAIR-HD consortium aims to establish all the components necessary for future high quality clinical studies of pluripotent stem cell transplantation in humans. This will include finalising the stem cell differentiation protocols; validating their functional efficacy in the best animal models; establishing clean room preparation to a medicinal-grade standard; building a cohort of well characterised HD patients willing to participants in a clinical trial; establishing the test batteries required to assess all aspects of disease symptoms and progression; and finally, engaging with national and European regulatory agencies to establish the ethical and safety approvals required to start a trial at the end of this preparatory programme.

5.2 Aims

5.2.1 Rationale

Central to the investigation of any experimental therapy is the proper design and application of valid assessment. This is particularly relevant in neural transplantation, where the numbers of trial patients will invariably be small, the potential benefits are slow to develop, and recovery is likely to require a considerable amount of time (potentially up to 10 years) to reach maximum levels. In addition, we need to be able to gauge improvements against a background of progressive deterioration in the underlying condition.

The original CAPIT (Quinn et al. 1996) consisted of the UHDRS (previously discussed in Chapter 1), an extensive battery of neuropsychological tests, comprehensive neuropsychiatric tests, and imaging. However since its development in 1996, there has been an emphasis on developing quantitative motor (Q-Motor) assessments (Tabrizi et al. 2012;

Reilmann et al. 2015), and the neuropsychiatric scales have been superseded by more specific and better validated measures such as the Problem Behaviours Assessment scale.

5.2.2 Study Objectives

The overall objective of the study is to develop a comprehensive battery of assessments for application in cell transplantation therapies in HD. A beta testing protocol for CAPIT-HD2 will be implemented across four Repair-HD sites in the UK, Germany and France. The number of HD patients recruited will remain flexible depending on the results of on going data analysis and the introduction of additional existing and novel assessments. Age matched healthy control participants will be recruited into the study (not exceeding more than one third of total participants) to provide reference data for the novel assessments. This flexible approach will ensure feasibility and that sufficient numbers are available to provide proper validation of CAPIT-HD 2.

Main Objectives:

1. Validate the discriminative ability of CAPIT-HD2 in HD for the a) motor, b) cognitive, c) psychiatric and d) functional domains of impairment in HD.
2. Assess the feasibility of the combined assessment battery in terms of visit completion rates, retention of recruited participants (longitudinally) and any documented study related events.

5.3 Study Design

This is an observational cohort study. The participants will be invited for a baseline assessment, lasting a total of 5 hours. On completion of the first assessment, all participants will be invited to return one month later, and one year later. The purpose of the one month assessment is to 'wash out' practise effects. The purpose of the one year assessment is to determine whether the testing can detect change over this period of time.

Practise effects are due to subjects becoming familiar with individual test items. It has been demonstrated that the effects of practise on cognitive assessments is maximal after the second exposure. Practise effects can be washed out by comparing a second visit to any subsequent visit (Bachoud-Lévi et al. 2001).

5.3.1 Recruitment of cohort

Most research sites are Registry/ENROLL-HD sites for the European Huntington's Disease Network (EHDN). The Registry/ENROLL-HD study is a full clinical dataset, including the full medical history (Orth et al. 2010). One of the optional components within this study is the giving of permission by participants to be contacted about other HD research projects. Those who provided such permission will receive an information sheet and an invitation letter about the study that will be sent with a letter confirming their appointment for their annual Registry/ENROLL-HD assessment. Whilst attending this assessment, the potential participant will be invited to discuss the study, and asked if they would like to participate in this study.

5.3.2 Ethical Approval

A favourable opinion was provided by the Health and Care Research Wales Research Ethics Service on 14th December 2015. The REC reference is 15/WA/0428.

5.3.3 Inclusion and exclusion criteria

Inclusion Criteria:

- Must be confirmed to carry the HD gene through genetic testing
- Must be 18 years of age
- Stage I or II disease

Exclusion Criteria:

- The inability to approve consent due to lack of capacity
- Any comorbid conditions that have the potential to confound the results of the study

Normal age matched controls will mostly be recruited by inviting relatives of patients attending the clinics.

5.4 Proposed protocol for measurement of eye movements in HD

5.4.1 Set-up and materials

Due to the start date, we decided to replicate the tests within the first HD study, as we would have the opportunity to test/retest over successive visits, and to supplement that study with effectively a longitudinal aspect, and other measurables.

5.4.2 Procedures

The test procedures shall be the same as those used in the first HD study, as detailed in 3.4.3. There will be no significant change to the instructions given to the participant.

5.4.2.1 Instructions for Pro-Saccade Paradigm

'In this test you will see a red dot on the screen, and it will move from the middle to different locations. All that you are needed to do is to follow it as it moves.'

5.4.2.2 Instructions for Anti-Saccade Paradigm

'In this test you will see a red dot on the screen, and it will move from the middle to different locations. When this dot is at the centre, I would like you to look at it. When it moves away from the centre, do not follow it. You must instead try to look in the equal and opposite direction like a mirror image. Do not worry if you don't get it right every time, you will make mistakes. But it is important that you try your best'.

5.4.2.3 Instructions for Smooth Pursuit

'In this test you will be shown a target moving back and forth across the screen in front of you. I would like you to follow this target to the best of your ability'

5.4.2.4 Instructions for OKN Paradigm

'In this test we will be testing optokinetic nystagmus. This is the sort of eye movement you may have experienced looking out of the train window, that wiggle that you feel your eyes do. To produce this movement, you will be shown a set of stripes moving across the screen. I would like you to try to keep looking at the middle. If you feel your eyes moving, that is fine. Please do not try to follow the stripes. Try to stare at the middle of the screen.'

5.5 Results

5.5.1 Pro-Saccade and Anti-Saccade latency

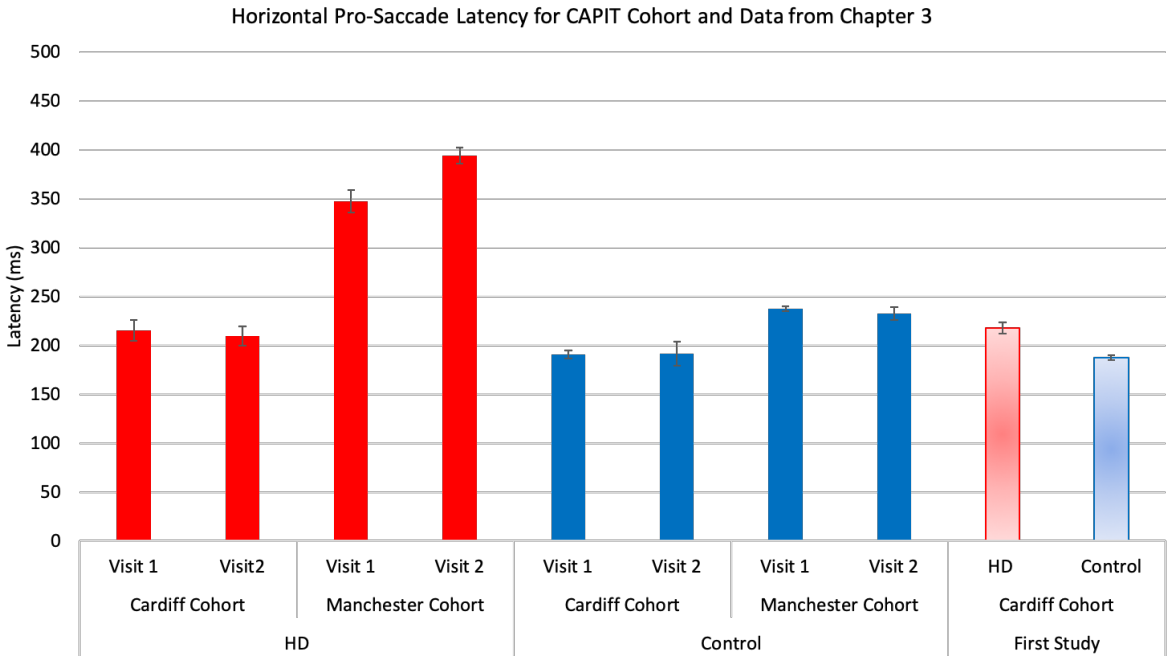


Figure 47 - Latencies for the horizontal Pro-Saccade task in the CAPIT cohort. Also shown is data collected in the 1st HD study for reference

As previously discussed, the oculomotor protocol the participants in the CAPIT-HD undertook is identical to that undertaken by the participants in the first HD study (chapter 3). The horizontal pro-saccade latencies observed in the cohort recruited in Cardiff are consistent with those found in the previous study. There is no significant difference between the pro-saccades latencies between the control cohort and the HD cohort. There is also no significant difference between the latencies recorded between visits for both cohorts in Cardiff, and in Manchester. The latencies recorded from the participants recruited in Manchester are substantially longer than those from Cardiff, for both the HD and control groups. This difference is statistically significant.

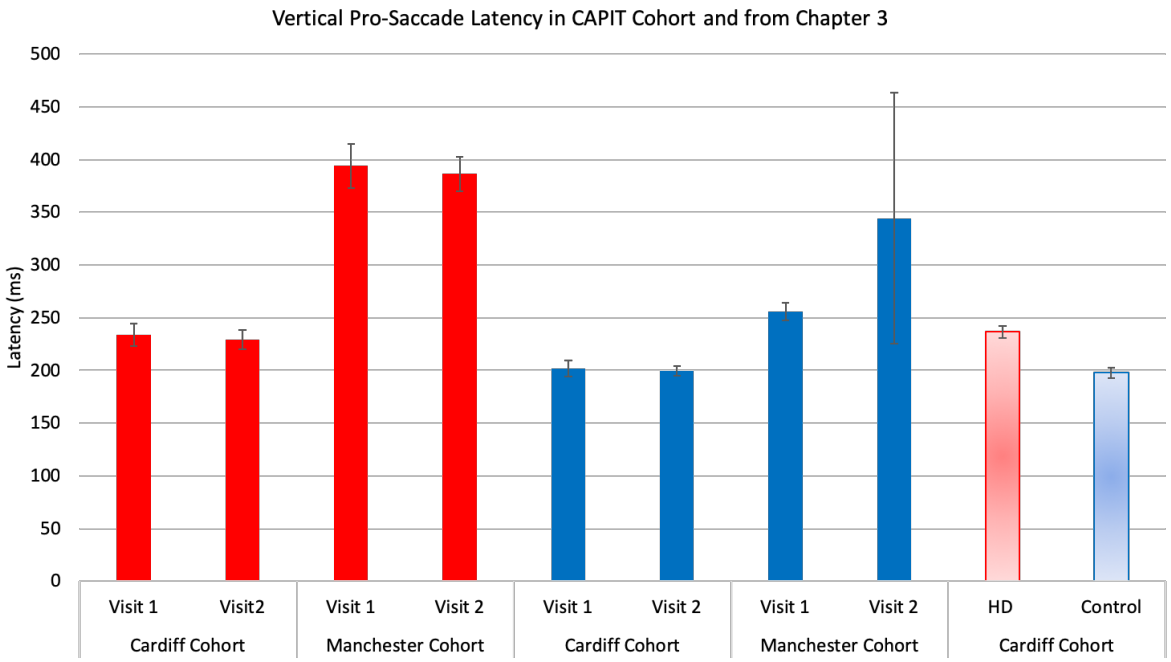


Figure 48 - Latencies for the vertical Pro-Saccade task in the CAPIT cohort. Also shown is data collected in the 1st HD study for reference

As with the horizontal pro-saccade task, there is no significant difference between the vertical pro-saccades latencies between the control cohort and the HD cohort. There is also no significant difference between the latencies recorded between visits for both cohorts in Cardiff, and in Manchester. The latencies recorded from the participants recruited in Manchester are substantially longer than those from Cardiff, for both the HD and control groups. This difference is statistically significant.

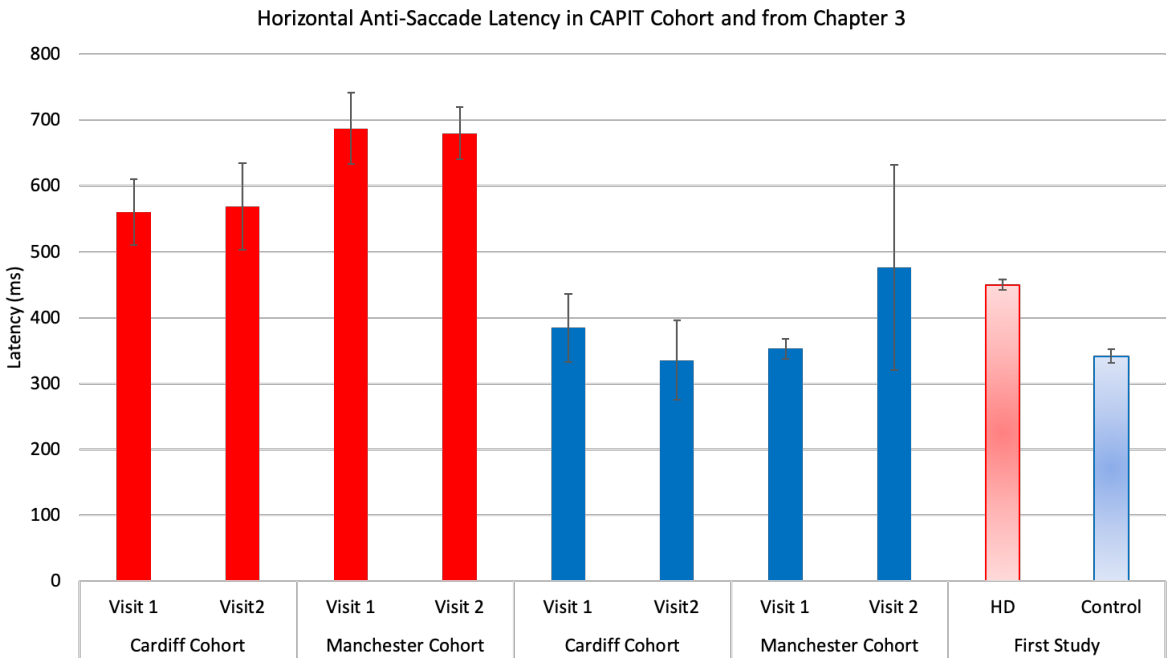


Figure 49 - Latencies for the horizontal Anti-Saccade task in the CAPIT cohort. Also shown is data collected in the 1st HD study for reference

Anti-saccade latency is greater in HD relative to the control cohort for participants recruited at both Manchester and Cardiff. The latencies for the control cohorts for both Cardiff and Manchester are reasonably consistent with that found in the previous HD study. For the Manchester cohort at the second visit there is significant variability in the anti-saccade latency for the control group. This is most likely confounded due to the small cohort (n=3) who returned for a second visit. The anti-saccade latencies for both HD cohorts are greater than those observed in the control cohorts, and are slightly longer than those observed in the previous HD study. There does not appear to be a significant difference in latencies across visits for any group.

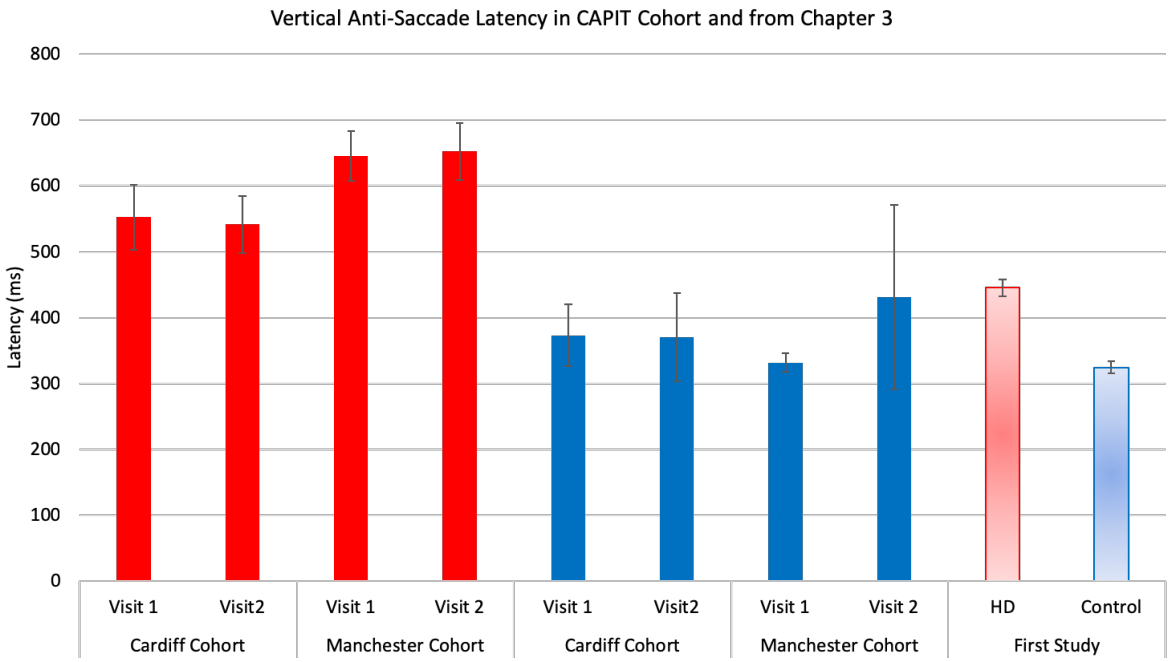


Figure 50 - Latencies for the vertical Anti-Saccade task in the CAPIT cohort. Also shown is data collected in the 1st HD study for reference

As seen in the horizontal task, anti-saccade latency in the vertical task is greater in HD relative to the control cohort for participants recruited at both Manchester and Cardiff. The latencies for the control cohorts for both Cardiff and Manchester are reasonably consistent with that found in the previous HD study. For the Manchester cohort at the second visit there is significant variability in the anti-saccade latency for the control group. The anti-saccade latencies for both HD cohorts are greater than those observed in the control cohorts, and are slightly longer than those observed in the previous HD study. There does not appear to be a significant difference in latencies across visits for any group.

5.5.2 Anti-Saccade Error Rate

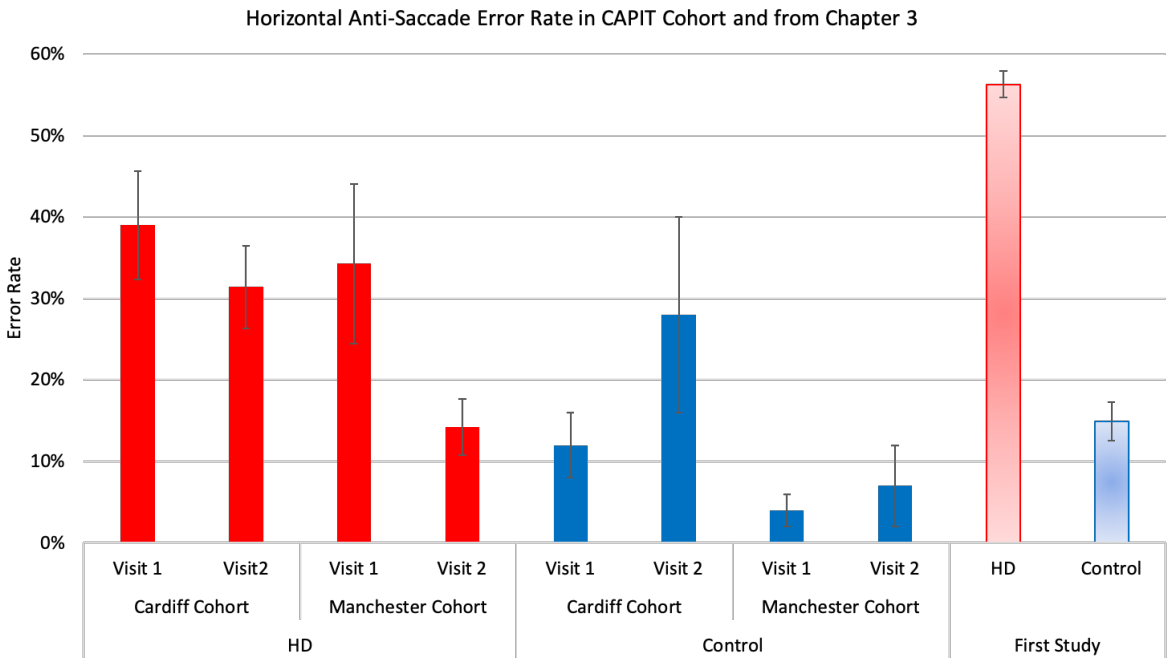


Figure 51 – Error rates for the horizontal Anti-Saccade task in the CAPIT cohort. Also shown is data collected in the 1st HD study for reference

As with the previous study, anti-saccade error rates are greater in the HD participants than that observed in the control participants. There is however a significant difference between visits for the Manchester HD cohort, and for the Cardiff control cohort. In the Manchester HD cohort, the error rate recorded at visit 2 is significantly lower than that observed in visit 1. For the Cardiff control cohort, the error rate is greater than that observed in visit 1. The cohort size for both the second visit at Manchester for HD, and visit 2 at Cardiff for controls are both small, resulting in some ambiguity regarding the accuracy. The error rate for both HD cohorts are lower than that found in the first HD study.

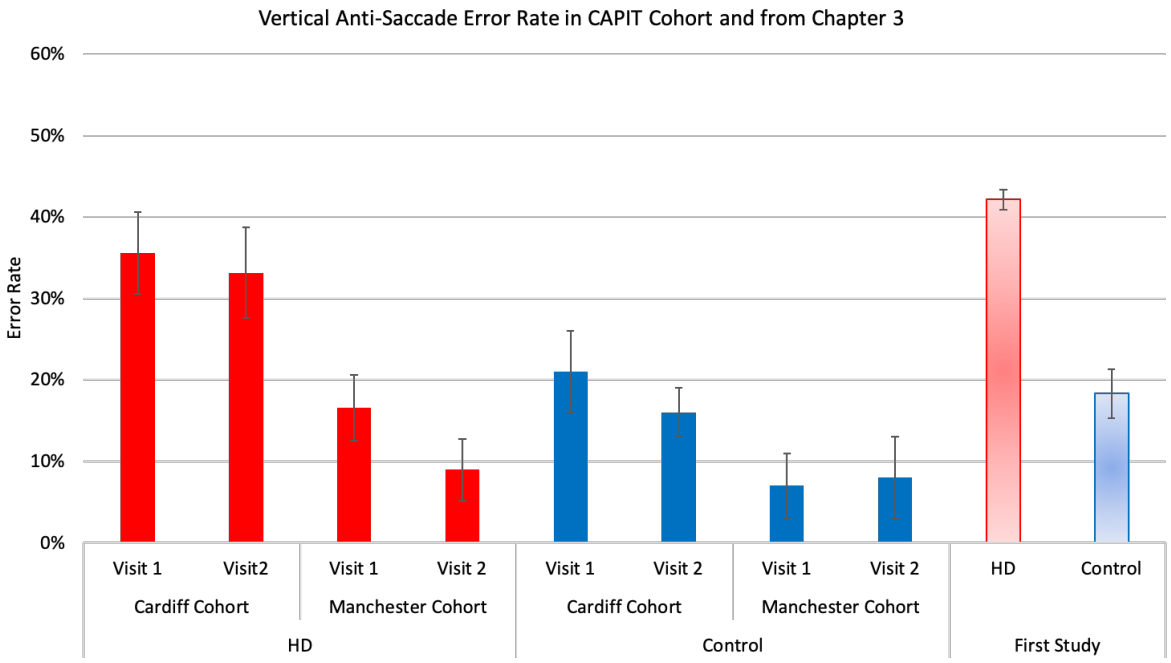
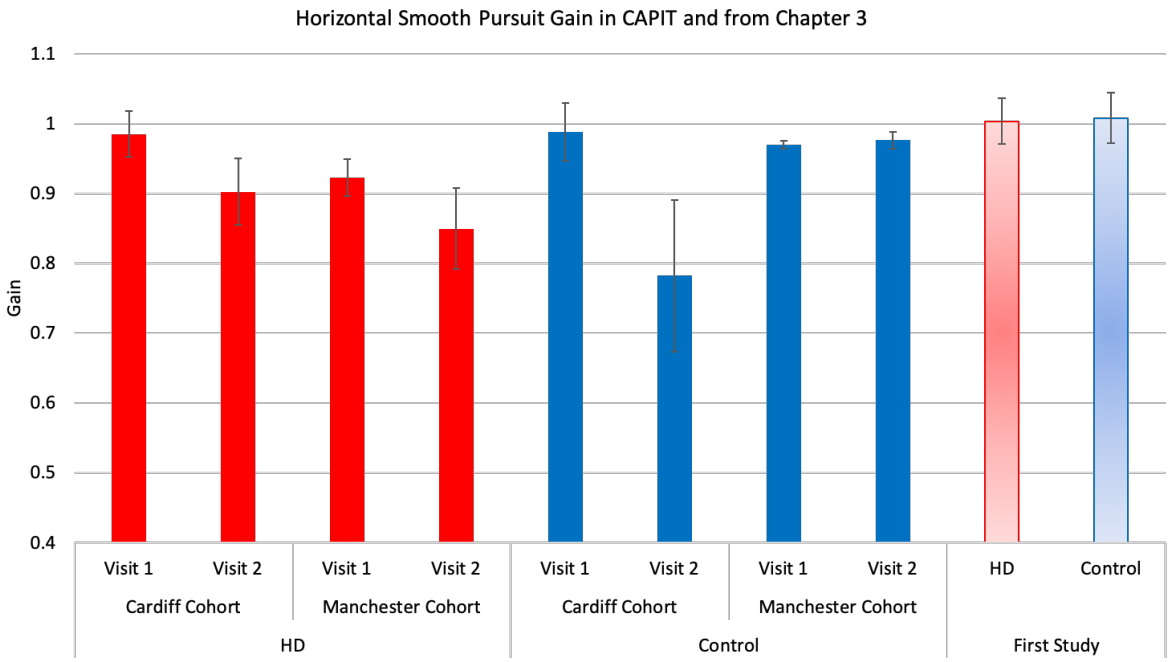


Figure 52 - Error rates for the vertical Anti-Saccade task in the CAPIT cohort. Also shown is data collected in the 1st HD study for reference

In the vertical anti-saccade task the error rates are significantly higher in the Cardiff HD cohort ($P<0.05$) compared to the control cohort. The error rates recorded in the Manchester HD cohort are greater than those observed in the control group. This difference is not significant

5.5.4 Smooth Pursuit



There is no statistically significant differences in the smooth pursuit gains between HD and control groups in both Manchester and Cardiff. This is consistent with that recorded within the first HD study. The gain values appears to be lower for visit 2 in the Manchester control cohort, however this is likely to be due to insufficient data quality, and the small sample size.

5.5.5 Optokinetic Nystagmus

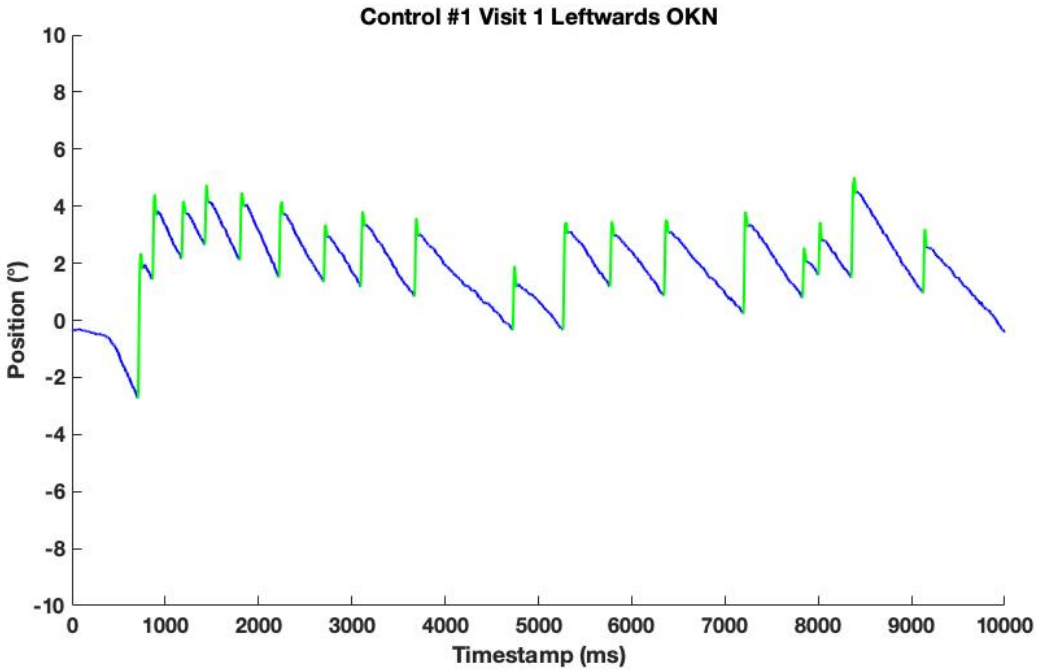


Figure 53 - Raw OKN eye trace from a control participant

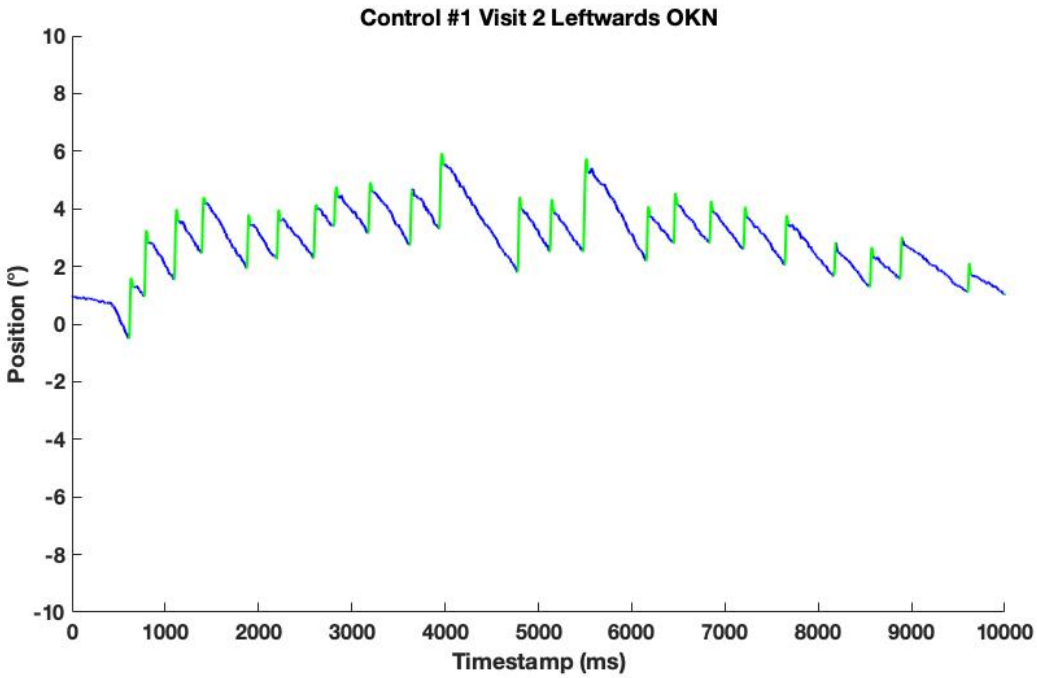


Figure 54 - Raw OKN eye trace from a control participant (the same participant as in the previous figure, recorded at a later date)

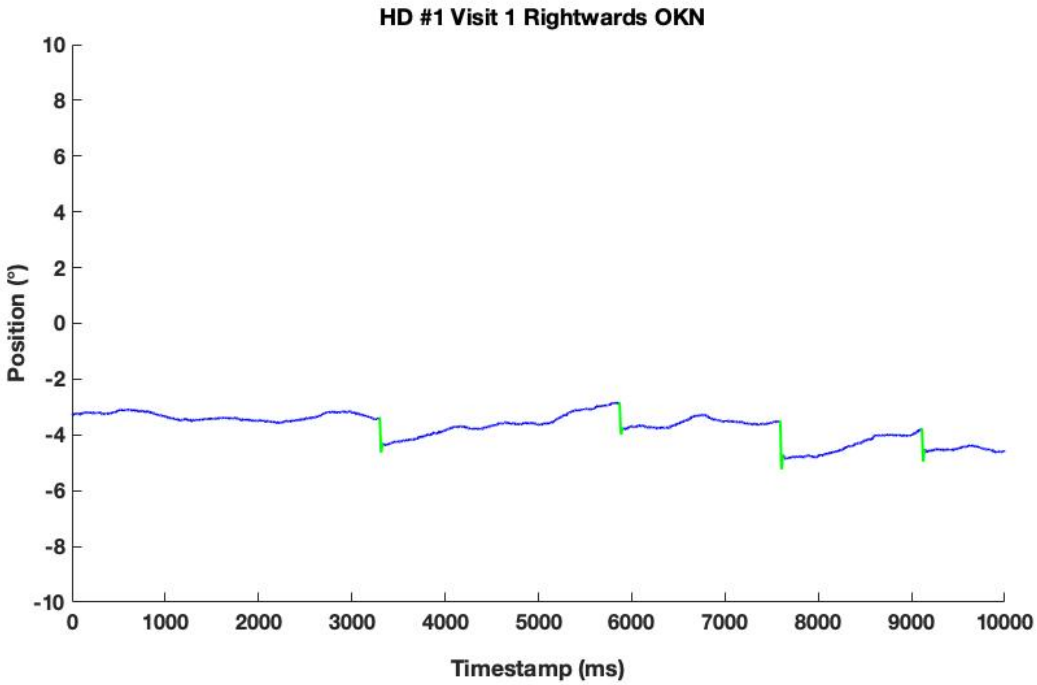


Figure 55 - Raw OKN eye trace from a HD participant

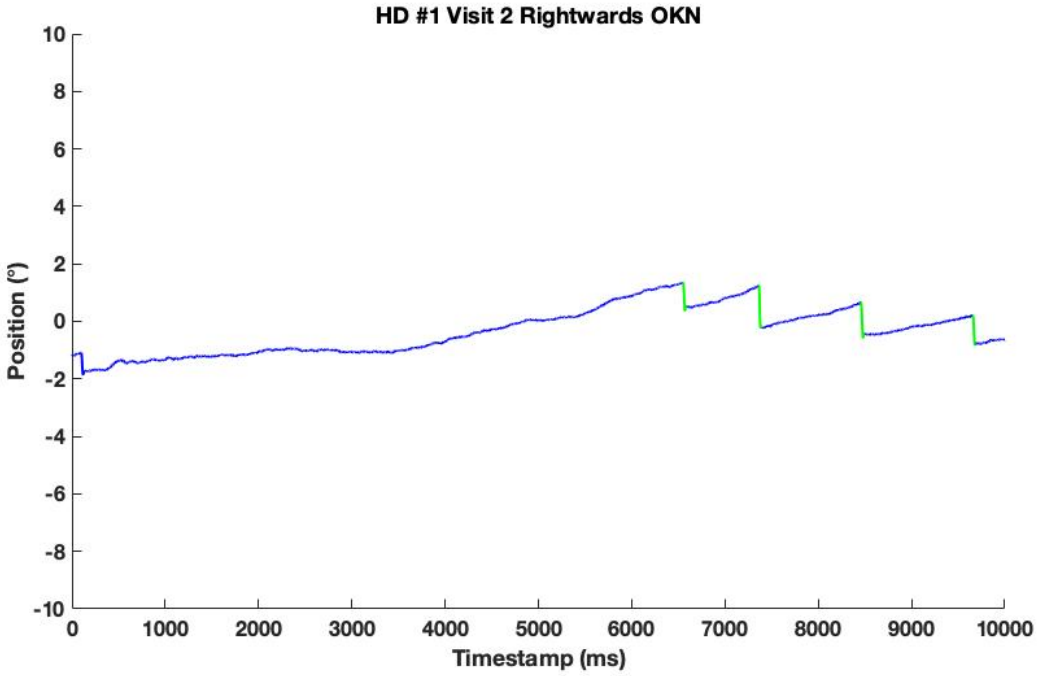


Figure 56 - Raw OKN eye trace from a HD participant (the same participant as in the previous figure, recorded at a later date)

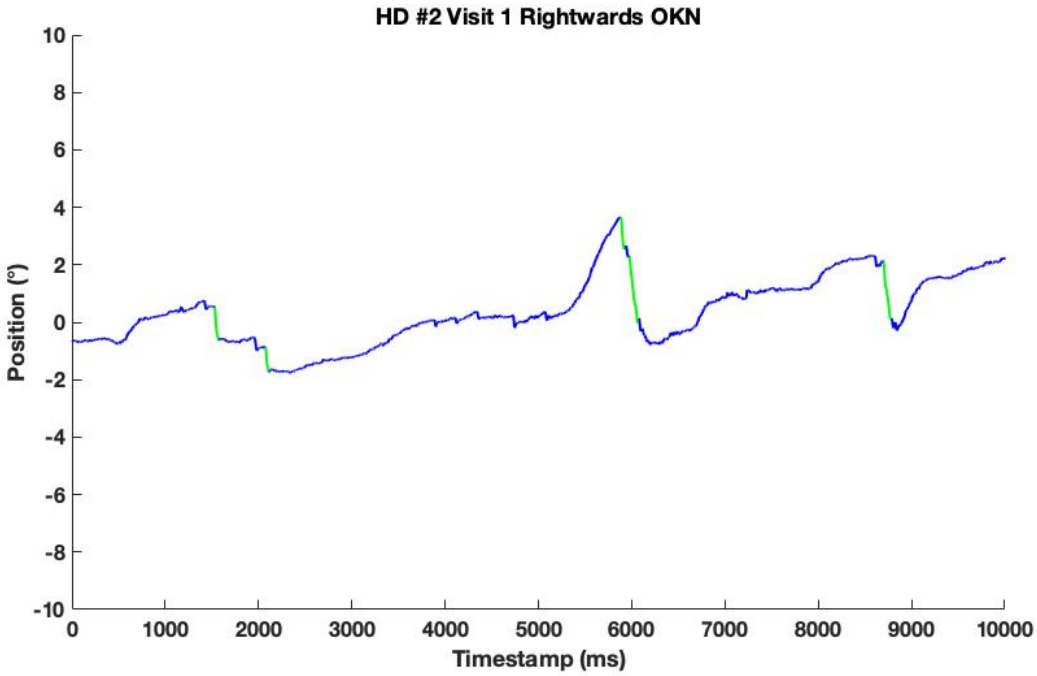


Figure 57 - Raw OKN eye trace from a second HD participant

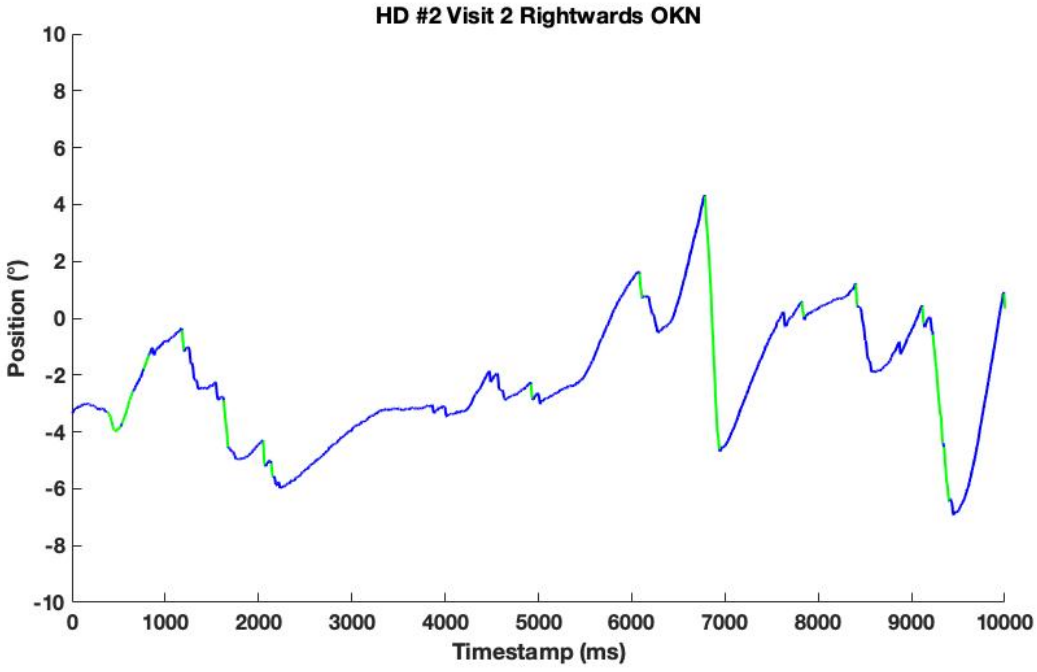


Figure 58 - Raw OKN eye trace from a second HD participant (the same participant as in the previous figure, recorded at a later date)

Figures 53-58 are eye traces recorded from participants who attended the Cardiff clinic. All three participants shown attended over two visits. In the control participant (figure 53 and 54), classical 'sawtooth' nystagmus waveform has been recorded showing alternation of saccades (green) and smooth pursuit (blue). The frequency is consistent throughout the duration of the recording.

The other four eye traces are from two different HD participants. These eye traces show a profoundly abnormal optokinetic response. In the first HD participant, the participant has maintained an almost constant fixation on the centre of the screen. There are small amplitude saccades during the recording that may be evidence of the optokinetic response being present. If this response is present, it is clearly deficient. The characteristic OKN waveform is again absent with the second HD participant. There are some periods of alternating pursuit and saccades, but the frequency and amplitude as well as the slow phase eye velocity are highly variable.

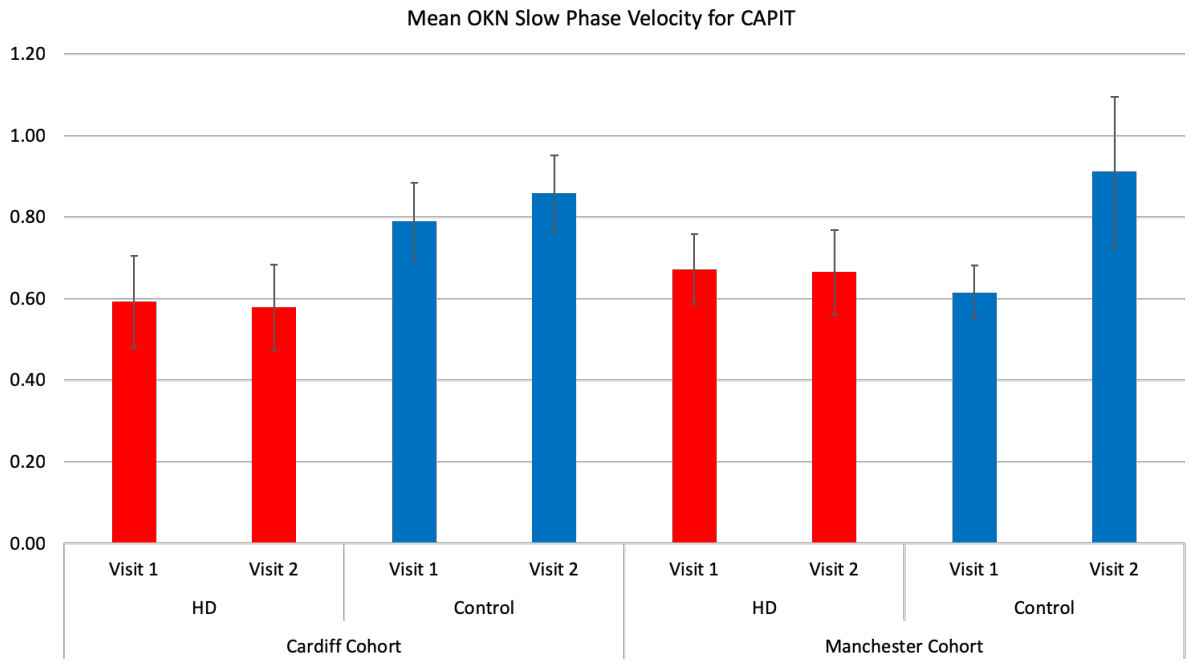


Figure 59 - Mean slow phase gain velocity for OKN in the CAPIT cohorts

The slow phase velocity gains shown in figure 59 consist of the mean values obtained from a combined mean of the 4 sets of OKN (up, down, left and right) undertaken by the participants. For the Cardiff cohorts, there is a statistically significant difference between the HD and control groups. This difference does not appear to be present in the Manchester HD cohort, however this is confounded by poor data quality throughout the task in both the control and HD groups, and the small number of participants.

5.5.6 Comparison of Oculomotor Data and Total Motor Score from UHDRS

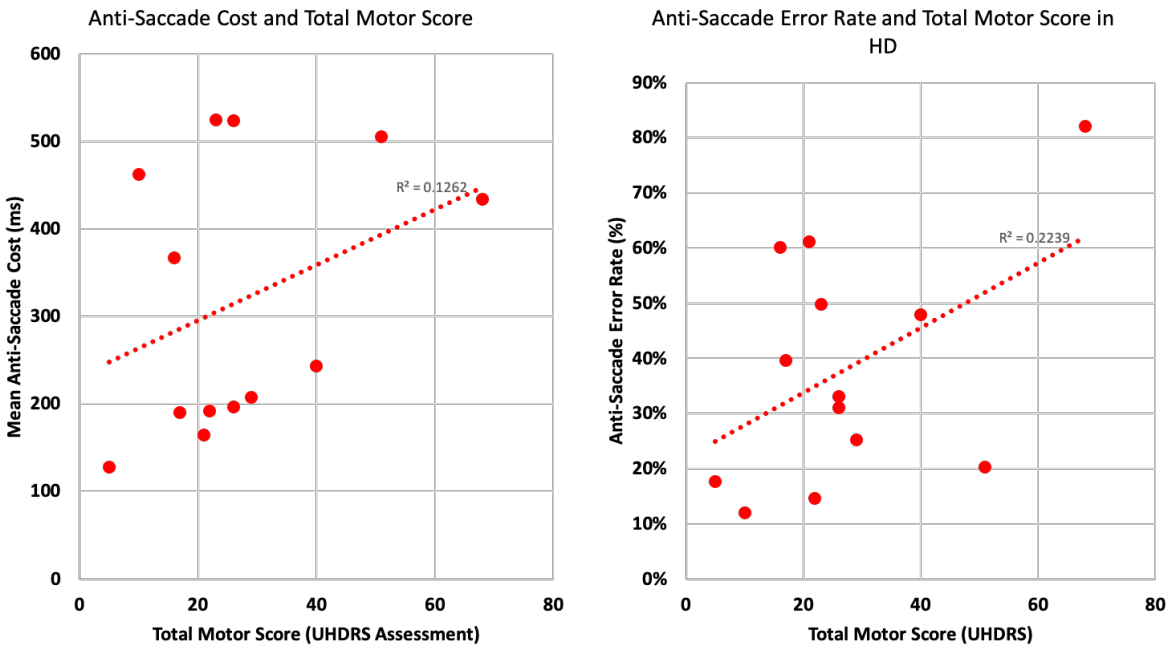


Figure 60 - Anti-Saccade Cost and Anti-Saccade Error Rates with regards to Total Motor Score

There appears to be a correlation (not particularly strong, but is present) between the performance in the anti-saccade task and also the Total Motor Score gathered for the participants in Cardiff, this was previously shown in the first HD study. This confirms the repeatability of such a relationship.

Figure 61 - OKN Slow Phase Gain versus Total Motor Score

There is a non-significant correlation between TMS and OKN slow phase gain (Figure 61). Participants with a pre-morbid diagnosis, or with a diagnosis with limited confidence are indicated by green crosses. Some data points are not included as participants were engaging 'look' as opposed to 'stare'. Of the participants included in the above figure, the participant with the highest TMS score produced a 'normal' OKN waveform for very limited period of the task. However, this was interspersed with periods of look OKN and periods of absolute abnormality.

5.6 Discussion

Participants enrolled on this study were due to attend for three total visits, baseline, 1 month, and 12 months. Unfortunately very few participants returned for their 3rd visit (n=8) compared to those who completed the baseline measurements (n=24), this resulted in little useful data to be analysed for the 3rd visit. One of the aims of the CAPIT study was to monitor longitudinal changes with the new measures, however as the two visits the participants did undertake (all 24 participants returned for the 2nd visit) were within 30 days of baseline, the time period is too short for changes to manifest. What this did permit however was to validate repeatability of the recordings over time.

Data collected from Manchester was of poor data quality, and very little could be analysed for the smooth pursuit and OKN tasks. On subjective assessment of the eye traces, smooth pursuit appeared to be intact, with the OKN waveform being erratic, if present. However the data, and eye trace are both noisy, and quantitative analysis could not be made.

5.6.1 Comparison to data collected in first HD study

The results recorded in pro-saccades, anti-saccades, pursuit and OKN were comparable to that reported in Chapter 3. The principle finding, abnormal OKN, is present in this cohort of HD participants. The abnormal OKN response is a repeatable finding in participants with HD, and is present in Manchester Cohort. It does not correlate to disease stage, and is also present in asymptomatic participants.

5.6.2 Repeatability of oculomotor assessment in HD

Data collected for between visits for the same participant is comparable, with no significant differences found in all tasks.

5.6.3 Data Quality Issues

There was significant variability in the quality of the data provided by the lab in Manchester, and this variability was present both within visit, and between visits. The data for the pro-saccade task would be of adequate quality, with the data from the anti-saccade task performed at the same visit being of poor quality. Data collected for the saccadic tasks was of superior quality to that of the smooth pursuit and OKN tasks. The reason for the poor quality data is not known.

Feedback provided by the person administering the oculomotor tests is that there was some difficulty experienced in regard to participant movement, and that it was difficult to for the participant to remain stationary throughout the task.

Chapter 6: Discussion and Future Work

6.1 General Discussion

The aim of the studies documented within this thesis has been to identify if eye movements can be used as a biomarker for the progress of Huntington's Disease. The importance of finding biomarkers for disease is discussed in detail in section 1.5, and as discussed in (Henley, Bates and Tabrizi 2005), the ideal biomarker for neurodegenerative diseases must possess certain characteristics.

6.1.1 First HD study

In the first HD experiment (Chapter 3), it was identified that there is no single comprehensive oculomotor study involving participants with HD. The studies in the current literature generally tested horizontal pro-saccadic EMs, and for those which tested smooth pursuit or OKN, these were generally done without saccadic testing. These paradigms are shown by Table 5 in 2.1.5. Our aim was to create a comprehensive battery of tests to measure the EMs in HD, and to identify which paradigms would most strongly indicate deficiency in HD.

In the first study, participants with HD showed no abnormality in the pro-saccade task when tested in both the horizontal and vertical meridians; saccadic latencies were within normal limits. Smooth pursuit also appeared to show no abnormality in both the horizontal and vertical meridians, with the smooth pursuit gain being within normal limits. Anti-saccade

latencies and error rates were clearly abnormal in the HD group compared to the control group. These findings corroborated what had been found in the literature.

Abnormal OKN has been reported in the literature, with several studies reporting reduced OKN gain (this was discussed in 1.8.3). Unfortunately the other studies did not record the nature of the abnormality. As can clearly be seen from the eye traces in 3.5.6, OKN is clearly deficient in HD, and this deficiency is not restricted to reduced gain. The characteristic 'sawtooth' waveform in several participants was absent, and in the vast majority of participants appeared to be abnormal, with variable frequency, amplitude and velocity.

This abnormality of OKN is presented in participants who are considered asymptomatic in the HD clinic. As both pro-saccades and smooth pursuit appear to be normal, this would suggest that the abnormal optokinetic response is not a motor issue, but rather a potential sensory issue. This finding is novel, and would appear to be reasonably compelling evidence for using OKN eye movements as a biomarker. As even asymptomatic participants were exhibiting abnormal OKN, eye movements could potentially be the earliest biomarker for the manifest onset of HD.

6.1.2 Second HD Study

Following such compelling results from the first HD study, it was imperative that these findings be further investigated. Therefore in the second HD study, OKN was tested under monocular and binocular conditions, with look OKN also investigated. The aim was to demonstrate repeatability of the abnormal OKN observed in the previous study. As it was

suspected that this abnormal response could be due to impaired motion sensitivity, a proof of concept motion sensitivity task was included within the new study. The increased saccadic latencies and error rates during the anti-saccade task appeared to be indicative of poor inhibitory control in HD. To further investigate this, the MDOR task was included within the protocol for the new study. Additionally the decision was made to include a self-paced saccade task, and to record participant IQ.

In the second HD study, abnormalities in OKN were again demonstrated under both monocular and binocular conditions. As with the previous study, some participants did not produce the 'sawtooth' waveform in response to the stimuli. Those who did, produced patterns with variable amplitude, frequency and velocity. There appeared to be no significant differences between the monocular and binocular conditions. Look OKN showed no abnormality relative to controls. The proof of concept motion coherence task showed clear deficiencies in the HD group relative to the control group. As with the abnormalities in OKN, these appeared to be present in asymptomatic participants. This could potentially prove to be another very early biomarker for the onset of manifest HD.

Self-Paced saccades were also measured in the second HD study. As those with HD who undertake UHDRS assessment are required to complete a self-paced finger tapping task, which is subjectively assessed, we proposed an oculomotor alternative that could be objectively measured. The HD group completed substantially fewer saccades during the task than the control group, irrespective of disease stage. As with the OKN and motion perception tasks, self-paced saccades appear to be sensitive to early changes, which have yet to be picked up during the UHDRS testing.

Participants also undertook the MDOR paradigm as part of the protocol, unfortunately both the HD group and the control group performed poorly in this task, and treated it as a pro-saccade task, so it is not possible to make a reasonable comparison between the groups. The pre-morbid and current IQ of the participants was also recorded, which demonstrated a substantial decline in IQ in the HD group.

6.1.3 CAPIT Study

Concurrent to the two studies, we had the opportunity to collect data as part of the CAPIT-HD2 study. This would allow us access to participants with HD over multiple visits at multiple centres. As this study began recruiting prior to the conclusion of the First HD study, we chose to use an identical protocol for those individuals. This data could then potentially supplement the data already being collected, but could also present the opportunity to monitor longitudinal changes, and also to trial the protocol using a different eye tracker.

Due to the lack of participants returning for their 3rd visit (12 months after the 1st visit), there was very little longitudinal data present to analyse, and therefore the data presented in Chapter 5, pertained to the first two visits only, which were separated by only 1 month. This period of time is too short to see any longitudinal changes. What this did permit however was to validate repeatability of the recordings over time in a clinical population where other measures, i.e. their TMS, can vary day to day. The primary finding of the first HD study, the abnormality in OKN, was shown to be repeatable across visits. The data quality of the recordings from Manchester, were of poor quality for the pursuit and OKN

tasks, which resulted in little to no analysable data. It remains to be seen if this was due to the eye tracker being used, or due to the set-up at that centre.

6.2 Potential New Biomarkers

Across the three experimental studies involving HD participants, there has been a clear deficiency in OKN, the nature of which is novel, and has not been observed previously. This deficiency is likely to be due to the deficiency of motion sensitivity, which was also observed.

From the data collected, and discussed in this thesis, there are three potential biomarkers for the progress of Huntington's Disease: OKN, motion coherence, and potentially self-paced saccades. As discussed in 1.5, Henley, Bates and Tabrizi (2005), listed the characteristics that the ideal biomarker for neurodegenerative diseases should possess. These potential biomarkers do appear to possess many of the characteristics required of an ideal biomarker:

- Easy to quantify in accessible tissue or biofluid

  OKN, perception and self-paced saccades are relatively easy to quantify in accessible tissue. OKN could be measured subjectively using an OKN drum in the clinical environment if a commercial eye tracker is not available, motion perception could be measured using any compatible device in which the participant could input their responses. Self-paced saccades can be measured subjectively, much in the same way that saccades are currently measured in the UHDRS

- Not subject to wide variation in the general population if used as a diagnostic biomarker

  The optokinetic response is innate and intact within healthy individuals, and the waveform profile is not subject to wide variation in the general population. Self-paced saccades, being nothing more than sequential pro-saccades, should not be subject to wide variation in the general population. As for motion perception, variation within the general population would be task dependent.

- Unaffected by unrelated conditions and co-morbid factors

  OKN is intact in virtually all other pathologies, and although there may be reduced gains as a result of medication, or co-morbidity, the OKN response remains robust. self-paced saccades have been shown to be slowed in Parkinson's disease, motion perception is also affected by unrelated conditions.

- Measurement is reliable and quick

  Reliable responses for OKN and self-paced saccades can be obtained in one minute, or less. For our proof of concept motion sensitivity experiment, the results were also obtained comfortably within a minute.

- Measurements are reproducible at a different time or in a different centre

  The abnormality in OKN has been demonstrated to be repeatable across multiple visits. This is yet to be confirmed with motion sensitivity and self-paced saccades.

- The biomarker changes linearly (either negatively or positively) with disease progression

  It is not possible to ascertain if our potential biomarkers change linearly, as they were generally present in participants who are deemed to be asymptomatic, with no

manifest signs of HD. It is possible that these changes are linear, but are present before other changes.

- The biomarker changes in response to a disease modifying therapeutic intervention that closely correlates with established clinic-pathological parameters of the disease. As these tasks were not completed on participants undergoing disease modifying therapeutic intervention, it is not possible to know if they would respond to such treatment.

Based on the above characteristics, and the data presented within this thesis, there is compelling evidence that eye movements, and motion perception have the potential to be powerful biomarkers in the earliest stages of HD.

6.3 Limitations of the studies

Huntington's Disease is not a common condition, and is prevalent in 4-8 per 100000 individuals (Harper, 1992). This severely restricts the pool of potential participants who can participate in research. The population of Wales is estimated to be 3.125 million (Welsh Government 2018), based on epidemiological data, this would estimate the number of people in Wales with HD as 125-250 individuals. Wales is a predominantly rural nation, with a sparsely distributed population. This geographical distribution reduces the number of individuals who can attend appointments in Cardiff. Once further accounting for those whom have not been formally diagnosed, who are under the age of 18, or who have advanced HD, the number of participants who can participate in research is severely restricted. Due to these reasons, we were unable to recruit a large cohort of participants. Fortunately we were able to recruit approximately 20 individuals for each study.

For the first HD study, recruitment of participants could only take place via the Cardiff Huntington's Disease Clinic. This meant that there was severe restriction on the access to participants. For the CAPIT study, there was a lack of follow up visits which resulted in the inability to garner longitudinal data. Almost all HD participants included within the first HD study and the CAPIT study, had already undertaken several hours of assessment prior to completing oculomotor testing. Hence, many participants were fatigued when presenting for assessment. Fortunately, participants recruited for the Second HD study were able to attend outside of the clinic.

One of the predominant limitations of the study is the tolerability of the set-up for participants with HD. Recommendations made by our collaborator Professor Anne Rosser, and the rest of the clinical team, were to restrict visits to approximately 30 minutes. Visits exceeding this time period could be stressful for the participants, particularly for those with chorea, who could find being required to remain stationary for prolonged periods of time uncomfortable.

6.4 Impact of Oculomotor Findings on Quality of Life

The main findings of the studies were that of abnormal OKN, and impaired motion sensitivity. It is possible that these findings may have a previously unknown impact on their quality of life. It is difficult to predict how our findings would impact on the quality of life of a participant. Impaired motion sensitivity could cause issues judging velocity and optic flow, which could have a potentially huge impact on a daily activity such as a driving. A participant

with impaired motion sensitivity may not be able to accurately estimate the speed that they are driving, and could therefore struggle with the task. There is no evidence in the literature that there are any vision problems associated with HD, however our collaborator Professor Anne Rosser believes that this an area worth investigating.

6.5 Future and On-going Work

6.5.1 TRIDENT-HD

Following the completion of CAPIT-HD2, the REPAIR-HD group have started collecting data for the TRIDENT-HD (TRIal designs for Delivery of Novel Therapies in Huntington's Disease) study, through which participants will receive cell replacement therapy. As with the CAPIT-HD2, participants will attend for visits at 3 months, and 12 months, and will undertake a battery of tests including brain imaging, cognitive testing, and motor testing.

As part of the motor testing, eye movements are being recorded in the participants. As the ethics did not include motion sensitivity testing, the participants are undertaking testing of OKN and self-paced saccades, as these appear to be the strongest oculomotor biomarker candidates.

6.5.2 Anti-Saccade Neural Modelling

At this time we are collaborating with Dr Vassilis Cutsuridis, University of Lincoln, to apply neural modelling to our anti-saccade data. Dr Cutsuridis is applying behavioural and computational models to our anti-saccade data, with a view to constructing a model of anti-saccadic response inhibition. Currently the computational models are being applied to the HD data.

6.5.3 Motion Sensitivity – Gabor Patches

Subsequent to the findings of our proof of concept motion sensitivity testing in the second HD study, the local and global sensitivity is being assessed in HD using Gabor patches. OKN is again being tested in this experiment, which is looking to establish more accurate thresholds of motion sensitivity, and to identify if the deficient motion sensitivity is a localised, or global phenomena.

6.5.4 Proposed Future Studies

6.5.4.1 – Subjective Measures of OKN

The abnormalities of OKN have been observed in a laboratory setting using high resolution monitors and high frequency eye trackers. Both of these items may not be financially feasible outside the clinical research environment. As mentioned in 1.6.4, OKN drums are used in paediatric optometry as a gross measure of visual acuity in young infants. The presence of abnormal OKN outside of the research environment using an OKN drum should be investigated. If the abnormality is present, it is significantly more feasible to purchase an OKN drum for a clinic, than the expense of a full eye tracking set-up. It would also be useful to ascertain if clinicians could subjectively identify abnormal OKN.

6.5.4.2 – Subjective Measures of Self-Paced Saccades

At this time, rudimentary oculomotor testing, saccades and pursuit, are measured routinely as part of the UHDRS. Subjective measurement of these eye movements can be administered quickly, and easily within the clinical environment. In Chapter 3, no difference was found between the pro-saccade latencies in the HD cohort, relative to the control cohort. In Chapter 4, significant differences between the two cohorts were found when the participants undertook a self-paced paradigm.

Self-paced saccades, at least in the lab environment, are deficient in HD relative to controls, and appear to be more sensitive to the presence of HD. It should be investigated if participants with HD make fewer saccades in a clinical environment than controls, as they did in the lab environment. Should this reduction in the frequency of self-paced saccades be present in the clinical environment, the self-paced task could potentially replace the existing saccadic testing used as part of the UHDRS.

6.5.4.3 – Smooth Pursuit on a Patterned Background

Upon speaking to members of the HD team, they were surprised at our finding that smooth pursuit appeared to be intact in HD. In their experience, pursuit is often deficient and/or saccadic in nature when tested as part of the UHDRS. It is quite possible that during the lab set-up, as there is a single stimuli presented on a black screen, the participants have no problem pursuing the only stimuli in their field of vision. Whereas in a clinical environment, there are numerous distractors in the background. Therefore it is worth exploring if smooth pursuit remains 'normal', with the introduction of a patterned background. If it does not

remain normal under these circumstances, it could correlate potentially to their deficient motion sensitivity.

6.5.4.4 – MDOR

In Chapter 4, the MDOR task was trialled unsuccessfully with both the control and HD cohorts. The task has been successfully completed before by Woolohan and Knox (2014) in a control group. Repeating this task with a new clinical group, with modified instructions should be attempted. The MDOR task appears to be a 'cleaner' measure of inhibitory control than the anti-saccade task, and due to the performance of the HD participants in the anti-saccade task, investigating inhibitory control using an oculomotor proxy should be further investigated.

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Appendix

Appendix I – Transcript of 'On Chorea' – Huntington 1872

"And now I wish to draw your attention more particularly to a form of the disease which exists, so far as I know, almost exclusively on the east end of Long Island. It is peculiar in itself and seems to obey certain fixed laws. In the first place, let me remark that chorea, as it is commonly known to the profession, and a description of which I have already given, is of exceedingly rare occurrence there. I do not remember a single instance occurring in my father 's practice, and I have often heard him say that it was a rare disease and seldom met with by him.

The hereditary chorea, as I shall call it, is confined to certain and fortunately a few families, and has been transmitted to them, an heirloom from generations away back in the dim past. It is spoken of by those in whose veins the seeds of the disease are known to exist, with a kind of horror, and not at all alluded to except through dire necessity, when it is mentioned as "that disorder." It is attended generally by all the symptoms of common chorea, only in an aggravated degree, hardly ever manifesting itself until adult or middle life, and then coming on gradually but surely, increasing by degrees, and often occupying years in its development, until the hapless sufferer is but a quivering wreck of his former self.

It is as common and is indeed, I believe, more common among men than women, while I am not aware that season or complexion has any influence in the matter. There are three marked peculiarities in this disease: 1. Its hereditary nature. 2. A tendency to insanity and suicide. 3. Its manifesting itself as a grave disease only in adult life.

1. *Of its hereditary nature. When either or both the parents have shown manifestations of the disease, and more especially when these manifestations have been of a serious nature, one or more of the offspring almost invariably suffer from the disease, if they live to adult age. But if by any chance these children go through life without it, the thread is broken and the grandchildren and great-grandchildren of the original*

shakers may rest assured that they are free from the disease. This you will perceive differs from the general laws of so-called hereditary diseases, as for instance in phthisis, or syphilis, when one generation may enjoy entire immunity from their dread ravages, and yet in another you find them cropping out in all their hideousness. Unstable and whimsical as the disease may be in other respects, in this it is firm, it never skips a generation to again manifest itself in another; once having yielded its claims, it never regains them. In all the families, or nearly all in which the choreic taint exists, the nervous temperament greatly preponderates, and in my grandfather 's and father 's experience, which conjointly cover a period of 78 years, nervous excitement in a marked degree almost invariably attends upon every disease these people may suffer from, although they may not when in health be over nervous.

2. *The tendency to insanity, and sometimes that form of insanity which leads to suicide, is marked. I know of several instances of suicide of people suffering from this form of chorea, or who belonged to families in which the disease existed. As the disease progresses the mind becomes more or less impaired, in many amounting to insanity, while in others mind and body both gradually fail until death relieves them of their sufferings. At present I know of two married men, whose wives are living, and who are constantly making love to some young lady, not seeming to be aware that there is any impropriety in it. They are suffering from chorea to such an extent that they can hardly walk, and would be thought, by a stranger, to be intoxicated. They are men of about 50 years of age, but never let an opportunity to flirt with a girl go past unimproved. The effect is ridiculous in the extreme.*

3. *Its third peculiarity is its coming on, at least as a grave disease, only in adult life. I do not know of a single case that has shown any marked signs of chorea before the age of thirty or forty years, while those who pass the fortieth year without symptoms of the disease, are seldom attacked. It begins as an ordinary chorea might begin, by the irregular and spasmodic action of certain muscles, as of the face, arms, etc. These movements gradually increase, when muscles hitherto unaffected take on the spasmodic action, until every muscle in the body becomes affected (excepting the*

involuntary ones), and the poor patient presents a spectacle which is anything but pleasing to witness. I have never known a recovery or even an amelioration of symptoms in this form of chorea; when once it begins it clings to the bitter end. No treatment seems to be of any avail, and indeed nowadays its end is so well-known to the sufferer and his friends, that medical advice is seldom sought. It seems at least to be one of the incurables.

Dr. Wood, in his work on the practice of medicine, mentions the case of a man, in the Pennsylvania Hospital, suffering from aggravated chorea, which resisted all treatment. He finally left the hospital uncured. I strongly suspect that this man belonged to one of the families in which hereditary chorea existed. I know nothing of its pathology. I have drawn your attention to this form of chorea gentlemen, not that I considered it of any great practical importance to you, but merely as a medical curiosity, and as such it may have some interest." (Huntington, G. 1872)

Appendix II – Ethical Approval for Pilot Study

SCHOOL OF OPTOMETRY AND VISION SCIENCES

HUMAN SCIENCE ETHICAL COMMITTEE

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Project Number: 1390

Project title: Evaulating eye movements as an indicator for monitoring the progression of Huntington's disease

Lead Investigators: James Brawn, Prof Jon Erichsen

Date: 21/04/2015

With reference to the above application, I am pleased to confirm that approval has been granted,

Please inform the Research Ethics Committee immediately of any changes to the protocol, changes to personnel involved, or of any unforeseen circumstances arising from the study.

Please note the data retention periods specified by the University

- For non-funded non-clinical research, data shall be retained for no less than 5 years, or 2 years post-publication
- Undergraduate project data shall be retained at least until the end of the University appeals process

Dr Julie Albon
Chairperson

Approval form

Appendix III – Participant Information Sheet (Pilot)

School of Optometry and Vision Sciences
Ysgol Optometreg a Gwyddorau'r Golwg

Head of School *Pennaeth Yr Ysgol* Professor *Yr Athro* Marcela Votruba

College of Biomedical and Life Sciences
Cardiff University
Maindy Road
Cardiff
CF24 4HQ
Wales UK

Tel *Ffôn* +44(0)29 2087 4374
Fax *Ffacs* +44(0)29 2087 4859
http://www.cardiff.ac.uk/optom/

Prifysgol Caerdydd
Heol Maindy
Caerdydd
CF24 4HQ
Cymru, Y Deyrnas Gyfunol

PARTICIPANT INFORMATION SHEET

Evaluating eye movements in a normative population as an indicator for monitoring the progression of Huntington's Disease (HD)

Approval No: 1389
Version: 1.0

What is this study about?
Huntington's Disease (HD) is a genetic, neurodegenerative disorder characterised by abnormalities in movement, cognitive decline and psychological problems. Since the discovery of the gene mutation causing HD in 1993, the understanding of the disease has increased exponentially, partly due to the establishment of international networks that have facilitated multisite clinical studies and interactions between scientists and clinics caring for HD patients. However, despite this progress, no disease-modifying treatment is available for HD, and symptomatic treatments are very limited and largely anecdotal rather than evidence based.

Abnormal eye movements are associated with the progression of HD and currently, subjective assessments of eye movements are included within the Unified Huntington Disease Rating Scale (UHDRS) motor testing. Quantifiable measurement of eye movements using an eye tracker has indicated oculomotor abnormalities in HD compared to people without HD (controls). These abnormalities agree strongly with the recognised diagnostic tests and can be used as a non-invasive diagnostic utility. Therefore, eye movements appear to be a reliable indicator for HD, and as such, an eye tracker could be used as a non-invasive measure of disease progression in future observational studies and drug trials.

Why have I been invited to take part?
You are being recruited as I require data for subjects without HD to use a baseline for a subsequent comparison with subjects with HD.

Do I have to take part?
Participation in this study is voluntary. You may withdraw from the study at any time without consequence.

What will happen to me if I take part?
The procedure will consist of visual tasks involving you being asked to either look towards a target, away from a target or to follow a target presented on a large screen. During each of these tasks, your eye movements will be monitored and recorded. For this study, you will only need to be present for one session lasting no more than 30 minutes.

Do I need to do anything special to take part?
Before you can participate in the project, we will require you to provide informed written consent. Subsequent to providing your written consent, if you decide that you no longer wish to be involved with the study, you will not be included.

What are the possible benefits of taking part?
There will be no direct benefit to the participants involved, however by participating you will help to validate the quality of the results taken from later studies involving subjects with HD. This may help other people in the future.

Are there any possible risks from taking part?
There are no risks in taking part in this study. The instrument we will use to measure the orientation and position of your eye is completely harmless and non-invasive. However, this study is not suitable for individuals with photosensitive epilepsy due to the health and safety issues that arise from the use of computer screens.

Expenses and payments.
Unfortunately, there will not be any expenses or payments available for participation in this study.

Will my results remain confidential?
In line with School Ethics guidelines, all information containing subject identifiers will be stored securely, either in locked storage cabinets or in password protected computer file space. If analysis takes place under non-secure conditions (such as paper copies, etc.), all data will be coded, and these codes will be stored separately and securely.
Security of data storage will be the responsibility of the lead researcher.
All procedures are compliant with the Data Protection Act 1998.

What will happen to the results of this study?
The results from this study will be published as part of a PhD thesis and may be used as baseline data in research paper(s). All results will be anonymised, and it will not be possible to identify individual subjects. If you would like to learn the results of the study once it is completed, please contact Mr James Brawn (brawnjn@cardiff.ac.uk).

Who is funding the research?
Cardiff University (JE Williams Studentship)

Who has reviewed the study?
All research at Cardiff University is reviewed by an independent group of people not involved in the study who comprise the Research Ethics Audit Committee, to protect your interests. This study has been reviewed and approved by the School of Optometry and Vision Sciences Research Ethics Committee (Cardiff University).

What if I have any questions or if I have a problem?
Should you have any questions, we would be very happy to discuss our project further with you.

If you have any questions about this research, please contact:

Mr James Brawn
Email: brawnjn@cardiff.ac.uk
School of Optometry and Vision Sciences, Maindy Road, CF24 4HQ

Professor Jonathan Erichsen
Email: erichsenjt@cardiff.ac.uk
School of Optometry and Vision Sciences, Maindy Road, CF24 4HQ

Professor Tom Freeman
Email: freemanT@cardiff.ac.uk
School of Psychology, Tower Building, 70 Park Place, CF10 3AT

Dr. Matthew Dunn
Email: dunnmj1@cardiff.ac.uk
School of Optometry and Vision Sciences, Maindy Road, CF24 4HQ

Thank you for taking time to read this information.

Appendix IV – Consent Form (Pilot)

School of Optometry and Vision Sciences
Ysgol Optometreg a Gwyddorau'r Golwg

Head of School *Pennaeth Yr Ysgol* Professor *Yr Athro* Marcela Votruba

College of Biomedical and Life Sciences
Cardiff University
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http://www.cardiff.ac.uk/optom/

Prifysgol Caerdydd
Heol Maindy
Caerdydd
CF24 4HQ
Cymru, Y Deyrnas Gyfunol

CONSENT FORM

Evaluating eye movements as an indicator for monitoring the progression of Huntington's Disease (HD)

Approval No: 1389
Version: 1.0

Name of Researchers:

Please initial box

1 I confirm that I have read and understand the Participant Information Sheet (Version: 1.0 Date TBA) for the above study and have had the opportunity to ask questions. ☐

2 I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. ☐

3 I agree to take part in the above study. ☐

4 I agree for my anonymised data to be used in future research and/or educational activities ☐

If you would like to receive a summary of the results of this study, please provide your contact details here:

_____

Name of Participant	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Appendix V – Extension Application for Ethics (First HD Study)

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

School of Biosciences
Ysgol y Biowyddorau
Head of School, Pennaeth Ysgol
Professor, Yr Athro Jim Murray PhD FLSW

Cardiff University
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Tel +44(0)29 2087 6675
Fax +44(0)29 2087 4116
Email
director-biosi@cardiff.ac.uk

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Prifysgol Caerdydd
Adeilad Syr Martin Evans
Rhodfa'r Amgueddfa
Caerdydd CF10 3AX
Cymru Y Deyrnas Unedig

Ffôn +44(0)29 2087 6676
Ffacs +44(0)29 2087 4116
E-bost
director-biosi@caerdydd.ac.uk

www.caerdydd.ac.uk/biosi/

North Wales Research Ethics Committee
Betsi Cadwaladr University Health Board
Ysbyty Gwynedd Hospital
Bangor
LL57 2PW

March 2nd 2016

Dear Dr Roberts,

Study Title:	**Quantitative assessment of eye movements in Huntington's disease**
REC Reference:	**13/WA/0162**
Protocol No:	**SPON-1215-13**
IRAS Project ID:	**12726**

In a previous letter dated October 16th 2015, we requested an extension to March 31st 2016 to enable our pilot study to continue. However, the pilot study is still recruiting and we wish to request an additional extension to September 30th 2016 to allow the completion of recruitment and the pilot data to be analysed. We will then submit a new ethical application for an expanded study.

I hope this meets with the Committee's approval. Should you require any additional information, do not hesitate to contact me.

Yours sincerely

Prof Anne Rosser
Professor of Clinical Neuroscience
Brain Repair Group, School of Biosciences
Cardiff University
Museum Avenue
Cardiff University
CF10 3AX

Email: rosserae@cardiff.ac.uk
Tel: 029 208 75188

Appendix VI – Participant Information Sheet: Control (First HD Study)

School of Optometry and Vision Sciences
Ysgol Optometreg a Gwyddorau'r Golwg

Head of School *Pennaeth Yr Ysgol* Professor *Yr Athro* Marcela Votruba

College of Biomedical and Life Sciences
Cardiff University
Maindy Road
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Wales UK

Tel *Ffôn* +44(0)29 2087 4374
Fax *Ffacs* +44(0)29 2087 4859
http://www.cardiff.ac.uk/optom/

Prifysgol Caerdydd
Heol Maindy
Caerdydd
CF24 4HQ
Cymru, Y Deyrnas Gyfunol

PARTICIPANT INFORMATION SHEET

Evaluating eye movements in a normative population as an indicator for monitoring the progression of Huntington's Disease (HD)

Approval No: 1389
Version: 1.0

What is this study about?
Huntington's Disease (HD) is a genetic, neurodegenerative disorder characterised by abnormalities in movement, cognitive decline and psychological problems. Since the discovery of the gene mutation causing HD in 1993, the understanding of the disease has increased exponentially, partly due to the establishment of international networks that have facilitated multisite clinical studies and interactions between scientists and clinics caring for HD patients. However, despite this progress, no disease-modifying treatment is available for HD, and symptomatic treatments are very limited and largely anecdotal rather than evidence based.

Abnormal eye movements are associated with the progression of HD and currently, subjective assessments of eye movements are included within the Unified Huntington Disease Rating Scale (UHDRS) motor testing. Quantifiable measurement of eye movements using an eye tracker has indicated oculomotor abnormalities in HD compared to people without HD (controls). These abnormalities agree strongly with the recognised diagnostic tests and can be used as a non-invasive diagnostic utility. Therefore, eye movements appear to be a reliable indicator for HD, and as such, an eye tracker could be used as a non-invasive measure of disease progression in future observational studies and drug trials.

Why have I been invited to take part?
You are being recruited as I require data for subjects without HD to use a baseline for a subsequent comparison with subjects with HD.

Do I have to take part?
Participation in this study is voluntary. You may withdraw from the study at any time without consequence.

What will happen to me if I take part?
The procedure will consist of visual tasks involving you being asked to either look towards a target, away from a target or to follow a target presented on a large screen. During each of these tasks, your eye movements will be monitored and recorded. For this study, you will only need to be present for one session lasting no more than 30 minutes.

Do I need to do anything special to take part?
Before you can participate in the project, we will require you to provide informed written consent. Subsequent to providing your written consent, if you decide that you no longer wish to be involved with the study, you will not be included.

What are the possible benefits of taking part?
There will be no direct benefit to the participants involved, however by participating you will help to validate the quality of the results taken from later studies involving subjects with HD. This may help other people in the future.

Are there any possible risks from taking part?
There are no risks in taking part in this study. The instrument we will use to measure the orientation and position of your eye is completely harmless and non-invasive. However, this study is not suitable for individuals with photosensitive epilepsy due to the health and safety issues that arise from the use of computer screens.

Expenses and payments.
Unfortunately, there will not be any expenses or payments available for participation in this study.

Will my results remain confidential?
In line with School Ethics guidelines, all information containing subject identifiers will be stored securely, either in locked storage cabinets or in password protected computer file space. If analysis takes place under non-secure conditions (such as paper copies, etc.), all data will be coded, and these codes will be stored separately and securely.
Security of data storage will be the responsibility of the lead researcher.
All procedures are compliant with the Data Protection Act 1998.

What will happen to the results of this study?
The results from this study will be published as part of a PhD thesis and may be used as baseline data in research paper(s). All results will be anonymised, and it will not be possible to identify individual subjects. If you would like to learn the results of the study once it is completed, please contact Mr James Brawn (brawnjn@cardiff.ac.uk).

Who is funding the research?
Cardiff University (JE Williams Studentship)

Who has reviewed the study?
All research at Cardiff University is reviewed by an independent group of people not involved in the study who comprise the Research Ethics Audit Committee, to protect your interests. This study has been reviewed and approved by the School of Optometry and Vision Sciences Research Ethics Committee (Cardiff University).

What if I have any questions or if I have a problem?
Should you have any questions, we would be very happy to discuss our project further with you.

If you have any questions about this research, please contact:

Mr James Brawn
Email: brawnjn@cardiff.ac.uk
School of Optometry and Vision Sciences, Maindy Road, CF24 4HQ

Professor Jonathan Erichsen
Email: erichsenjt@cardiff.ac.uk
School of Optometry and Vision Sciences, Maindy Road, CF24 4HQ

Professor Tom Freeman
Email: freemanT@cardiff.ac.uk
School of Psychology, Tower Building, 70 Park Place, CF10 3AT

Dr. Matthew Dunn
Email: dunnmj1@cardiff.ac.uk
School of Optometry and Vision Sciences, Maindy Road, CF24 4HQ

Thank you for taking time to read this information.

Cardiff University School of Optometry and Vision Sciences
Maindy Road
Cardiff CF24 4HQ

Quantitative assessment of eye movements in Huntington's disease

Participant information sheet; Version 1.1

We would like to invite you to take part in a research study that is investigating how eye movements change in Huntington's disease. This is a study that has been put together by researchers in the Cardiff University Huntington's disease clinic and the School of Optometry and Vision Sciences. This is a pilot study of around 20 people with HD. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and to discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not to participate.

What is the purpose of this study?
This study is aiming to understand whether eye movement abnormalities can be measured in HD and whether they change at different stages of the condition. We want to know this because we are hoping to use eye movement measurements in the future to assess how useful new treatments are, and also because we think that eye movement abnormalities may be important for some symptoms such as falling in HD. We are hoping that the information we collect in this study will allow us to develop methods for measuring eye movement abnormalities in HD that can be used for future studies.

Why have I been invited?
You have been invited because you carry the HD gene and/or you have been clinically diagnosed with HD.

Do I have to take part?
It is entirely up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you do decide to take part, you are still free to withdraw at any time in the future without giving a reason. A decision to withdraw or not to take part will not affect your clinical care in any way.

What will happen to me if I take part?
If you do decide to take part, we will arrange for you to come to the Cardiff University School of Vision Sciences on Maindy Road for an eye test and some eye

movement measurements. Together these will take between an hour and one and a half hours.

Eye movement measurements
We will be using one of two pieces of equipment to assess your eye movements. The first is the "Tobii TX300", which will not involve any contact: you will simply need to sit in front of the device at the right distance and head height and then look at a variety of visual stimuli as they are presented on the screen. An alternative piece of equipment that we may use is the "Eyelink 1000", which uses a chin rest and has the option of a head rest. We will need to make a decision on the day as to which piece of equipment we will use. This will depend on a number of factors, including our results with other subjects up to that point, and whether you have involuntary head movements or not. We will tell you which piece of equipment we plan to use with you on the day of your visit.

What are the possible benefits of taking part?
This study aims to understand whether the Tobii TX300 equipment can be used to measure eye movements accurately in HD and whether we can pick up changes in eye movements at different stages of the condition. We are hoping to use eye movement measurements in the future to assess the effectiveness of new treatments and to understand some of the symptoms in HD such as falls.

What happens when the research study stops?
As during the study, when the study stops, your care will continue as normal. We will analyse the results of this study and will provide you with some feedback on the results of the research. We may publish the results in scientific journals.

What if relevant new information becomes available?
No information that affects your care or treatment is likely to arise from this study. However, should something emerge from our research that has direct relevance to your care we would get in touch with you if that is what you would like.

What if there are problems?
If you have any concern about any aspect of this study, you should speak to Matthew Dunn, who will do his best to answer the questions or to direct you to the appropriate person. If you remain unhappy and want to complain formally, you can do this by contacting Ms Helen Falconer, R&D officer, Cardiff University (phone 02920879130)

Are there any compensation arrangements if something goes wrong?
In the unlikely event of anything untoward happening and this being due to someone's negligence, then you may have grounds for a legal action for compensation against Cardiff University. You may have to pay your own legal costs.

Will my taking part in this study be kept confidential?
All information about you during the course of this research will be kept strictly confidential. Personal data relating to you will be available to the research team at the School of Vision Sciences during your visit but will not be kept there long term (less than 3 months). During this time it will be stored securely (in a locked filing cabinet in a lockable room and on computer in encrypted folders). After this period, any data

pertaining to you in the School of Vision Sciences will be identified by a number only. We may share our data with other scientists and clinicians or publish it in scientific journals. In all these cases we will remove any potentially identifying information and you will be referred to by your gender, age and non-identifying characteristic, such as right or left handedness.

Will my General Practitioner be notified of my participation in the research?
Yes, unless you wish us not to do so. Your GP will receive some information about the study, but they will not be sent the results. The exception to this is if something unexpected is discovered that is important for your care. In this case we would make a special arrangement and would inform your GP.

What will happen to the results of the research study?
Once data from all participants is available, it will be analysed and if possible, written up for publication or presentation. We hope that the results may also be used as the foundation for further studies.

Who is funding the research?
The equipment has been purchased through an endowment fund for HD research and through a University Research fund in Vision Sciences.
Other elements of the study are funding through research monies within Cardiff University.

Who has reviewed the study?
All research in the NHS is examined by an independent group of people called the Research Ethics committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by the South East Wales Research Ethics Committee.

Further information
If you would like further information or would like to discuss any aspect of the proposed research, then please contact:

Matthew Dunn, BSc (Hons) OPTOM
School of Optometry and Vision Sciences
Maindy Road
Cardiff CF24 4HQ

Tel 02920870556

Appendix VIII – Consent Form: Control (First HD Study)

Cardiff University School of Optometry and Vision Sciences
Maindy Road

Quantitative assessment of eye movements in Huntington's disease

Control consent sheet; Version 1.1

To confirm agreement with each of the statements below, please initial in the box

1. I confirm that I have read and understood the information sheet for the above study (*Eye movements in Huntington's disease; Control Information Sheet; Version 1 Date)*. I have had the opportunity and time to consider the information, ask questions and have had these answered satisfactorily. ☐

2 I understand that my participation is voluntary, and that I am free to withdraw my consent at any time, without giving any reason, and without my medical care or legal rights being affected. ☐

3. I understand that the study will not benefit me or my family directly ☐

4. I give permission for my GP to be informed that I am taking part in this study. ☐

5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Cardiff University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

6. I agree to participate in the above study ☐

Participant

Name (BLOCK letters)	Date	Signed
_____	_____	_____

PERSON TAKING CONSENT
I have explained the study to the above patient and she has indicated her willingness to take part.

Name (BLOCK letters)	Signed	Date
_____	_____	_____

Appendix IX – Consent Form: HD (First HD Experiment)

Cardiff University School of Optometry and Vision Sciences
Maindy Road

Quantitative assessment of eye movements in Huntington's disease

Participant consent sheet; Version 1.1

To confirm agreement with each of the statements below, please initial in the box

1. I confirm that I have read and understood the information sheet for the above study (*Eye movements in Huntington's disease; Patient Information Sheet; Version 1.1 Date*). I have had the opportunity and time to consider the information, ask questions and have had these answered satisfactorily. ☐

2 I understand that my participation is voluntary, and that I am free to withdraw my consent at any time, without giving any reason, and without my medical care or legal rights being affected. ☐

3. I understand that the study will not benefit me or my family directly ☐

4. I give permission for my GP to be informed that I am taking part in this study. ☐

5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Cardiff University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

6. I agree to participate in the above study ☐

PATIENT

Name (BLOCK letters)	Date	Signed
_____	_____	_____

PERSON TAKING CONSENT

I have explained the study to the above patient and he/she have indicated their willingness to take part.

Name (BLOCK letters)	Signed	Date
_____	_____	_____

Appendix X – Ethical Approval (Second HD Study)

North of Scotland Research Ethics Committee (1)
Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net

NHS Grampian

26 July 2017

Professor Anne E Rosser
Professor of Clinical Neuroscience
Cardiff University
Dept of Psychological Medicine & Neurology
School of Medicine
Heath Park
CARDIFF
CF14 4XN

Dear Professor Rosser

Study title:	**Quantitative assessment of eye movements in Huntington's disease: sensitivity to disease progression and functional impact**
REC reference:	**17/NS/0031**
IRAS project ID:	**198487**

Thank you for your letter of 13th July 2017, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the Lead Reviewer.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see

"Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only): Cardiff University Indemnity Insurance		18 July 2016
IRAS Checklist XML: Checklist 26.07.2017		26 July 2017
Letter from sponsor: Sponsorship Acceptance Letter		23 January 2017
Non-validated questionnaire: Exit Questionnaire	1.2	10 July 2017
Eyelink SetUp		20 March 2017
Lab Setup		21 March 2017*
TOPF Word Card		20 March 2017
WASI Stimulus Book 1		20 March 2017
WASI Stimulus Book 2		20 March 2017
WASI Blocks		20 March 2017
Pro forma IRAS 198487		20 March 2017
Statistical Review Email		06 July 2017
Response to Review	1	13 July 2017
Participant consent form: Participant Consent Form (Control)	1.3	10 July 2017
Participant consent form: Participant Consent Form (HD)	1.3	10 July 2017
Participant information sheet (PIS): Participant Information Sheet (Control)	1.3	10 July 2017
Participant information sheet (PIS): Participant Information Sheet (HD)	1.3	10 July 2017
REC Application Form	198487/1111477/1/324	15 March 2017
Research protocol or project proposal: Research Protocol	1.6	10 July 2017
Summary CV for Chief Investigator (CI): Anne Rosser	1	02 March 2017
Summary CV for student: James Brawn	1	01 March 2017
Summary CV for supervisor (student research): Jon Erichsen	1	22 February 2017

*date received

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance

on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our RES Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/NS/0031	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Professor Helen Galley
Chair

Enclosures: "After ethical review – guidance for researchers" SL-AR2

Copy to: Helen Falconer
Ms Lee Hathaway, University Hospital of Wales

Cardiff University School of Optometry and Vision Sciences
Maindy Road
Cardiff CF24 4HQ

Quantitative assessment of eye movements in Huntington's disease

Participant information sheet (Control); Version 1.4 10/05/2018

We would like to invite you to take part in a research study that is investigating how eye movements change in Huntington's disease. This is a study that has been put together by researchers in the Cardiff University Huntington's disease clinic and the School of Optometry and Vision Sciences. This is a study involving people with HD, and a cross-matched control group. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and to discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not to participate.

What is the purpose of this study?
This study is aiming to understand whether eye movement abnormalities can be measured in HD and whether they change at different stages of the condition. We want to know this because we are hoping to use eye movement measurements in the future to assess how useful new treatments are, and also because we think that eye movement abnormalities may be important for some symptoms such as falling in HD. We are hoping that the information we collect in this study will allow us to develop methods for measuring eye movement abnormalities in HD that can be used for future studies. This study will also be used for the purposes of a PhD.

Why have I been invited?
You have been invited to be part of the control group as someone without HD.

Do I have to take part?
It is entirely up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you do decide to take part, you are still free to withdraw at any time in the future without giving a reason. A decision to withdraw or not to take part will not affect your clinical care in any way.

Will I be reimbursed for my time and/or expenses
There will be no reimbursement for your time or any expenses accrued to partake in the study

What will happen to me if I take part?
If you do decide to take part, we will arrange for you to come to the Cardiff University School of Vision Sciences on Maindy Road for an IQ test and some eye movement measurements. Together these will take no more than 60 minutes.

Eye movement measurements
We will be using the "Eyelink 1000", which uses a chin rest and has the option of a head rest and 'head free' tracking. You will simply need to look at a variety of visual stimuli as they are presented on the screen.

IQ measurements
We will be using two IQ tests; the TOPF (Test of Premorbid Function) and the WASI-II (Wechsler Abbreviated Scale of Intelligence). You will be required to read a list of words from a card and to solve some simple puzzles.

What are the possible benefits of taking part?
There is no direct benefit to yourself for taking part in this study. This study aims to understand whether the Eyelink 1000 can be used to measure eye movements accurately in HD and whether we can pick up changes in eye movements at different stages of the condition. We are hoping to use eye movement measurements in the future to assess the effectiveness of new treatments and to understand some of the symptoms in HD such as falls.

What happens when the research study stops?
As during the study, when the study stops, your care will continue as normal. We will analyse the results of this study and will provide you with some feedback on the results of the research. We may publish the results in scientific journals.

What if there are problems?
If you have any concern about any aspect of this study, you should speak to James Brawn, who will do his best to answer the questions or to direct you to the appropriate person. If you remain unhappy and want to complain formally, you can do this by contacting Dr Lee McIlreavy, lecturer, School of Optometry & Vision Sciences, Cardiff University Cardiff University (phone 02920875665)

Are there any compensation arrangements if something goes wrong?
In the unlikely event of anything untoward happening and this being due to someone's negligence, then you may have grounds for a legal action for compensation against Cardiff University. You may have to pay your own legal costs.

Will my taking part in this study be kept confidential?
All information about you during the course of this research will be kept strictly confidential. Personal data relating to you will be available to the research team at the School of Vision Sciences during your visit but will not be kept there long term (less than 3 months). During this time it will be stored securely (in a locked filing cabinet

in a lockable room and on computer in encrypted folders). After this period, any data pertaining to you in the School of Vision Sciences will be identified by a number only. We may share our data with other scientists and clinicians or publish it in scientific journals. In all these cases we will remove any potentially identifying information and you will be referred to by your gender, age and non-identifying characteristic, such as right or left handedness.

Will my General Practitioner be notified of my participation in the research?
No, due to the nature of the measurements we will be taking, it is unlikely that anything unexpected in nature relevant to your current health will be found.

What will happen to the results of the research study?
Once data from all participants is available, it will be analysed and if possible, written up for publication or presentation. The data from this study will be used for the purposes of a PhD. We hope that the results may also be used as the foundation for further studies and for potential publication.

Who is funding the research?
The equipment has been purchased through an endowment fund for HD research and through a University Research fund in Vision Sciences.
Other elements of the study are funding through research monies within Cardiff University.

Who has reviewed the study?
All research in the NHS is examined by an independent group of people called the Research Ethics committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and approved by the North of Scotland Research Ethics Committee.

Compliance with General Data protection Regulations (GDPR).
Cardiff University is the Data Controller and is committed to respecting and protecting your personal data in accordance with Data Protection legislation. The University has a Data Protection Officer who can be contacted at inforequest@cardiff.ac.uk. Further information, including your rights and details of how to lodge a complaint, can be found at the following website: https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection"

Under data protection law we have to specify the legal basis that we are relying on to process your personal data. We will process your personal data on the basis that doing so is necessary for our public task for scientific research purposes.

Further information
If you would like further information or would like to discuss any aspect of the proposed research, then please contact:

James Brawn, BSc (Hons) MCOptom
School of Optometry and Vision Sciences
Maindy Road
Cardiff CF24 4HQ Tel 02920870556

Cardiff University School of Optometry and Vision Sciences
Maindy Road
Cardiff CF24 4HQ

Quantitative assessment of eye movements in Huntington's disease

Participant information sheet (HD); Version 1.3 10/07/2017

We would like to invite you to take part in a research study that is investigating how eye movements change in Huntington's disease. This is a study that has been put together by researchers in the Cardiff University Huntington's disease clinic and the School of Optometry and Vision Sciences. This is a study involving people with HD, and a cross-matched control group. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and to discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not to participate.

What is the purpose of this study?
This study is aiming to understand whether eye movement abnormalities can be measured in HD and whether they change at different stages of the condition. We want to know this because we are hoping to use eye movement measurements in the future to assess how useful new treatments are, and also because we think that eye movement abnormalities may be important for some symptoms such as falling in HD. We are hoping that the information we collect in this study will allow us to develop methods for measuring eye movement abnormalities in HD that can be used for future studies. This study will also be used for the purposes of a PhD.

Why have I been invited?
You have been invited because you carry the HD gene and/or you have been clinically diagnosed with HD.

Do I have to take part?
It is entirely up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you do decide to take part, you are still free to withdraw at any time in the future without giving a reason. A decision to withdraw or not to take part will not affect your clinical care in any way.

Will I be reimbursed for my time and/or expenses
There will be no reimbursement for your time or any expenses accrued to partake in the study

What will happen to me if I take part?
If you do decide to take part, we will arrange for you to come to the Cardiff University School of Vision Sciences on Maindy Road for an IQ test and some eye movement measurements. Together these will take no more than 60 minutes.

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What are the possible benefits of taking part?
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What happens when the research study stops?
As during the study, when the study stops, your care will continue as normal. We will analyse the results of this study and will provide you with some feedback on the results of the research. We may publish the results in scientific journals.

What if relevant new information becomes available?
No information that affects your care or treatment is likely to arise from this study. However, should something emerge from our research that has direct relevance to your care we would get in touch with you if that is what you would like.

What if there are problems?
If you have any concern about any aspect of this study, you should speak to James Brawn, who will do his best to answer the questions or to direct you to the appropriate person. If you remain unhappy and want to complain formally, you can do this by contacting Dr Lee McIlreavy, lecturer, School of Optometry & Vision Sciences, Cardiff University Cardiff University (phone 02920875665)

Are there any compensation arrangements if something goes wrong?
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All information about you during the course of this research will be kept strictly confidential. Personal data relating to you will be available to the research team at the School of Vision Sciences during your visit but will not be kept there long term (less

than 3 months). During this time it will be stored securely (in a locked filing cabinet in a lockable room and on computer in encrypted folders). After this period, any data pertaining to you in the School of Vision Sciences will be identified by a number only. We may share our data with other scientists and clinicians or publish it in scientific journals. In all these cases we will remove any potentially identifying information and you will be referred to by your gender, age and non-identifying characteristic, such as right or left handedness.

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Further information
If you would like further information or would like to discuss any aspect of the proposed research, then please contact:

James Brawn, BSc (Hons) MCOptom
School of Optometry and Vision Sciences
Maindy Road
Cardiff CF24 4HQ

Tel 02920870556

Email: brawnjn@cardiff.ac.uk

Cardiff University School of Optometry and Vision Sciences
Maindy Road

Quantitative assessment of eye movements in Huntington's disease

Participant consent sheet (Control); Version 1.4 10/05/2018

To confirm agreement with each of the statements below, please initial in the box

1. I confirm that I have read and understood the information sheet for the above study (*Eye movements in Huntington's disease; Patient Information Sheet (Control); Version_____)*. I have had the opportunity and time to consider the information, ask questions and have had these answered satisfactorily. ☐

2 I understand that my participation is voluntary, and that I am free to withdraw my consent at any time, without giving any reason, and without my medical care or legal rights being affected. ☐

3. I understand that the study will not benefit me or my family directly ☐

4. I understand that relevant sections of the data collected during the study may be looked at by individuals from Cardiff University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

The data controller is Cardiff University and the Data Protection Officer is Matt CooperCooperM1@cardiff.ac.uk . The lawful basis for the processing of the data you provide is consent.

5. I agree to participate in the above study ☐

PATIENT

Name (BLOCK letters)	Date	Signed
_____	_____	_____

PERSON TAKING CONSENT

I have explained the study to the above patient and he/she have indicated their willingness to take part.

Name (BLOCK letters)	Signed	Date
_____	_____	_____

Cardiff University School of Optometry and Vision Sciences
Maindy Road

Quantitative assessment of eye movements in Huntington's disease

Participant consent sheet (HD); Version 1.3 10/07/2017

To confirm agreement with each of the statements below, please initial in the box

1. I confirm that I have read and understood the information sheet for the above study (*Eye movements in Huntington's disease; Patient Information Sheet (HD); Version _____*). I have had the opportunity and time to consider the information, ask questions and have had these answered satisfactorily. ☐

2 I understand that my participation is voluntary, and that I am free to withdraw my consent at any time, without giving any reason, and without my medical care or legal rights being affected. ☐

3. I understand that the study will not benefit me or my family directly ☐

4. I understand that relevant sections of the data collected during the study may be looked at by individuals from Cardiff University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

5. I agree to participate in the above study ☐

PATIENT

Name (BLOCK letters)	Date	Signed
_____	_____	_____

PERSON TAKING CONSENT

I have explained the study to the above patient and he/she have indicated their willingness to take part.

Name (BLOCK letters)	Signed	Date
_____	_____	_____

Appendix XV – Recruitment Letter for Participants

Dear

You are being contacted as you have previously indicated an interest in being involved in, or have been involved with research studies into Huntington's Disease, through our clinic at Cardiff University.

I am due to start a new study looking into using eye movements to help diagnose and manage Huntington's Disease. This is a non-invasive study consisting of a single visit lasting approximately 45 minutes at the School of Optometry, Cardiff University (next door to the HD clinic). During this visit you will be required to look at objects on a screen, and to answer a short IQ test.

We are flexible on times and are happy to work around your schedule with appointments 9am to 5pm Monday to Friday. We are looking to commence this study 9th April 2018, so would be happy to book you in any date from then.

If you would like to take part in this study, or if you have any questions, please contact me on brawnjn@cardiff.ac.uk

Please find enclosed the participant information sheet for this study.

Kindest regards

James Brawn BSc (Hons) MCOptom
School of Optometry and Vision Sciences
Maindy Road
Cardiff CF24 4HQ
brawnjn@cardiff.ac.uk

Appendix XVI – Exit Questionnaire

Cardiff University School of Optometry and Vision Sciences
Maindy Road

Quantitative assessment of eye movements in Huntington's disease

Feedback Questionnaire; Version 1.2 10/07/2017

If it can be demonstrated that the tests you undertook today can reliably and accurately measure the disease progression in HD, it is likely that they may be used in a clinical setting for routine assessment, or used as an outcome measure in future trials. Therefore it is important that we understand the experience of those who have participated in this study, so we can optimize our future designs. Completing this questionnaire is entirely voluntary, and all answers will be anonymised, so that you cannot be identified from your responses.

Please answer the following questions as follows:
1. Strongly disagree, 2. Disagree, 3. Neither agree nor disagree, 4. Agree, 5. Strongly agree

1. How did you find the duration of the eye movement tests?

   1 2 3 4 5

2. How did you find the duration of the IQ tests?

   1 2 3 4 5

3. How did you find the difficulty of the eye movement tests?

   1 2 3 4 5

4. How did you find the difficulty of the IQ tests?

   1 2 3 4 5

5. Was there anything you did not like about the tests today?

   ……

6. Overall, what was your impression of the tests you undertook today?

   ……

7. Do you have any suggestions in how we may improve our testing?

   ……

8. Would you sit for these tests again?

   Yes No

Appendix XVII – TOPF Score Sheet

TOPF^{UK} Record Form

Test of Premorbid Functioning – UK Edition

	Calculation of Examinee's Age		
	Year	Month	Day
Test Date			
Birth Date			
Test Age			

Examinee Name:

Examiner Name:

Additional Demographics Questions

Gender

Male	
Female	

Tick box as appropriate

Years of Education

Years of full-time education		
Years of part-time education	(x 0.5)	+
Total years of education		=

Hand-Scoring Calculations

Estimate ability from:

	TOPF^{UK} only (use Tables C.1, C.3)
	TOPF^{UK} plus demographics (use Appendix B)

Tick box as appropriate

TOPF^{UK} Raw Score

Analysis of Results

Index	Obtained Score	Estimated Premorbid Score	Discrepancy (Obtained minus Estimated)	Percentage of normative population expected to exhibit a lower discrepancy score: Point Estimate (plus 95% CI)
WAIS-IV^{UK}				
FSIQ				
VCI				
PRI				
WMI				
PSI				
WMS-IV^{UK}				
IMI				
DMI				
VWMI				

PEARSON PsychCorp

Administration

Place the TOPF[UK] Word Card in front of the examinee. Point to the card and say, **Beginning with the first word on the list, read each word aloud. Start with this word** (point to Item 1), **and go down this column** (move finger down first column). **When you finish the first column, go to the next column** (point to the second column). **Try to pronounce each word, even if you are unsure. Do you understand?** Explain further if necessary; then say, **Begin**.

Additional prompts, given during testing, are included on the item response pages.

If the examinee has not met the discontinue criterion on Item 36, say, **Turn the card over and keep going**. Continue administration until the examinee completes the items or the discontinue criterion has been met.

If the examinee meets the discontinue criterion, say, **Stop**.

Published by Pearson Assessment, 80 Strand, London WC2R 0RL

Printed in China.(CTPS/05)

15 16 17 18 E F G H

ISBN: 978 0 749160 10 4

Materials	Start	Discontinue	Score
TOPF[UK] Word Card	**Ages 16-90:** Item 1	After 5 consecutive scores of 0	Score 0 or 1 point for each response.

Additional Prompts

If, at any time during administration, you are unsure which word the examinee is reading, say, **Point to the word you are reading.**

If the examinee's rate of reading is too rapid for accurate scoring, say, **You are going too fast for me to keep up. Please read the words more slowly.**

If the examinee's response is unclear, say, **Say it again.**

If the examinee asks what to do if he or she makes a mistake, say, **You can try it again.** If the examinee self-corrects his or her initial response, award credit appropriately. Examinees may correct their initial response(s) at any time during administration.

If the examinee provides multiple responses to an item, score only the intended response. If it is not clear which one is the intended response, say, **You pronounced the word more than one way. Which one did you mean?**

Give no further assistance except to remind the examinee to continue until told to stop (if necessary) or to redirect the examinee to the appropriate word or column.

Item		Score	
1. two	(TOO)	0	1
2. address	address (uh-DRESS) or (ah-DRESS) or (AD-dress)	0	1
3. whole	(HOHL)	0	1
4. eye	(I)	0	1
5. again	(ah-GAIN) or (ah-GEHN) or (uh-GAIN) or (uh-GEHN)	0	1
6. enough	(ee-NUHF) or (uh-NUHF) or (in-NUHF)	0	1
7. already	(awl-RED-ee)	0	1
8. cough	(KAWF) or (kof)	0	1
9. fuel	(FYOOL)	0	1
10. climb	(KLIM)	0	1
11. most	(MOHST)	0	1
12. excitement	(ik-SITE-munt) or (eck-SITE-munt)	0	1
13. mosquito	(muh-SKEE-toh)	0	1
14. decorate	decorate (DEK-oh-rate) or (DEK-uh-rate)	0	1
15. fierce	(fee-us) or (feerss)	0	1
16. plumb	(PLUM)	0	1
17. knead	(NEED)	0	1
18. vengeance	(VEN-jnss) or (VEN-junss)	0	1

Item		Score	
19. gnat	(NAT)	0	1
20. prestigious	(pre-STIJ-us) or (pre-STEEJ-us)	0	1
21. amphitheatre	(AM(p)-fih-thee-uh-ter) or (AM(p)-fih-theeta)	0	1
22. lacuna	(la-KOO-nuh)	0	1
23. iridescent	(ihr-ih-DESS-unt) or (ihr-uh-DESS-unt)	0	1
24. lieu	(LOO) or (l(y)oo)	0	1
25. wily	(WI-lee)	0	1
26. aesthetic	(ess-THET-ik) or (ees-THET-ik)	0	1
27. equestrian	(eh-KWESS-tree-un) or (ih-KWESS-tree-un)	0	1
28. porpoise	(POR-poyz; Scots) or (PAW-pus) or (POR-pus)	0	1
29. subtle	(SUH-tuhl)	0	1
30. palatable	(PAL-ah-tuh-bul) or (PAL-uh-tuh-bul)	0	1
31. homily	(HOM-ih-lay) or (HOM-ih-lee)	0	1
32. ogre	(OH-gur)	0	1
33. liaison	(lee-AY-zon(g)) or (lee-AH-zn)	0	1
34. xenophobia	(zen-oh-FO-bee-uh) or (zen-uh-FO-bee-uh)	0	1
35. piquant	(PEE-kuhnt) or (PEE-kwant)	0	1
36. menagerie	(meh-NA-juh-ree)	0	1

Additional Prompts

If, at any time during administration, you are unsure which word the examinee is reading, say, Point to the word you are reading.

If the examinee's rate of reading is too rapid for accurate scoring, say, You are going too fast for me to keep up. Please read the words more slowly.

If the examinee's response is unclear, say, Say it again.

If the examinee asks what to do if he or she makes a mistake, say, You can try it again. If the examinee self-corrects his or her initial response, award credit appropriately. Examinees may correct their initial response(s) at any time during administration.

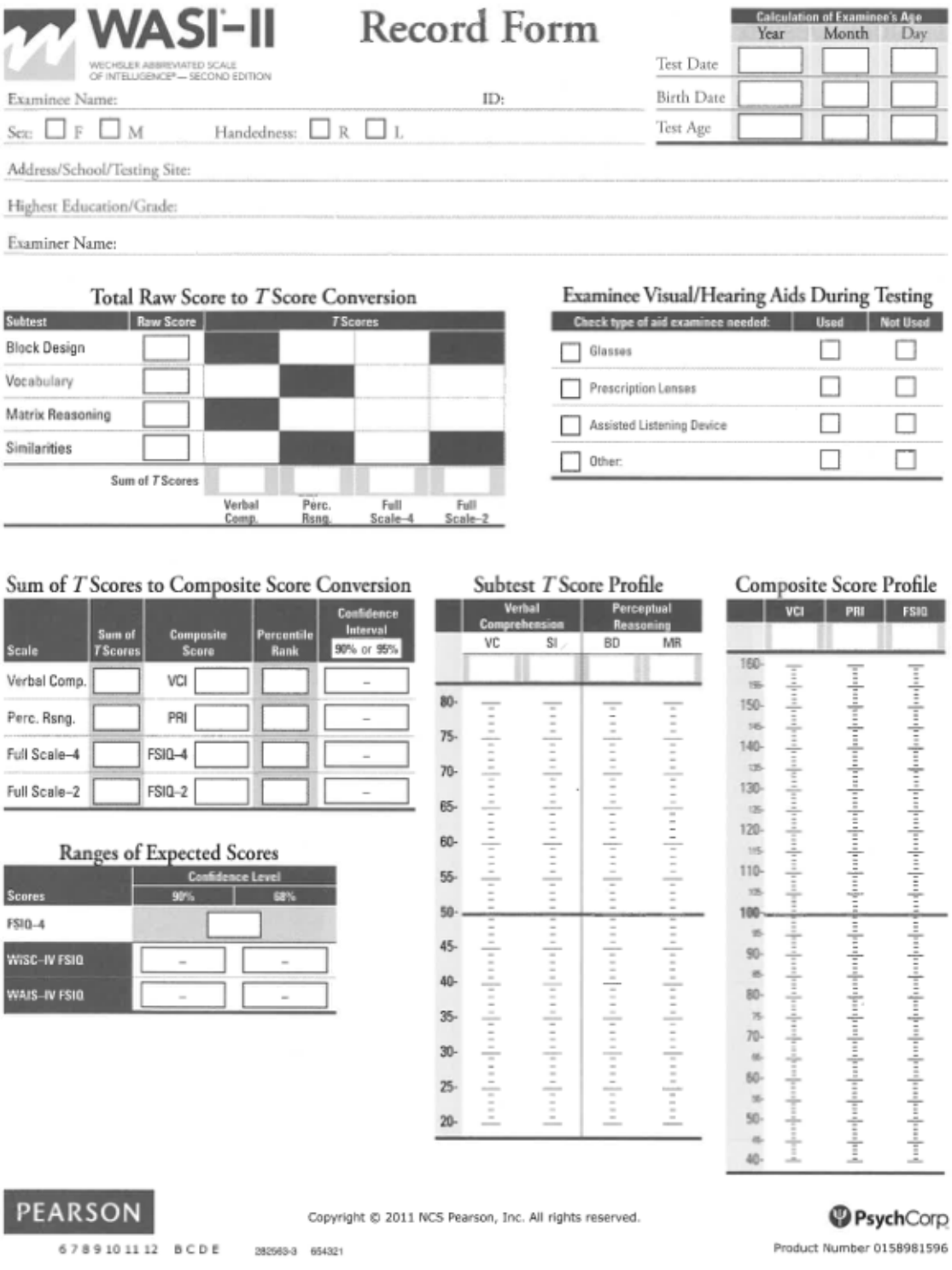
If the examinee provides multiple responses to an item, score only the intended response. If it is not clear which one is the intended response, say, You pronounced the word more than one way. Which one did you mean?

Give no further assistance except to remind the examinee to continue until told to stop (if necessary) or to redirect the examinee to the appropriate word or column.

Item		Score	
37. umbrage	(UHM-brihj)	0	1
38. fecund	(FE-cund) or (FEE-cund)	0	1
39. scurrilous	(SKUH-ruh-lus) or (SKUR-ih-lus) or (SKUR-uh-lus) or (SKUH-rih-lus)	0	1
40. heinous	heinous (HE-nus) or (HEE-nus) or (HAY-nuss)	0	1
41. obfuscate	(OB-fuh-skat)	0	1
42. plethora	(PLETH-oh-rah) or (PLETH-eh-rah)	0	1
43. exigency	(eks-IH-jen-say) or (eks-IH-jen-see)	0	1
44. lascivious	(lah-SIH-vee-uhs) or (luh-SIH-vee-uhs)	0	1
45. picot	(PEE–koh)	0	1
46. cretonne	(kre-TON) or (KRE-ton)	0	1
47. vicissitude	(vi-SI-si-tyood)	0	1
48. ethereal	(ih-THEE-ree-ul) or (ih-THEER-ee-ul)	0	1
49. uxorious	(uhk-SOHR-ee-uhs) or (uhg-SOHR-ee-uhs)	0	1
50. lugubrious	(loo-GOOB-ree-uss) or (luh-GOOB-bree-uss)	0	1
51. misogyny	(meh-SAW-jeh-nee) or (mih-SAW-jin-ay)	0	1
52. perspicuity	(per-spuh-KYEW-ih-tay) or (per-speh-KYEW-uh-tee) or (per-speh-KYEW-uh-tay)	0	1
53. ubiquitous	(you-BIC-wih-tiss) or (you-BIC-wuh-tiss) or (you-BIC-wuh-tuss)	0	1

Item		Score	
54. dichotomy	(dye-KAW-toh-may) or (dye-KAW-toh-mee)	0	1
55. facetious	(fuh-SEE-shuhss) or (fah-SEE-shuss)	0	1
56. treatise	(TREE-tiss) or (TREET-iss) or (TREE-tiz) or (TREET-iz)	0	1
57. paradigm	(PAH-rah-dime)	0	1
58. macabre	(mah-KABR) or (mah-KAAB)	0	1
59. anechoic	(ah-nih-KOH-ihk)	0	1
60. acquiesce	(ah-kwee-EHSS)	0	1
61. dilettante	(DILL-ih-tan-tay) or (DILL-uh-tahnt)	0	1
62. eyrir	(AY–rihr)	0	1
63. hyperbole	(hy-PER-bu-lay) or (hy-PUR-bu-lay)	0	1
64. vertiginous	(ver-TIH-juh-nuhss) or (ver-TIDJ-in-iss)	0	1
65. hegemony	(HEH-geh-mon-ee) or (heh-GEM-o-nee) or (heh-JEM-o-nee)	0	1
66. insouciant	(in-SOO-see-(y)ant) or (ihn-SOO-see-unt) or (in-SOO-see-(y)unt)	0	1
67. vide	(VI-day) or (VI-dee) or (VEE-day)	0	1
68. ceilidh	(KAY-lee)	0	1
69. vivace	(vee-VAH-chay) or (vee-VAH-chee)	0	1
70. chthonic	(THON-ik)	0	1
	Test of Premorbid Functioning Total Raw Score (Max = 70)		

Appendix XVIII – WASI-II Score Sheet



WASI-II Record Form

WECHSLER ABBREVIATED SCALE OF INTELLIGENCE — SECOND EDITION

Examinee Name: ID:

Sex: F M Handedness: R L

Address/School/Testing Site:

Highest Education/Grade:

Examiner Name:

Calculation of Examinee's Age	Year	Month	Day
Test Date			
Birth Date			
Test Age			

Total Raw Score to *T* Score Conversion

Subtest	Raw Score	*T* Scores			
Block Design					
Vocabulary					
Matrix Reasoning					
Similarities					
Sum of *T* Scores					
		Verbal Comp.	Perc. Rsng.	Full Scale–4	Full Scale–2

Examinee Visual/Hearing Aids During Testing

Check type of aid examinee needed:	Used	Not Used
Glasses		
Prescription Lenses		
Assisted Listening Device		
Other:		

Sum of *T* Scores to Composite Score Conversion

Scale	Sum of *T* Scores	Composite Score	Percentile Rank	Confidence Interval 90% or 95%
Verbal Comp.		VCI		–
Perc. Rsng.		PRI		–
Full Scale–4		FSIQ–4		–
Full Scale–2		FSIQ–2		–

Ranges of Expected Scores

Scores	Confidence Level 90%	68%
FSIQ–4		
WISC–IV FSIQ	–	–
WAIS–IV FSIQ	–	–

Subtest *T* Score Profile

Verbal Comprehension		Perceptual Reasoning	
VC	SI	BD	MR

80 75 70 65 60 55 50 45 40 35 30 25 20

Composite Score Profile

VCI	PRI	FSIQ

160 150 140 130 120 110 100 90 80 70 60 50 40

PEARSON

6 7 8 9 10 11 12 B C D E 282563-3 654321

PsychCorp

Product Number 0158981596

2. Vocabulary

Start
Ages 6–90: Item 4

Reverse
Ages 6–90: Does not obtain a perfect score on *either* Item 4 or Item 5, administer the preceding items in **reverse** order until two consecutive perfect scores are obtained.

Discontinue
After **3** consecutive scores of 0.

Stop
Age 6: After Item 22.
Ages 7–11: After Item 25.
Ages 12–14: After Item 28.

Record & Score
Items 1–3: Score **0** or **1** point.
Items 4–5: Score **0** or **2** points.
Items 6–31: Score **0**, **1**, or **2** points.
See the Manual for sample responses.

	Item	Response	Score
	1. Fish		0 1
	2. Shovel		0 1
	3. Shell		0 1
6–90	†4. Shirt		0 2
	5. Car		0 2
	6. Lamp		0 1 2
	7. Bird		0 1 2
	8. Tongue		0 1 2
	9. Pet		0 1 2
	10. Lunch		0 1 2
	11. Bell		0 1 2
	12. Calendar		0 1 2
	13. Alligator		0 1 2
	14. Dance		0 1 2

†If the examinee provides a 2-point response that requires feedback or gives an incorrect (0 point) response, provide corrective feedback as instructed in the Manual.

continue

Product Number 0158981596

Vocabulary *(continued)*

Discontinue after **3** consecutive scores of 0.

	Item	Response	Score
	15. Summer		0 1 2
	16. Reveal		0 1 2
	17. Decade		0 1 2
	18. Entertain		0 1 2
	19. Tradition		0 1 2
	20. Enthusiastic		0 1 2
	21. Improvise		0 1 2
	22. Haste		0 1 2
STOP	23. Trend		0 1 2
	24. Impulse		0 1 2
	25. Ruminate		0 1 2
STOP	26. Mollify		0 1 2
	27. Extirpate		0 1 2
	28. Panacea		0 1 2
STOP			

continue

2. Vocabulary *(continued)*

Discontinue after **3** consecutive scores of 0.

Item	Response	Score
29. Perfunctory		0 1 2
30. Insipid		0 1 2
31. Pavid		0 1 2

Maximum Raw Score
Age 6: 41
Ages 7–11: 47
Ages 12–14: 53
Ages 15–90: 59

Vocabulary Total Raw Score ____

3. Matrix Reasoning

Start
Ages 6–8: Sample Items A & B, then Item 1
Ages 9–90: Sample Items A & B, then Item 4

Reverse
Ages 9–90: Does not obtain a perfect score on *either* Item 4 or Item 5, administer the preceding items in **reverse** order until two consecutive perfect scores are obtained.

Discontinue
After **3** consecutive scores of 0.

Stop
Ages 6–8: After Item 24.

Record & Score
Score **0** or **1** point.
Correct responses are in **color**.

	Item	Response	Score
6–90	SA.	1 **2** 3 4 5	
	SB.	1 2 **3** 4 5	
6–8	1.	1 **2** 3 4 5	0 1
	2.	**1** 2 3 4 5	0 1
	3.	1 2 **3** 4 5	0 1
9–90	4.	**1** 2 3 4 5	0 1
	5.	1 2 3 4 **5**	0 1
	6.	**1** 2 3 4 5	0 1
	7.	1 2 **3** 4 5	0 1
	8.	1 2 **3** 4 5	0 1
	9.	1 2 3 **4** 5	0 1
	10.	1 **2** 3 4 5	0 1
	11.	1 2 **3** 4 5	0 1
	12.	1 2 3 **4** 5	0 1
	13.	**1** 2 3 4 5	0 1
	14.	1 2 3 **4** 5	0 1
	15.	1 **2** 3 4 5	0 1
	16.	1 2 3 4 **5**	0 1
	17.	1 2 3 **4** 5	0 1
	18.	1 **2** 3 4 5	0 1
	19.	1 2 3 **4** 5	0 1
	20.	1 **2** 3 4 5	0 1
	21.	1 2 **3** 4 5	0 1
	22.	1 2 **3** 4 5	0 1
	23.	**1** 2 3 4 5	0 1
6–8 STOP	24.	1 2 3 **4** 5	0 1
	25.	1 2 3 **4** 5	0 1
	26.	1 **2** 3 4 5	0 1
	27.	1 2 3 4 **5**	0 1
	28.	1 2 3 4 **5**	0 1
	29.	**1** 2 3 4 5	0 1
	30.	1 **2** 3 4 5	0 1

Maximum Raw Score
Ages 6–8: 24
Ages 9–90: 30

Matrix Reasoning Total Raw Score ____