The Development of Novel Social Cognitive Tests in Frontotemporal Dementia

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SIGNED DECLARATION

I, Lucy Russell confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Signature:

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ABSTRACT

Frontotemporal dementia (FTD) is the second most common cause of early onset dementia in individuals under the age of 65, and in around one third of cases there is a known genetic cause: mutations in chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*) or microtubule-associated tau (*MAPT*). Language and behaviour are severely affected over the course of the disease, which consequently leads to the breakdown of social relationships. There are a number of problems with the current measures of social cognition, and the focus is mainly on symptomatic individuals, therefore missing those at-risk of FTD. Consequently, it is important to assess these tests in the at-risk cohort as we move towards therapeutic trials, and to also develop novel, more specific, and sensitive tasks. This thesis aims to address these issues using the current standardised tests, and modifying them into eye-tracking equivalents. The results highlight that the current measures are able to detect early social change, but only in individuals carrying a *C9orf72* mutation who are within five years to their estimated onset. Two of the novel social cognitive tests showed promise as symptomatic individuals with FTD were able to complete them, but to a lesser extent than controls. Performance was not due to oculomotor deficits. An anti-saccade test also displayed deficits in executive function in symptomatic individuals compared to controls. When these eye-tracking tasks were trialled in an at-risk cohort, the anti-saccade test displayed decreased performance in the *C9orf72* presymptomatic carriers compared to non-carriers; no differences were observed on the social cognitive tests. Consequently, this thesis demonstrates the need for new, more sensitive and specific tests for both symptomatic and presymptomatic individuals with FTD. This work highlights the need for careful test design, but it is clear that some tests are able to identify very early presymptomatic change in FTD.

IMPACT STATEMENT

It is estimated that around 850,000 people in the UK are living with dementia (Prince et al., 2014), of which around 16,000 of these are individuals living with Frontotemporal Dementia (FTD). In the UK at present, it is thought that dementia costs society around £26 billion per year. With no curative treatment yet to be found for any type of dementia, it is likely that the number of people living with this devastating disease will continue to increase, and so too will the cost. It is therefore vital that we work towards finding a cure.

Frontotemporal dementia is an ideal candidate for treatment trials as there is a clear known genetic cause for the condition, in particular the three-main mutations in *C9orf72*, *GRN* and *MAPT*. By targeting these mutations, it provides a mechanism which treatment can focus on, leading to specific and hopefully successful trials. In order to do this however, robust measures of disease progression are required to monitor the efficacy of the treatments. The work in this thesis may therefore influence the types of psychometric tests selected as cognitive outcome measures by pharmaceutical companies when designing their therapeutic trials. It indicates that the current tests used in the symptomatic FTD literature may not be sensitive enough for use in presymptomatic trials. It provides some suggestions for alternative tests through the use of eye-tracking. If treatment trials are one day successful, they will of course, not only impact the individuals themselves but also their loved ones, families and friends, in addition to reducing the cost to society.

Furthermore, this work furthers the academic field as it provides insight into social cognition in a presymptomatic cohort of individuals at-risk of developing FTD. In addition, when presenting this work at the International Conference of FTD, it encouraged other academics to think more broadly about their task designs, and urged them to design tests that are specific to the

cohort they are assessing. By challenging others to be more creative and specific with their task design, it will hopefully make psychometric testing more reliable, accurate and accessible.

Many family members and friends of loved ones with FTD have participated in the work in this thesis. It can be a very upsetting, frustrating and difficult position for them to be in, as it is a challenging disease to cope with. To try and help, I have presented this work at the rare dementia support group to provide information about the way in which these social interactions may break down, and provide a listening ear to those with problems or questions. If this work has helped even just one family member or carer understand the condition a little better, and alleviated some pain in their grief, in my opinion, it makes this work worthwhile.

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I would firstly like to dedicate this work to all those individuals, their carers, family members and friends who participated in this research. Without you, we would never be able to understand this devastating disease and be able to have some hope, that one day we may find a cure. Your stories are inspirational, and demonstrate that no matter what life may throw at you, there is always more you can give, so thank you.

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I would also like to thank all those who work on GENFI, both near and far. It is amazing the amount of data that is collected as part of the project, and experiments such as mine would not be able to happen if it was not for you all.

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To Joan, Ernie, Maureen, and Gordon, you are forever in my thoughts. This was for you.

DIVISION OF LABOUR

The work in this thesis was carried out by LLR in collaboration with researchers on the GENFI project and colleagues at the Dementia Research Centre. See below for an outline of contributions.

CONTRIBUTIONS	
Chapter 3: Emotion processing and theory of mind in a familial cohort of FTD: A GENFI study	
Experimental design	LLR in collaboration with JDR
Construction of tests	LLR in collaboration with KMM, JDR
Data collection	LLR and research assistants across the GENFI sites
Data analysis	LLR in collaboration with JMN
Writing	LLR
Chapter 5: Basic oculomotor function in FTD	
Experimental design	LLR in collaboration with DK, JDR
Construction of tests	LLR in collaboration with DK
Data collection	LLR
Data analysis	LLR
Writing	LLR
Chapter 6: Novel social cognitive eye-tracking tests	
Experimental design	LLR in collaboration with SJC, SP, JDR
Construction of tests	LLR
Data collection	LLR
Data analysis	LLR in collaboration with JMN
Writing	LLR
Chapter 7: Emotion processing eye-tracking tests in a presymptomatic FTD cohort	
Experimental design	LLR in collaboration with JDR
Construction of tests	LLR
Data collection	LLR in collaboration with RSC
Data analysis	LLR
Writing	LLR

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ABBREVIATIONS

AD	-	Alzheimer's Disease
ALLFTD	-	ARTFL and LEFFTDS Longitudinal Study
ALS	-	Amyotrophic lateral sclerosis
ANG	-	Anger
ARTFL	-	Advanced research and treatment for frontotemporal lobar degeneration
BPVS	-	British picture vocabulary scale
bvFTD	-	Behavioural variant Frontotemporal Dementia
C9orf72	-	Chromosome 9 open reading frame 72
CBI	-	Cognitive behavioural inventory
CBS	-	Corticobasal syndrome
CDR	-	Clinical dementia rating scale
CF	-	Cumulative frequency
CHMP2B	-	Charged multivesicular body protein 2b
CI	-	Confidence intervals
CSF	-	Cerebrospinal fluid
D-KEFS	-	Delis-Kaplan executive system
D-NOS	-	Dementia - not otherwise specified
DARTEL	-	Fast-diffeomorphic image registration algorithm
DEU	-	German
DIS	-	Disgust
DLPFC	-	Dorsolateral prefrontal cortex
DRC	-	Dementia Research Centre
EC	-	Empathic concern
EET	-	Emotional evaluation test
EF	-	Executive Function
ENG	-	English
EP	-	Emotion processing
ESP	-	Spanish
EX	-	Sensitivity to expressive behaviour
EYO	-	Estimated years to onset
FCSRT	-	Free and cued selective reminding test
FDA	-	Food and drug association
FER	-	Facial Emotion Recognition
FP	-	Faux-Pas
FRA	-	French
FRS	-	Frontotemporal dementia rating scale
FS	-	Fantasy
FTDC	-	International behavioural variant frontotemporal dementia consortium

FTLD	-	Frontotemporal Lobar Degeneration
FUS	-	Fused in sarcoma
FWE	-	Family-wise error
GENFI	-	Genetic frontotemporal dementia initiative
GM	-	Grey matter
GNT	-	Graded naming test
GP	-	General practitioner
GRN	-	Progranulin
HAP	-	Happiness
HC	-	Healthy control
IA	-	Interest area
IQ	-	Intelligence quotient
IRI	-	Interpersonal reactivity index
ITA	-	Italian
LEFFTDS	-	Longitudinal evaluation of familial frontotemporal dementia subjects
LIFTD	-	Longitudinal investigation of frontotemporal dementia
LMM	-	Linear mixed model
lvPPA	-	Logopenic variant Primary Progressive Aphasia
MAPT	-	Microtubule-associated protein tau
mIRI	-	Modified interpersonal reactivity index
MMSE	-	Mini mental state examination
MND	-	Motor Neurone Disease
MNI	-	Montreal neurological institute
MRI	-	Magnetic Resonance Imaging
ms	-	milliseconds
NA	-	Not applicable
NAAC	-	The national Alzheimer's coordinating centre
NART	-	National adult reading test
nfvPPA	-	Non-Fluent Variant Primary Progressive Aphasia
NHNN	-	National Hospital for Neurology and Neurosurgery
NLDS	-	Dutch
PD	-	Personal distress
PET	-	Positron Emission Tomography
PI	-	Principle investigator
PNG	-	Portable network graphics
PPA	-	Primary Progressive Aphasia
PPA-NOS	-	Primary Progressive Aphasia - not otherwise specified
PRT	-	Portuguese
PSP	-	Progressive Supranuclear Palsy
PT	-	Perspective taking
QC	-	Quality checked
Q-Q	-	Quantile-Quantile

RBG - Red, green and blue
RMIE - Reading the mind in the eyes test
RMT - Recognition memory test
ROI - Region of interest
RSMS - Revised self-monitoring scale
SAD - Sadness
SD - Standard deviation
SEA - Social and emotional assessment
SI-M - Social inference minimal test
SOB - Sum of boxes
SP - Self-presentation
SPECT - Single Photon Emissions computed Tomography
SPM - Statistical parametric mapping
SQSTM1 - Sequestosome 1
SQWJ - Square wave jerks
SUR - Surprise
svPPA - Semantic variant Primary Progressive Aphasia
SWE - Swedish
TASIT - The awareness of social inference test
TBK1 - TANK-binding kinase 1
TDP-43 - TAR DNA-binding protein 43
TMT - Trails making test
ToM - Theory of mind
TREM2 - Triggering receptor expressed on myeloid cells 2
TV - Television
UCL - University College London
VA - Visual angle
VBM - Voxel based morphometry analysis
VCP - Valosin-containing protein
VMPFC - Ventromedial prefrontal cortex
VOSP - Visual object and space perception test
WASI - Wechsler abbreviated scale of intelligence
WM - White matter
XNAT - Extensible neuroimaging archive toolkit
ZM - Zygomaticus major

CHAPTER 1: INTRODUCTION

1.1 History and Overview of FTD

August H., a 71-year-old man, was seen by Professor Arnold Pick in 1892. He presented with a progressive deterioration in cognition over a two-year period. He displayed abnormal behaviours, for example, threatening his wife in bouts of anger, language, speech and memory disturbances, and acting in a childlike manner (Pick, Girling, & Berrios, 1994). At post mortem, he was found to have narrowed gyri and marked atrophy, particularly in the left temporal lobe and Pick argued that this was the cause of the patient's symptoms. By 1911, Alois Alzheimer suggested that argyrophilic globular neuronal cytoplasmic inclusions (later termed Pick bodies), were the pathological cause of the atrophy experienced by August H (Alzheimer, 1911). After many clinical and pathological observations of other individuals with similar behavioural and speech problems, the term Pick's disease had emerged to describe their symptoms (Onari & Spatz, 1926).

Throughout the next 30 years, very little research emerged. However, from the 1970's onwards, research into the field began to increase (Hodges, Patterson, Oxbury, & Funnell, 1992; Sasanuma & Monoi, 1975; Snowden, Goulding, & Neary, 1989; Warrington, 1975). The development of the term Primary Progressive Aphasia (PPA) emerged in 1987 (Mesulam, 1987) and the first Frontotemporal Dementia (FTD) criteria (which is now known as behavioural variant FTD) materialised in 1994 (Englund et al., 1994). This work therefore lead to the development of the term FTD which was used to describe a group of heterogeneous diseases, with predominant frontal and/or temporal lobe atrophy (Brun, 1987; Mann, South, Snowden, & Neary, 1993). Since then, it has been established that not all clinical cases present with Pick

bodies at post mortem (Cooper, Jackson, Lennox, Lowe, & Mann, 1995). It is now known that there are multiple clinical phenotypes that are caused by a wide variety of different pathologies (Arai et al., 2006; Neumann et al., 2009; Neumann et al., 2006), and a number of genetic factors (Cruts et al., 2006; Lashley, Rohrer, Mead, & Revesz, 2015; Poorkaj et al., 1998; Renton et al., 2011) (see *Figure 1-1*).

Therefore, FTD is now an umbrella term used to describe a heterogeneous group of progressive neurodegenerative diseases, which are characterised by selective atrophy in the frontal and/or temporal lobes (Kessels et al., 2007; Woollacott & Rohrer, 2016) with non-Alzheimer's type pathology (Lashley et al., 2015). While the term FTD refers to the clinical condition, the term frontotemporal lobar degeneration (FTLD) specifically describes the pathological syndrome (Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011). Around 90% of FTD cases can be attributed to TDP-43 and Tau pathologies, but there are other distinct pathologies, for example FTLD-FUS (Lashley et al., 2015). The disease progresses from a specific onset of behavioural and/or language changes and cognitive decline, towards a more generalised dementia (Seelaar et al., 2011). It is the second most common cause of young onset dementia, after Alzheimer's disease (AD) and is predicted to occur in around 15-20 people per 100,000 (Onyike & Diehl-Schmid, 2013). It often occurs in individuals under the age of 65, but it is estimated that around 25% of cases do occur in older age (Onyike & Diehl-Schmid, 2013).

1.2 Clinical Phenotypes

Despite the complexity of FTD, the current consensus is that there are two clinical phenotypes: behavioural variant Frontotemporal Dementia (bvFTD) which typically affects one's behaviour, and primary progressive aphasia (PPA) which causes problems with an individual's speech and language. PPA

can be split into three further subdivisions: semantic variant PPA (svPPA) which leads to impaired single word comprehension due to the gradual breakdown of semantic memory; non-fluent/agrammatic variant PPA (nfvPPA) that is characterised by effortful speech as a result of progressive decline in language output; and logopenic variant PPA (lvPPA) in which impaired sentence repetition and pauses in speech are observed (Gorno-Tempini et al., 2011; Warren, Rohrer, & Rossor, 2013). In addition to bvFTD and PPA, there are a number of other clinical syndromes that are associated with FTD. These include, but are not limited to, corticobasal syndrome (CBS), progressive supranuclear palsy (PSP) and motor neurone disease/amyotrophic lateral sclerosis (MND/ALS). This thesis however, will focus on bvFTD, but it is worth noting the relationship with these disorders.

1.2.1 Behavioural variant FTD

BvFTD involves a progressive decline in interpersonal and executive skills (Rascovsky et al., 2011; Warren et al., 2013). Altered emotional responses, the development of obsessions and/or rituals, plus the emergence of a variety of abnormal behaviours such as apathy, disinhibition and hyperorality, are all key characteristics of bvFTD (Rascovsky et al., 2011; Warren et al., 2013). It is often the case that the symptoms are reported by a spouse, family member, or close friend, and is often unseen by the individual themselves (Mendez & Shapira, 2011). These problems tend to be detected due to breakdowns in personal relationships, or a result of problems arising in the work place. Often, the symptoms are classed as "a mid-life crisis" or "marital problems", and can go undiagnosed and undetected for many years (Besser & Galvin, 2019). It can also be misdiagnosed as a variety of other conditions, such as depression, schizophrenia, and AD (Woollacott & Rohrer, 2016). Clinicians should therefore ensure that both the patient and the informant are carefully

questioned and consider all information provided, to safeguard against a misdiagnosis (Besser & Galvin, 2019).

A variety of brain imaging techniques, such as magnetic resonance imaging (MRI), functional MRI (fMRI), single photon emission computed tomography (SPECT) and positron emission tomography (PET) have been used to monitor the effects of bvFTD in the brain (Gordon, Rohrer, & Fox, 2016). Individuals with bvFTD have consistently shown grey matter volume loss in the prefrontal cortex, the anterior cingulate, anterior insula, and the temporal lobe (Schroeter, Raczka, Neumann, & Von Cramon, 2007, 2008). Hypometabolism is also present in bvFTD patients in the rostral medial frontal, frontal pole, dorsolateral frontal and orbitofrontal areas, as well as the temporal lobe, the anterior cingulate, anterior insula, hippocampus, and subcortical areas such as the striatum (Ishii, 2014; Verfaillie et al., 2015).

In an attempt to improve the reliability of diagnosis, in 2011 the diagnostic criteria were revised by the International Behavioural Variant FTD Criteria Consortium (FTDC). The aim was to overcome some of the ambiguity of behavioural descriptions in the previous criteria, as well as to overcome the rigidity of meeting all five core features, which will not be sensitive enough in upcoming clinical trials (Rascovsky et al., 2011). This led to the splitting of the diagnosis into possible and probable bvFTD (see Table 1-1). Possible FTD requires three out of six clinical symptoms to be present, as well as a progressive decline in the individuals behaviour and/or cognition as reported by an informant. To be classed as having probable bvFTD, the conditions of possible FTD must be met, along with consistent imaging results. This revision has improved the accuracy of a bvFTD diagnosis. It is able to distinguish between individuals with bvFTD that have FTLD pathology at postmortem and those that do not, with a sensitivity rate of around 75-85%, and has a 82-95% specificity rate (Harris et al., 2013; Rascovsky et al., 2011).

Table 1-1: The international consensus criteria for bvFTD.

INTERNATIONAL CONSENSUS CRITERIA FOR BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA

I. Neurodegenerative Disease:

A. Must show a progressive deterioration of behaviour and/or cognition by observation or history (from a knowledgeable informant)

II. Possible bvFTD:

THREE OF THE FOLLOWING MUST BE PRESENT. SYMPTOMS MUST BE PERSISTENT AND NOT A SINGLE CASE OR RARE EVENT. FOR A-E, ONE OF THE CRITERIA MUST BE PRESENT. FOR F, ALL CRITERIA MUST BE MET.

A. Behavioural disinhibition
   - *A.1. Socially inappropriate behaviour*
   - *A.2. Loss of manners or decorum*
   - *A.3. Impulsive, rash or careless actions*

B. Early apathy or inertia
   - *B.1. Apathy*
   - *B.2. Inertia*

C. Early loss of sympathy or empathy
   - *C.1. Diminished response to others needs*
   - *C.2. Diminished social interested, interrelatedness or personal warmth*

D. Early preservative, stereotyped or compulsive/ritualistic behaviour
   - *D.1. Simple repetitive movements*
   - *D.2. Complex, compulsive or ritualistic behaviours*
   - *D.3. Stereotypy of speech*

E. Hyperorality and dietary changes
   - *E.1. Altered food preferences*
   - *E.2. Binge eating, increased consumption of alcohol or cigarettes*
   - *E.3. Oral exploration or consumption of inedible objects*

F. Neuropsychological symptoms
   - *F.1. Deficits in executive function*
   - *F.2. Relative sparing of episodic memory*
   - *F.3. Relative sparing of visuospatial skills*

III. Probable bvFTD:

ALL OF THE FOLLOWING SYMPTOMS MUST BE PRESENT. FOR C, ONE CRITERIA MUST BE MET.

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline from caregiver reports or by using the clinical dementia rating scale or functional activities questionnaire score

C. Imaging results are consistent with bvFTD
   - *C.1. Frontal and/or anterior temporal atrophy on MRI or CT*
   - *C.2. Frontal and/or anterior temporal hypofusion or hypometabolism on PET or SPECT*

IV. BvFTD with definite FTLD pathology

MUST MEET CRITERION A AND EITHER B OR C.

A. Meets criteria for possible or probably bvFTD

B. Histopathological evidence of FTLD on biopsy or at post mortem

C. *Presence of a known pathogenic mutation*

V. Exclusionary criteria for bvFTD

CRITERIA A AND B MUST BE ANSWERED NEGATIVELY FOR ANY BVFTD DIAGNOSIS. CRITERION C CAN BE POSITIVE FOR POSSIBLE BVFTD, BUT MUST BE NEGATIVE FOR PROBABLE BVFTD.

A. Deficits better accounted for by other non-degenerative nervous systems or medical disorders

B. Behavioural disturbances better explained by a psychiatric disorder

C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative disorder

** Early refers to the first 3 years*

1.3 Genetics of FTD

Whilst the majority of individuals with FTD are sporadic, FTD also has a number of genetic causes (Chow, Miller, Hayashi, & Geschwind, 1999). In around a third of individuals with FTD there is a known autosomal dominant genetic mutation (Beck et al., 2008; Rohrer et al., 2009). In those without a known genetic mutation, around 30-50% report a positive family history (Goldman et al., 2005; Rohrer et al., 2009). Three genes are most commonly associated with FTD: chromosome 9 open reading frame 72 (*C9orf72*) (DeJesus-Hernandez et al., 2011; Renton et al., 2011), progranulin (*GRN*) (Baker et al., 2006; Cruts et al., 2006), and microtubule-associated protein tau (*MAPT*) (Hutton et al., 1998), and mutations in these genes explains the majority of familial FTD (Sieben et al., 2012). There are a number of other genetic causes of familial FTD which include much rarer mutations in CHMP2B (2005), VCP (2004), FUS (2009), TBK1 (2015) and SQSTM1 (2012) genes, but these are not the focus of this thesis. The clinical presentation of the familial forms of FTD is usually bvFTD, rather than other clinical subtypes, but there are exceptions. The different mutations can also result in different pathology (see *Figure 1-1* for a summary of the clinical, pathological, and genetic interactions).

1.3.1 *MAPT*

Mutations in the *MAPT* gene were the first identified causative factor of FTD (Hutton et al., 1998; Poorkaj et al., 1998). The average age at onset in *MAPT* mutation carriers ranges from 20-80 years of age, with the mean age at onset around 50 years (Snowden et al., 2015). The average disease duration is around 8 years, but this can range from 3-30 years as some individuals are very slow to progress (Snowden et al., 2015).

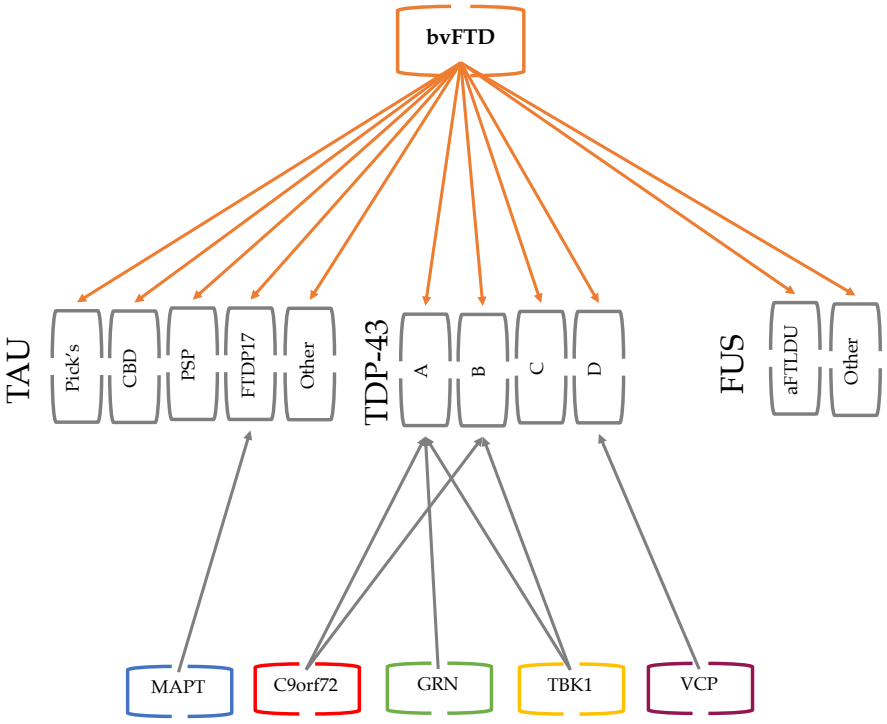

Figure 1-1: Displays the relationship between the clinical phenotype, the genetic cause and the underlying pathology of bvFTD.

The main clinical phenotype is of bvFTD, but this can be accompanied by a parkinsonian disorder such as CBS or PSP (Benussi, Padovani, & Borroni, 2015; Binnig, Rohrer, Gerber, & Weibel, 1982; Rohrer & Warren, 2011; Van Swieten & Spillantini, 2007). The most common symptoms observed in *MAPT* mutation carriers are increased inattention, disinhibition, and obsessional/impulsive behaviours (Ghetti et al., 2015). Episodic memory and semantic impairments often accompany this set of symptoms associated with *MAPT* mutations as well (Seelaar et al., 2011; Snowden et al., 2015). Grey matter atrophy has been found to occur in the anterior temporal lobe, which is relatively symmetrical, and also in the orbitofrontal cortices (Rohrer et al., 2010; Rohrer & Rosen, 2013; Whitwell et al., 2009).

1.3.2 *GRN*

In individuals with *GRN* mutations, the range of onset is between 35-89 years of age, with typical onset occurring in the late 50's and early 60's (Snowden et al., 2015). A similar disease duration occurs in *GRN* carriers as in *MAPT,* with a mean of around 9 years (range: 3-22) (Snowden et al., 2015).

Typical symptoms include more apathy and social withdrawal than the other two genetic mutations (Le Ber et al., 2008; Woollacott & Rohrer, 2016), and this is often accompanied by psychiatric problems such as hallucinations and delusions (Momeni et al., 2010). In some cases, episodic memory and more parietal functions, such as difficulties with calculation and visuospatial abilities, can also be affected (Snowden et al., 2015). In terms of clinical presentation, it is often mixed. While some individuals present with behavioural changes which is followed by language problems, others present with a PPA that does not fit cleanly into the three distinct profiles; it is therefore unspecified (PPA-NOS) (Rohrer et al., 2010). There is an asymmetrical involvement of either the right or left hemispheres, plus the involvement of the temporal, inferior frontal and inferior parietal lobes (Rohrer et al., 2010; Rohrer & Rosen, 2013; Whitwell et al., 2009).

1.3.3 *C9orf72*

The range in age at onset in *C9orf72*, is similar to the other two genetic mutations from 21-83 years of age, with the mean around 58 years (Snowden et al., 2015). The range in disease duration has been observed at the lower end, ranging from 1-22 years, however the mean does still fall around 8-9 years as in the other two mutations (Snowden et al., 2015).

Whilst *C9orf72* mutation carriers can present with bvFTD alone, they can also present with pure MND or a combination of the two (FTD-MND) (Lillo &

Hodges, 2009). In individuals with a *C9orf72* mutation, a presentation of one of the PPA syndromes is much less common. Typical symptoms include apathy and disinhibition, as well as unusual, repetitive and complex behaviours (Snowden et al., 2015). Psychosis and/or anxiety with very odd delusions and hallucinations are also common, in addition to problems with episodic memory, executive function, and parietal lobe deficits such as apraxia and dyscalculia (Mahoney, Beck, et al., 2012). Typically, there is symmetrical involvement of the frontal and temporal lobes, but also involvement of the more posterior cortical areas, as well as the thalamus and the cerebellum (Mahoney, Beck, et al., 2012; Mahoney, Downey, et al., 2012; Rohrer & Rosen, 2013; Sharon et al., 2012).

1.3.4 Individuals living at risk

For individuals with one of the known genetic mutations in a first degree relative, there is a 50% chance that they will develop FTD at some point in their lifetime (Woollacott & Rohrer, 2016). For any research studies of this population, a natural control group is generated i.e. those without the mutation, and a presymptomatic group i.e. those with the genetic mutation. This is important as clinical trials are about to begin, but there are still very few markers of disease progression that will help assess the effectiveness of the treatments. Whilst there is a move towards using neurofilament light chain (NfL), progranulin, and poly-GP dipeptide repeat proteins as blood and CSF biomarkers, and MRI scans as imaging markers of disease progression (Greaves & Rohrer, 2019), there are very few studies that have investigated the reliability and validity of neuropsychological assessments for this purpose.

Previously, one of the biggest challenges for research in this area, is that the studies are often made up of small cohorts, or even case studies. Due to these

small sample sizes, it is difficult to draw conclusions about the meaning of small psychological studies. However, this problem is overcome with the development of large cohort studies such as the Genetic Frontotemporal Dementia Initiative (GENFI) in Europe and Canada, and the ALLFTD study (previously the ARTFL and LEFFTDS studies) in America. The aim of these projects is to identify individuals with a known genetic mutation, and follow their family members over their lifetime. This monitoring of individuals allows the identification of the run-in period to the start of the symptom onset. It will provide the ability to more accurately stage the illness, learn more about the age at onset, disease duration, changes in the brain, blood and CSF, as well as identifying cognitive changes through clinical assessments and multiple neuropsychological tests. The increased number of participants in the studies, with a somewhat equal control and presymptomatic group, will allow for greater analysis and understanding of the changes that are happening prior to one's onset of symptoms.

One of the first studies produced as part of these projects, identified changes in the brain up to 25 years prior to symptom onset, and differences were identified in a number of neuropsychological tests when individuals were less than 5 years prior to their estimated onset (EYO) (Rohrer et al., 2015). The EYO was calculated by subtracting the individuals age away from the mean age at onset in the family. The main problem with this study however, was that there were not enough participants to identify differences between the genetic mutations. As the studies are ongoing, the number of participants taking part in the research continues to increase, thus improving the quality of the research and helping to understand more about the individual mutations in the early stages of the disease.

1.4 Social cognition in FTD

Despite the high sensitivity and specificity of the diagnostic criteria as mentioned in section 1.2.1, it does overlook the impairment of social cognitive abilities that are seen in the majority of FTD patients. Social cognition is defined as the ability to perceive, interpret and generate a response to the intentions, behaviours, and feelings of others (Adolphs, 2009); it is a set of skills that underlie our interactions with others. However, it is not a unitary concept and covers a wide variety of different processes (Pinkham, 2014). Two of these processes are emotion processing (EP) and theory of mind (ToM), both of which have been found to be impaired in bvFTD.

1.4.1 Emotion processing

Emotion processing is the ability to perceive, recognise and use emotional information from another to establish how they are feeling. This can be both verbal and/or non-verbal. Body movements, facial expressions including the eyes, vocal prosody, and tone, are all features which aid emotion processing and recognition. Ekman, Friedsen and Ellsworth (1972) describe six universal emotions that have been cross-culturally validated and these are: happiness, sadness, fear, disgust, anger, and surprise. The majority of emotion processing studies in FTD have based their tasks around these six emotions in a variety of different ways.

Facial emotions

When looking at the FTD spectrum, individuals have displayed difficulties with processing emotions in a face when asked to select an emotional label that matches the facial expression (Narme, Mouras, Roussel, Devendeville, & Godefroy, 2013; Narme, Roussel, Mouras, Krystkowiak, & Godefroy, 2016). This is especially the case in bvFTD when compared to healthy controls,

psychiatric patients, and other neurodegenerative diseases (Gossink et al., 2018; Kumfor, Ibanez, et al., 2018). While bvFTD patients appear to be able to recognise that an emotion is present, they find it challenging to identify which emotion is being shown (Bertoux, Cova, et al., 2014; Bertoux, de Souza, Sarazin, et al., 2015; Couto et al., 2013; Diehl-Schmid et al., 2007; Funkiewiez, Bertoux, de Souza, Lévy, & Dubois, 2012; Kumfor, Irish, Hodges, & Piguet, 2014; Omar, Rohrer, Hailstone, & Warren, 2011a). This is especially the case for negative emotions such as anger, sadness, and disgust, where individuals with bvFTD particularly struggle (Fernandez-Duque, Hodges, Baird, & Black, 2010; Kipps, Mioshi, & Hodges, 2009; Lavenu, Pasquier, Lebert, Petit, & Van der Linden, 1999). Neuroanatomical correlates associated with processing negative emotions are centred around the anterior temporal regions, whilst the fronto-parietal regions are thought to be involved with the processing of positive emotions in FTD (Park et al., 2017). In addition to this, the medial prefrontal cortex (Bertoux et al., 2012), as well as the left dorsolateral prefrontal cortex region (Bertoux, Volle, et al., 2014) are also thought to be involved with the processing of emotions. While this work indicates that there is a problem with emotion processing in bvFTD, the underlying cause needs further investigation.

It was hypothesised that this inability to process emotions in the face may be due to the expression not being exaggerated or clear enough for individuals with bvFTD to interpret. By altering the intensity of the emotions, it was found that the ability to understand them increased for positive emotions, but not for negative ones (Buhl, Stokholm, & Gade, 2013; Chiu et al., 2016; Kessels et al., 2007; Lough et al., 2006; Savage et al., 2014). It also transpires that the ability to classify the intensity of an emotional face, is also impaired in bvFTD (Chiu et al., 2018) and when asked to match emotional faces together, this still remained difficult (Kamminga et al., 2015; Shany-Ur et al., 2012). Despite this,

a more recent study using real life vignettes depicting facial emotions in response to positive or negative news, found that individuals with bvFTD processed the emotions better if they were of a higher intensity then a lower one for both positive and negative emotions (Carr, Ashla, Jimenez, & Mendez, 2018).

Other tests designed to be more ecologically valid, have also been developed. Using actors to express different emotions in short film clips, participants were asked to identify the emotion. This was the Emotional Evaluation test (EET) which is a subset of the TASIT – the Awareness of Social Inference test. Even though this task is more realistic, those with bvFTD still struggled to identify the emotions compared to controls (Downey et al., 2013; Kumfor et al., 2017; Sedeno et al., 2016), especially on items of sadness, fear, and disgust (Baez et al., 2014).

A more difficult test of emotion processing has been carried out in bvFTD patients – the Reading the Mind in the Eyes test. As expected, patients were impaired at processing more complex emotions from only the eye region of a face (Baez et al., 2014; Buhl et al., 2013; Couto et al., 2013; Schroeter et al., 2018; Sedeno et al., 2016). The hippocampus, para-hippocampal gyrus, the putamen and precuneus, as well as the right temporo-parietal junction (Baez et al., 2017) are brain regions associated with performance in bvFTD on this test. The gyrus rectus was also found to be involved (Couto et al., 2013). While the results from this test are not surprising, it has been suggested that it is a better diagnostic predictor than more typical measures of executive function, such as the Delis-Kaplan executive system (D-KEFS) colour/word inference test or the Trail Making Test (Schroeter et al., 2018). Furthermore, while it may be difficult for symptomatic individuals, it is possible that the greater complexity and difficulty of the test, might lend itself well to presymptomatic testing.

Other emotional processes

As a result of this work, it is clear that individuals with bvFTD have a deficit in their ability to process emotions in faces. However, it is not only the face that they struggle to process emotions in: auditory interpretation of emotions, understanding emotions in voice (Klimkowicz-Mrowiec et al., 2016; Shany-Ur et al., 2012) processing emotions in sound/music (Agustus et al., 2015; Fletcher et al., 2015; Omar, Henley, et al., 2011), as well as the ability to comprehend emotions in bodies are all affected (Jastorff et al., 2016; Van den Stock et al., 2015).

Embodied cognition

In order to understand the breakdown of the ability to process emotions, research has begun to investigate our bodily reactions to emotions – referred to as embodied cognition. When individuals with FTD are asked to produce a particular intentional facial expression in relation to an emotion, they find this difficult to do (Scherling et al., 2017), and in particular, those with bvFTD are unable to do this (Gola et al., 2017). Areas such as the insula, the inferior frontal gyrus, the medial orbitofrontal cortex/ventral medial prefrontal cortex, inferior frontal gyrus, right supramarginal gyrus and frontal opercula are all areas thought to be associated with this mimicry ability (Gola et al., 2017).

Despite all this, individuals with FTD are still able to produce automatic emotional expressions i.e. smiling when watching emotional films or looking at happy faces, but this is still lower than healthy controls (Chen et al., 2017; Marshall, Hardy, Russell, et al., 2018), and often the incorrect facial emotion is expressed i.e. amused face when watching a disgusting film clip (Chen et al., 2017). Consequently, this suggests that individuals with FTD are experiencing a variety of unrelated emotions when they receive emotional information. This may cause confusion as to what the target emotion actually

is, so they are unable to imitate it, and understand what the other person is feeling, thus resulting in the inability to process emotions.

A variety of other underlying mechanisms have also been investigated as the cause of this disrupted emotion processing network. With regards to the generation and identification of emotional faces, it has been suggested that this could be due to the inaccurate activation of the facial muscles. The zygomaticus major (ZM: the muscle involved in displaying positive emotions such as smiling) was shown to produce greater activation in individuals with bvFTD during neutral, negative, self-conscious, and positive stimuli when compared to healthy controls (Hua et al., 2018). This increase in reactivity was found to be associated with decreased emotion recognition and real-world empathy as evaluated on a caregiver rating scale (Hua et al., 2018). A number of neural correlates were also found to be associated with the increase in ZM reactivity including the: thalamus, posterior insula, the amygdala and inferior frontal gyrus (Hua et al., 2018). Another explanation of decreased emotional response comes from a reduction in cardiac reactivity. This appears to be reduced in individuals with bvFTD relative to healthy controls (Marshall et al., 2019) and correlates with frontal, insula, and cingulate grey matter volume (Marshall, Hardy, Allen, et al., 2018). Finally, skin conductance levels are also affected in emotion processing in patients with bvFTD, suggesting an overall dampening of responses to emotional stimuli (Gola et al., 2017; Kumfor, Hazelton, Rushby, Hodges, & Piguet, 2018; Mendez, Fong, Ashla, Jimenez, & Carr, 2018).

Embodied cognition is an emerging and interesting field. Whilst it is clear, there is a deficit in emotion processing in bvFTD, this work tries to explain which mechanisms are not functioning correctly, and what may be causing the deficit in emotion processing. Both intentional and automatic facial production appears to be affected in bvFTD. If they are unable to express the

emotions on their own faces, then it would be very challenging to understand that in others. This leads to the question of how individuals with bvFTD are meant to understand what others may be thinking, if they are unable to understand others emotions?

1.4.2 Theory of mind

Theory of mind is also known as mental state attribution, and refers to the ability to make inferences about the thoughts, beliefs and intentions of others. It allows us to have a theory about another's mind, enabling us to understand that another individual may have different beliefs and knowledge to our own. Much of the literature breaks down theory of mind into cognitive and affective theory of mind; (Shamay-Tsoory & Aharon-Peretz, 2007; Torralva, Gleichgerrcht, Torres Ardila, Roca, & Manes, 2015). The former refers to the ability to process inferences about others beliefs, while the latter refers to the processing of others emotions. For this section, ToM will refer to cognitive ToM only, as the affective ToM has previously been discussed (see section 1.4.1).

The faux-pas test

A faux-pas is a good example of when theory of mind occurs in everyday life. A faux-pas arises when someone has said something awkward or inappropriate in a social situation. The individual however, has not realised that their actions may have caused offence or upset to another. In order to detect this, one must have the ability to infer what both individuals in the situation may be thinking.

This ability to detect faux-pas in social situations however, is compromised in individuals with bvFTD (Bertoux, de Souza, O'Callaghan, et al., 2015; Bertoux, Funkiewiez, O'Callaghan, Dubois, & Hornberger, 2013; Funkiewiez et al.,

2012) (Giovagnoli, Bell, Erbetta, Paterlini, & Bugiani, 2019; Gossink et al., 2018; Narme et al., 2016). When breaking the test down, individuals with bvFTD were giving more false positives suggesting that a faux-pas has been committed when it had not (Giovagnoli et al., 2019; Gregory et al., 2002). While it appears that individuals with bvFTD are able to comprehend the stories (Guevara et al., 2015), the same pattern of results occurs even after taking comprehension into consideration (Narme et al., 2013). The medial rostral prefrontal cortex, extending to the dorsal anterior cingulate, correlated with performance on the faux-pas test (Bertoux et al., 2012; Bertoux, Volle, et al., 2014). It has also been suggested that the right dorsolateral prefrontal cortex, right orbitofrontal cortex, left lateral pre-motor cortex, left medial pre-motor cortex and left superior temporal cortex are involved (Guevara et al., 2015).

False belief tests

False belief tests assess how competent one is at understanding that someone else has a belief (which may be mistaken or not – 2nd vs 1st order false beliefs respectively), that is different to our own. This is a core feature of our theory of mind ability. In bvFTD, this is a difficult concept to process, and performance is significantly lower on tests assessing this (Shany-Ur et al., 2012). When breaking down 1st and 2nd order false beliefs, 1st order false beliefs are understood much better than 2nd order ones in bvFTD (Eslinger, Moore, Antani, Anderson, & Grossman, 2012; Fernandez-Duque, Baird, & Black, 2008). However, it has been suggested that despite this, 1st order beliefs are also significantly impaired in bvFTD (Gregory et al., 2002).

Non-Verbal ToM test

In order to remove the amount of language required as part of the ToM tests, in case this was the reason for the decreased performance, a non-verbal test

was designed to assess the ability to predict and envisage what will happen next in a given social scenario. In order to do this, one must be able to guess what another may be thinking, in order to predict their behaviour. It appears that this ToM ability is also impaired in bvFTD – they found it difficult to identify the picture that depicts the next logical event (Eslinger et al., 2007).

These non-verbal cartoon tests are important as they remove the impact that language has on the patient. This inability to predict social scenarios perhaps goes some way to explaining the unusual reactions seen in bvFTD patients. If they are unable to anticipate what will happen in a situation that they are in, it would be very difficult to expect them to respond appropriately.

Social Inference Minimal test (SI-M – TASIT sub-test)

As in section 1.4.1, the literature surrounding ToM abilities in FTD moved towards developing more ecologically valid tests. This ensures that there is a deficit in these abilities, and not a consequence of test design. The social inference minimal test (a subset of the TASIT), was developed to use sarcasm in actors as a way of investigating ToM in speech. It relies on an individual to understand that what someone else is saying, may be different to what they mean.

It appears that sarcasm is poorly interpreted in bvFTD (Buhl et al., 2013; Downey et al., 2015; Kipps, Nestor, Acosta-Cabronero, Arnold, & Hodges, 2009a; Kosmidis, Aretouli, Bozikas, Giannakou, & Ioannidis, 2008; Kumfor et al., 2017; Kumfor, Irish, Leyton, et al., 2014). In a shorter version of the task, due to the original being quite lengthy, similar results were found; performance in bvFTD was impaired (Kumfor et al., 2017). The temporal lobes, hippocampal gyri, the right middle temporal gyrus, the right superior frontal gyrus, and the head of the caudate were correlated with sarcasm in bvFTD (Kipps, Nestor, Acosta-Cabronero, Arnold, & Hodges, 2009b; Rankin

et al., 2009). In the shorter version of the test, sarcasm items were associated with the right amygdala and the left anterior fusiform cortex in bvFTD (Kumfor et al., 2017). This decreased ability to understand sarcasm, could in real life lead to patients having a heightened sense of confusion, again causing surprising responses that would perhaps not be expected.

1.4.3 Summary of social cognition in sporadic bvFTD

Emotion processing and theory of mind are therefore clearly affected in bvFTD, and it may go some way to explaining some of the abnormal behaviours that are exhibited in the patients. The processing of emotions in faces, bodies and sounds are all impaired, particularly on negative emotions. It is likely that this is due to problems with underlying bodily responses such as facial mimicry, activation of incorrect facial muscles, and problems with cardiac reactivity and skin conductance. Moreover, problems with theory of mind are observed when understanding social inconveniences, beliefs about others and predicting the actions of others, even when using more realistic scenarios.

1.4.4 Social cognition in familial FTD

There have however, been very few studies investigating emotion processing and theory of mind in familial cases of FTD, particularly in presymptomatic individuals. Two studies suggest that social cognition begins to decline in *MAPT* carriers around five years prior to their estimated onset (Jiskoot et al., 2016) and when following this longitudinally in converters (those who were originally recruited to the study as presymptomatic and then changed to having a clinical diagnosis), only those with a *MAPT* mutation declined over time on tests of social cognition (Jiskoot et al., 2018). This starts to suggest that there are some differences occurring between the genetic mutations. This

would be in line with the different clinical phenotypes and neuroanatomical profiles that are observed, and should be investigated further.

1.4.5 Problems with the current social cognitive tests

There are however a number of problems, pitfalls and limitations with the current tests being used. One of the biggest problems with the social cognitive testing is the production of a type I error. That is, producing a positive result that is not actually there. This may occur because individuals are unable to comprehend the test, due to the complexity of test instructions or stories that arise as a result of the linguistic demands of the tasks. As a consequence, they display a theory of mind deficit, when this may not actually be the case. Alternatively, individuals may not be able to comprehend certain aspects of the test, such as the emotional labels, and thus, deficits may appear when in fact this is not the case; rather the test is not suitable for the cohort and may not be measuring emotion processing. This leads onto controlling for confounding factors. It is vital that performance on these social cognitive tests are controlling for things such as executive function and comprehension, as they can lead to altered performance, particularly as these abilities are affected in bvFTD as outlined in the criteria (see Table 1-1).

Furthermore, there are a number of other issues to consider when interpreting the results. Firstly, many of the tests used produce qualitative data, for example the faux-pas test. This is data that does not have an explicitly correct result, but one that is interpreted by the researcher as right or wrong. This makes the data subjective, thus leading to problems with inter-rater reliability. Secondly, these tests are sometimes repeated by the same participant, and they may be exposed practice effects resulting in increased performance. Finally, some of the studies have very few participants. While this may be a result of how rare the condition is and how difficult it is to recruit participants,

it nevertheless, may lead to results that are not representative or ecologically valid.

When looking at the social cognitive literature in FTD as a whole, there are a few components that have been overlooked. Most of the neural correlates have arisen as a result of VBM analyses. Now whilst this is an automated test, that is objective and exploratory, there are issues associated with false positives and negatives, not to mention difficulties using it as a tool to assess changes in the brain over time. In addition to this, a large cohort of individuals with genetic FTD have been overlooked. Despite approximately a third of individuals with FTD having an autosomal dominant genetic mutation that causes their condition, there has been very little research so far investigating social cognition in genetic FTD.

1.5 Potential areas for future research

Given the difficulties with many of the task designs, future studies should aim at making simpler, more accessible and ecologically valid tests that try to prevent the possibility of a type I error. Furthermore, these tests should be more quantitative in nature to overcome the problems of inter-rater reliability. The progress of the large cohort studies such as GENFI and ALLFTD, will begin to overcome the problem of small sample sizes, a lack of longitudinal data, and performance in presymptomatic individuals that are approaching the time to symptom onset. It is important that these studies do focus on the impact of decreased social cognition and the impact this has on the individuals wellbeing, as well as their relationships; a breakdown in communication can heavily affect the individuals support network, and can place a great burden on their families and friends. By identifying these changes earlier, and knowing which mechanisms are causing the breakdown of the social cognitive skills, it may be possible to make improvements to the

quality of life, for both the individual and their families. It may also improve the diagnosis of the condition, and help towards identifying effective treatments by using psychological markers for disease progression.

1.6 Eye-tracking in FTD

Eye-tracking tasks have been used for many years to assess cognition in psychology. The first initial observation that the eyes do not move fluidly, but rather in what are known as saccades and fixations, was by Javel in 1879 when he was performing observations while participants were reading. This led to the development of the first eye tracker in 1908 by Edmund Huey, however this was highly intrusive. It was not until 1935, when Buswell developed an eye-tracking machine which used beams of light to track the eyes, that they became less invasive. Spanning through the 70's and 80's, eye-tracking machines continued to become more accessible and accurate, with the ability to separate the head and eye movements (Cornsweet & Crane, 1973). They are now currently video based.

Eye-tracking tasks are able to improve reliability of psychometric tests by providing a more quantitative analysis of the participants performance. The tests can be very simple and straightforward without the need for complex test instructions. This is beneficial as it requires less information to be understood by the participant, yet still provides insight as to their cognitive functioning. The eye trackers themselves are highly flexible and can meet a wide variety of task demands; the development of experiments is also relatively straight forward and easy to run. It does not require complex coding knowledge nor artificial intelligence/deep learning mechanisms to process the data (although this can be done) (Primativo et al., 2017). It has been a popular tool for social cognitive assessments in a variety of different populations, including infants (Yeung, Denison, & Johnson, 2016), adolescence

(Symeonidou, Dumontheil, Chow, & Breheny, 2016), autism spectrum disorders (Chevallier et al., 2015; Schwartzman, Velloso Rde, D'Antino, & Santos, 2015), and in schizophrenia (Bortolon, Capdevielle, Salesse, & Raffard, 2016; Roux, Smith, Passerieux, & Ramus, 2016). This demonstrates that eye-tracking is viable in a variety of different and difficult to test populations, and thus it may be a beneficial tool for psychometric testing in individuals with bvFTD as well.

1.6.1 Neuropsychological tests

There has been one study that has used eye-tracking as a tool to measure cognitive function in bvFTD. An instructionless adaptation of the Brixton spatial anticipation test was compared with the pen and paper original version. They found that the pen and paper test identified deficits in 7/12 participants with bvFTD, but this increased to 11/12 in the eye-tracking metric. This gives an indication that eye-tracking may be used as a tool to assess cognition. Furthermore, as this test was instructionless, it further adds weight to the benefits of using this method, as it keeps the test simple and straightforward for participants to understand. One concern addressed in the study, was that problems may be due to oculomotor functions. A number of measures were assessed (first saccade latency, time to fixate on the first target, the mean fixation duration and saccade velocity) using the stimuli in the study but it was found that none of the measures showed any deficits in the groups (Primativo et al., 2017).

1.6.2 Oculomotor functions

Whilst the study above used the task stimuli to assess basic oculomotor functions, a number of studies have been specifically designed for this purpose in FTD. The main focus has been three areas: pro-saccades (eye-movement towards a target), anti-saccades (eye-movement in the opposite

direction to a target) and pursuit tests (the ability to track a target as it moves across the screen).

Pro-Saccades

There are a number of metrics used to analyse pro-saccades. Saccade latency refers to the length of time taken to generate a saccade towards a target, amplitude error refers to how accurate the saccade is at meeting the target, and peak velocity is the maximum speed at which the eye moves towards the target during the saccade (Shakespeare et al., 2015).

A number of studies have suggested that saccade latency is significantly delayed in patients with bvFTD when compared to healthy controls (Burrell, Hornberger, Carpenter, Kiernan, & Hodges, 2012; Douglass, Walterfang, Velakoulis, & Abel, 2018; Meyniel, Rivaud-Pechoux, Damier, & Gaymard, 2005). However in another study, this difference was only found in vertical eye movements (Garbutt et al., 2008). In others, no difference in saccadic latency was found at all (Boxer et al., 2006). The amplitude error has also been found to be impaired in patients with bvFTD when compared to controls (Douglass et al., 2018; Garbutt et al., 2008). Despite this, some studies have found no such deficits on measures of peak velocity or the accuracy of the saccades (Boxer et al., 2006; Burrell et al., 2012).

Anti-Saccades

In contrast to the conflicting results on the pro-saccades, performance on anti-saccade tests unanimously indicates that individuals with FTD have difficulties with correctly completing the anti-saccade test as they were making fewer correct anti-saccades (Boxer et al., 2006; Boxer et al., 2012; Burrell et al., 2012; Douglass et al., 2018; Garbutt et al., 2008; Meyniel et al., 2005). However, in all the studies above, except for Boxer et al. (2012), the

individuals with FTD display no difficulties in correcting themselves once they realise they have committed an error.

Pursuit

Finally, it is also believed that the ability to follow a target is also impaired in individuals with bvFTD (Boxer et al., 2006; Garbutt et al., 2008).

1.6.3 Summary of eye-tracking in FTD

While there have been several studies using eye-tracking with individuals with bvFTD to measure eye movements, the results are conflicting and there has only been one study assessing cognition.

Differences in the equipment used for the oculomotor tests (only three out of the six studies used the same eye-tracking equipment) are likely to account for the variation observed on the tests. The test design and set up of the trials may also have contributed. It is likely that pro-saccades are not going to inhibit performance on test performance but given the conflicting results, basic eye movements should be considered as a pre-screen before completing any neuropsychology tests that use eye-tracking as its main metric.

1.7 Thesis rationale

BvFTD is a very complex and heterogeneous illness, and there are currently no disease modifying treatments available. While clinical trials are on the horizon for the three main genetic causes of FTD (Greaves & Rohrer, 2019), the ability to detect the effectiveness of such treatments remains difficult, given that there are few reliable and validated markers of disease progression, particularly psychometric ones. This issue is further compounded when considering that there is a lack of psychometric data in presymptomatic cases of FTD, especially in social cognition. Whilst it is known that social cognition

is affected in bvFTD from the studies discussed, there are some conflicting results and very little is understood about the changes in social cognition presymptomatically.

As there are conflicting results using the standardised pen and paper tests and there are a number of pitfalls and problems with them, the idea of using eye-tracking to overcome these problems is interesting. The few studies that have used eye-tracking in bvFTD provide some promise that it may be a useful tool for neuropsychological assessment in bvFTD. It demonstrates that individuals with bvFTD are able to use the eye tracker, despite all the symptoms that they experience. Furthermore, it removes a number of the problems associated with the standard psychometric tests. It is able to provide a quantitative analysis of cognition and potentially be extremely simple in design removing the need for complex test instructions and stories. Additionally, it may be more sensitive to change than the standardised pen and paper measures, as it gains specific and accurate time measurements that may reveal subtle changes in one's cognition early on in the disease.

1.8 Thesis outline

This project therefore aims to use eye-tracking as the main assessment tool for assessing social cognition in bvFTD. The reliability, accuracy, and sensitivity of a standard social cognitive test, is first established in a familial cohort. Then a novel set of tests assessing emotion processing and theory of mind in individuals with bvFTD is developed. This will improve our understanding of social cognitive deficits in bvFTD, particularly in familial FTD. Hopefully it may help with the staging of the condition, and provide psychometric markers for future clinical trials.

In chapter 3, the sensitivity of the Mini-social and Emotional Assessment (Mini-SEA) is assessed, which is comprised of an emotion processing and a

theory of mind test. All participants involved are enrolled in GENFI. This work specifically looks at identifying changes in the presymptomatic cohort across the three main genetic mutations involved in FTD: *C9orf72*, *GRN* and *MAPT*. It also investigates performance in symptomatic individuals.

Chapter 5, assesses the oculomotor functions of individuals with symptomatic bvFTD, and is made up of both sporadic and genetic cases, relative to healthy controls. Metrics associated with pro-saccades, anti-saccades, fixations and pursuit are measured to ensure that any deficits found in the eye-tracking tests are not a result of problems with eye movements. Neuroanatomical correlates are investigated with performance on these metrics, as well as examining the correlation with standard neuropsychometric tests.

Chapter 6 examines whether or not the novel eye-tracking tests are effective at measuring emotion processing and theory of mind in healthy controls, and then contrasts this to the performance in individuals with bvFTD. The aim is to identify a deficit in individuals with bvFTD, while at the same time, demonstrating that they do understand and comprehend the test.

Finally, in Chapter 7, the novel tests are implemented in a presymptomatic group of individuals that form a subset of GENFI at UCL. This is a pilot study which aims to assess whether or not, eye-tracking could be a more sensitive tool for assessing social cognition than the standardised pen and paper test. Given that the number of participants is not as large as those in Chapter 3, the aim is to establish if there is potential for these tests, and if it should be examined in a larger cohort of individuals.

CHAPTER 2: METHODS I – STANDARDISED MEASURES

2.1 Chapter overview

The aim of this research is to assess the sensitivity of a standard social cognitive test – the Mini-SEA, in a familial FTD cohort, and to develop a more accurate a reliable measure of social cognition through the use of eye-tracking. This chapter will therefore outline the general methods for the work in this thesis, and explain why certain procedures were chosen. Initially, the two cohorts of participants used in this thesis will be summarised, followed by a discussion around ethical procedures. The general study protocol, including the standard psychometric tests will be explained. An outline of the imaging procedures and statistical analysis will also be discussed.

2.2 Participant cohorts

Participants were recruited from two cohorts of individuals with FTD: one familial and one sporadic. The general assessment procedures were the same for both cohorts. The participants included were a subset of individuals from the main cohorts; not all participants in the cohorts completed the work associated with this thesis.

2.2.1 GENFI

The Genetic Frontotemporal Dementia Initiative (GENFI) focuses specifically on familial forms of FTD. The initiative is run from the Dementia Research Centre (DRC), University College London (UCL), but it encompasses 25 sites from across Europe and Canada. Symptomatic individuals are eligible for this study if they have a confirmed genetic diagnosis of FTD, of one of the three main genetic mutations: *C9orf72*, *MAPT* and *GRN*. Symptomatic participants are usually recruited from local cognitive disorders clinics.

Presymptomatic individuals are also eligible for the study if they have a first degree relative with a genetically confirmed diagnosis of FTD. Their relative does not have to participate in the study, however they must have proof of the genetic condition in order to be eligible. These participants can be contacted via their relative, a cognitive disorders clinic or if they have expressed a direct interest in the study. The presymptomatic individuals make up two groups: those that carry the mutation (presymptomatic mutation carriers), and those who do not (mutation negative controls). Participants are not required to know their own genetic status in order to participate in the study.

The project started in 2012. Since then, there have been four time points at which the data has been frozen, in order for it to be collated, managed and redistributed. This is referred to as a data freeze. For the work in Chapter 3, data has been used from data freeze four (DF4) as this was the most up to date at the time the analysis started. At this time, a total of 684 participants were enrolled in the study: 263 non-mutation carriers (controls), 294 presymptomatic mutation carriers and 127 symptomatic mutation carriers.

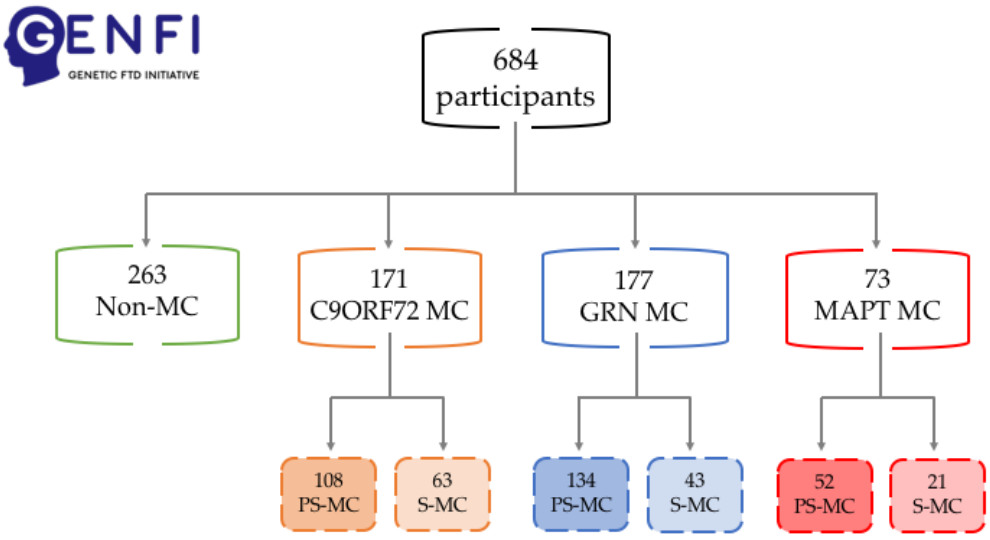

Figure 2-1: Displays the number of participants involved in the GENFI study across all 25 sites. MC: mutation carriers; PS-MC: presymptomatic mutation carriers; S-MC: Symptomatic mutation carriers.

Given the need for sensitivity towards the genetic status of the presymptomatic cohort, all data is collected with the genetic status of the individual unknown (unless known and expressed by the participant themselves). This aims to prevent any bias occurring during testing by the researchers. Once the data has been collected and managed by the GENFI study data manager, it is sent to the genetic guardian. The genetic guardian receives the results of the genetic tests for every individual in the study, and is able to match these results to the data to anonymise it. This allows for the analysis between the mutation carriers and non-carriers to be run, without compromising the genetic status of the individuals.

2.2.2 LIFTD

Whilst GENFI focuses specifically on familial forms of FTD, the Longitudinal Investigation of Frontotemporal Dementia (LIFTD) focuses on sporadic forms of FTD. This study has been carried out at the DRC since 2015. The aim of the study is to annually follow individuals who have been given a diagnosis of bvFTD or PPA over a period of three years. None of these participants have a

genetic cause for their condition. All participants are recruited from the Specialist Cognitive Disorders Clinic at the National Hospital of Neurology and Neurosurgery (NHNN), or have been referred from another cognitive neurology clinic. These participants are then screened by the neurologists at the NHNN, by speaking to the participants own neurologist, gaining copies of their clinic letters, and where possible, an MRI scan. This is to confirm the diagnosis ensuring that the individuals are representative of a true FTD cohort. Healthy controls with no cognitive complaints are also recruited into the study as a comparison group. At present, a total of 129 participants have taken part in the study (see *Figure 2-2*) with some of these individuals returning for multiple repeat visits over the years (total of 244 visit points).

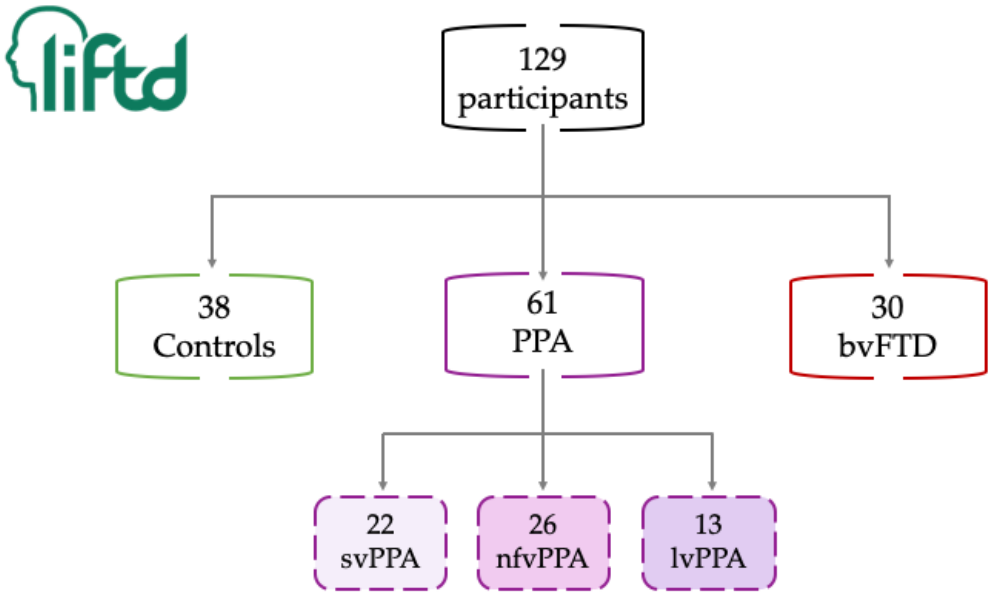

Figure 2-2: Displays the number of participants involved in the LIFTD study.

2.3 Ethics

Ethical clearance was gained from the local Research Ethics Committee, with the consent form in line with the Declaration of Helsinki for both cohorts (for LIFTD at UCL only, and for GENFI at each of the 25 sites).

2.3.1 Information and consent

Both participant and informant information sheets, alongside the relevant consent forms, were all approved during the ethics application. The information sheets are sent to the participants when contact is first made. This ensures that they are clear about what is involved in the studies if they decide to participate, and what would be required of them. On arrival at the research centres, they are presented with the information sheets and the researcher checks that they have read it, and asks if they have any questions. After all questions have been answered, the researcher takes the participant and their informant through the consent form, point by point, making sure they are fully informed about what they are signing. Once completed, a copy is given to the participant to keep. The original is retained and stored safely and securely in the research centres.

Within the consent form, it explains that the data will be kept anonymously and confidentially. In order to do this, each participant is given a numbered code, and all information collected is stored under this code. Information gathered is done so on a need-to-know basis, and no more information than is necessary is kept.

2.3.2 Data collection

For both studies, the medical, biosample and neuropsychometric data is collected and recorded using pen and paper. As soon as testing is complete, the data is processed and uploaded by the researcher to a secure online database, known as XNAT. This has been specifically designed for the data obtained in these cohorts. The MRI scans are also uploaded to this database once they have been completed. The scans are reviewed by a neurologist within a week of the scan to check for any unusual findings. If nothing

unusual is detected, it is uploaded. If the scan does detect an anomaly, this is discussed with the principle investigator (PI) of the study, and clinical follow up is arranged via the participant and their general practitioner (GP). Inclusion in the study is then discussed once the results of the abnormal finding has been fed back to the study PI. By using XNAT, it ensures that all data is kept confidentially, in an organised and comprehensive manner. It allows easy access to the data and is able to be checked, monitored and audited to ensure that it is correct.

2.3.3 Reducing the risk of harm

To reduce the risk of harm to the researcher and participant, some precautions are taken during the research visit. Each participant provides details of their emergency contact at the start of the visit, and the PI should always be available to contact either in person, or over the phone, in case they are needed. Throughout any cognitive examinations or neuropsychology assessment, the researcher should always be looking for any signs of distress. This may be physical or emotional discomfort. As there is no benefit to the participant for completing these tests, testing should be stopped and continuation discussed with the participant. A break may be appropriate to reduce the distress but if not, the testing should be stopped immediately. In certain cases, particularly in semantic dementia and in the presymptomatic cohort, there is a greater risk of anxiety and depression (Marshall, Hardy, Volkmer, et al., 2018; Quaid, 2011). This is a sensitive topic and one that should remain confidential. However, to ensure that the participant is safe and looked after, the researcher should discuss with the participant about informing the PI or the study doctor about what has been said. This ensures that safeguarding and further care of the individual is in place, to ensure they remain safe.

2.4 Study protocol

Both the GENFI and LIFTD study protocol are based on the same standardised structure. Participants are contacted and receive a copy of the study information sheets. The visit date is selected and the research visit will be completed over one or two days, depending on which procedures the participant is willing to have (see Table 2-1). Assessments include medical, cognitive, neuropsychological, imaging, and biosample assessments. Each participant is given an hour lunch break, as well as short breaks between the sessions.

Symptomatic participants are asked to attend with an informant, this is someone who knows the individual well and is usually a spouse, family member or close friend. This is to provide some reassurance to the participant, ensuring that they are not on their own during the lunch hour. It is also to provide extra information about the participant which gives a different perspective about the individual's condition. For presymptomatic participants and controls, an informant is not required to attend on the day of the visit (although they can if they would like to). Instead, an information pack is sent to their informant, with a copy of the informant information sheet, consent form and a variety of questionnaires for them to complete and return to us in a prepaid envelope. Expenses are paid to the participant and their informant, covering any travel, accommodation and subsidiary costs that they may incur as a result of attending the research visit. No other payment is given for the study in line with the study ethics.

Table 2-1: An example timetable of what a participant in both the LIFTD and GENFI studies would be asked to complete.

Procedure	Time	Day 1		Day 2	
		AM	PM	AM	PM
Consent	30 minutes	X			
Medical and Examination	75 minutes	X			
Blood and urine collection	15 minutes	X			
Neuropsychology	120 minutes		X		
MRI Scan	60 minutes			X	
Informant questionnaire	60 minutes			X	
Lumbar puncture	120 minutes				X
Total time:	**480 mins / 8 hrs**				

2.4.1 Medical assessments

The medical assessment is a chance for the participant to meet with a clinical neurologist and have a comprehensive discussion about their condition. It starts with basic demographic information, for example their age, education level, language and occupation, and moves onto information about their family history, their own medical history (presymptomatic/symptomatic, changes to behaviour, neuropsychiatric symptoms, language, cognition, motor and autonomic symptoms, as well as any other relevant symptoms). From this, a disease severity score is generated. This is known as the Clinical Dementia Rating Scale (CDR). The abilities discussed during the medical history are scored on a scale from 0 "Absent" to 3 "Severe". A global score can be generated from the ratings on these sections or they can be added up to generate a Sum of Boxes score. The National Alzheimer's Coordinating Centre (NACC) devised an additional set of questions to be added onto the CDR in order for the measure to be specific to FTD. This is therefore referred to as the CDR with the FTLD NACC component and includes both the behaviour and language components. A list of medications is also taken and is accompanied

by a physical and cognitive (Mini-Mental State Examination - MMSE) neurological examination. During this assessment, participants are also asked to give a blood and urine sample.

2.4.2 Informant questionnaires

As previously discussed in section 2.4, the participants' informant is provided with a set of questionnaires to complete. These include the Cambridge Behavioural Inventory (CBI), the Frontotemporal Dementia Rating Scale (FRS), the modified Interpersonal Reactivity Index (mIRI) and the Revised Self-Monitoring Scale (RSMS) (see Appendix 1). The informant completes the questionnaires at some point during the participants visit if they have accompanied them, or is sent to them in the post. The mIRI and the RSMS are of particular interest as they are measures of social abilities and are used as correlates in Chapter 6.

The modified Interpersonal Reactivity Index (mIRI)

The mIRI is based on the interpersonal reactivity index (IRI). This is a 28 item questionnaire that aims to measure both cognitive and emotional components of empathy (Davis, 1983). It includes two seven item subscales measuring cognitive empathy: Perspective Taking (PT) and Fantasy (FS) and two more seven item subscales measuring emotional empathy: Empathic Concern (EC) and Personal Distress (PD). It uses a 5-point Likert response scale from 1 – 5 from "Does NOT describe well" to "Describes VERY well" respectively. PT and FS correspond to an assessment of cognitive empathy, while EC and PD contribute towards an assessment of emotional empathy. The modified version consists only of subscales PT and EC, and is 14 items long. Both subscales are scored out of 35 giving a total score out of 70. Caregivers are asked to complete the questionnaire about the patient and are given the

following instructions: "Please indicate how well each statement describes the subject's CURRENT behaviour. There are no right or wrong answers. We just want to get your impression of how you think the subject typically behaves."

The Revised Self-Monitoring Scale (RSMS)

The RSMS (Lennox & Wolfe, 1984) is a 13-item questionnaire based upon the Self-Monitoring Scale (Snyder, 1974) and is made up of two subscales: the EX and SP subscales. The EX subscale investigates the participants' sensitivity to expressive behaviour and is made up of 7 items. The SP subscale on the other hand, measures the tendency to monitor self-presentation and is made up of 6 items. The questionnaire uses a 6-point Likert scale ranging from 0: "Certainly, always false" to 5: Certainly, always true". The EX subscale is scored out of 30 and the SP is scored out of 35 giving a total score of 65. Caregivers are asked to complete the questionnaire about the patient and are given the following instructions: "Please indicate how well each statement describes the subject's CURRENT behaviour. There are no right or wrong answers. We just want to get your impression of how you think the subject typically behaves."

2.4.3 Standard neuropsychological assessments

A standard battery of neuropsychology tests was previously devised to cover most aspects of cognitive performance, from verbal and performance IQ, to episodic memory, executive function, naming and social cognitive tests (see Table 2-2 for a full list of tests and references).

An additional set of neuropsychology tests is administered as part of the GENFI study that further assesses comprehension, episodic memory, executive function, naming, posterior cortical skills and short-term memory (see Table 2-3 for full list of additional tests). For all the neuropsychology data

collected as part of GENFI, the raw scores are turned into Z scores. This is done by taking the individuals score away from the mean score of the mutation negative controls. The result is then divided by the mean standard deviation of the mutation negative controls. For tests that are language specific (Digit span, Camel and Cactus Test, Boston Naming Test, Free and Cued Selective Reminding Test (FCSRT), Delis Kaplan Executive System (D-KEFS) Delayed Recall, Verbal Fluency, and the Faux-Pas Test – see Table 2-2 and Table 2-3), the mean score and the mean of the standard deviation is calculated for all mutation negative controls for each language.

When completing the neuropsychometric tests, participants are sat at a table across from the researcher in a room with very little distractions. Often the psychology assessments are the part of the day that the participants are most worried about. It makes it clear if they are struggling with certain aspects of their thoughts, i.e. presymptomatic individuals are worried about the onset of symptoms, and symptomatic individuals are noticing that things are getting worse. The anxiety and worry associated with this could actually impact an individual's performance. In order to reduce this, a good rapport is built with the participant on arrival at the research centre, and at the start of the testing session to try and put them at ease. Throughout the testing, the participant is reassured that they are doing well. If any breaks are needed, they are given. If the participant is aware that they are not performing as well on particular tests, this is acknowledged. They are encouraged that the tests are designed to be difficult, and that some are harder than others, so they should try their best. If they seem distressed, as mentioned in the ethics section 2.3.3, the tests are discontinued.

Table 2-2: Summary of the standardised neuropsychometric tests used in the LIFTD and GENFI cohorts.

Cognitive Domain and test	Reference
General Intellect	
WASI Performance IQ	Wechsler (1981)
WASI Verbal IQ	Wechsler (1981)
Episodic Memory	
Recognition Memory Test for Words	Warrington (1984)
Recognition Memory Test for Faces	Warrington (1984)
Digit Span Forwards*	Wechsler (1987)
Executive Function/Speed of processing	
Digit Span Reverse*	Wechsler (1987)
Fluency – Letter	In house (Appendix 2)
Fluency – Categories (Animals)	In house (Appendix 3)
Trails Making Test	Tombaugh (2004)
D-KEFS Colour-Word Inference Test	Delis, Kaplan, and Kramer (2001)
Language	
NART	(Nelson, 1982)
BPVS	Dunn and Whetton (1982)
Graded Naming Test	McKenna and Warrington (1980)
Posterior cortical skills	
Graded Difficulty Arithmetic	Jackson and Warrington (1986)
VOSP – Object Decision	Warrington and James (1991)

WASI, Wechsler Abbreviated Scale of Intelligence; D-KEFS, Delis Kaplan Executive System; NART, National Adult Reading Test; BPVS, British Picture Vocabulary Scale; VOSP, Visual Object and Space Perception Test. *Indicates language specific tests.

Table 2-3: Summary of additional GENFI neuropsychology tests. *Indicates language specific.

Cognitive Domain and test	Reference
Comprehension	
Camel and Cactus Test (Modified)*	In house (Appendix 4)
Episodic Memory	
Benson Figure Recall	Based on the Rey-Osterrieth figure developed by Benson
FCSRT – Delayed Recall*	(Ivnik et al., 1997)
Executive Function	
Verbal Fluency (A and S)*	In house (Appendix 2)
Naming	
Boston Naming Test*	(Kaplan, Goodglass, & Weintraub, 2001)
Posterior Cortical Skills	
Benson Figure Recall	Based on the Rey-Osterrieth figure developed by Benson
Short term memory	
FCSRT*	(Ivnik et al., 1997)

2.5 Social cognitive assessment

The Mini-SEA is a shorter version of the Social and Emotional Assessment (SEA) (Funkiewiez et al., 2012) and consists of two tests: the Facial Emotion Recognition (FER) Test (Ekman & Friesen, 1975) and the Faux-Pas (FP) Test (Stone, Baron-Cohen, & Knight, 1998) and is scored out of 30. It is a paper-based task that takes around 15-30 minutes to complete but there is no time limit on the task. There are no strict stopping criteria, however should the participant become distressed or is having difficulty completing the task, the researcher may end the testing session. The task stimuli can be found in Appendix 5.

For the purpose of GENFI, the test was selected as it is a relatively short test that covers multiple aspects of social cognition. As it had to fit in with many other psychological tests, it was deemed to be the most appropriate. Furthermore, as GENFI is a multi-centre site that is spread across Europe and

Canada, the tests needed to be translated into multiple languages. The advantage of the Mini-SEA is that it is already translated and validated into many languages. Consequently, this ensures consistency of the test across the different sites.

2.5.1 The Facial Emotion Recognition Test (FER)

The FER Test uses the six universal emotions: happiness, surprise, anger, fear, disgust, and sadness. Participants are presented with the different faces and required to select the correct written emotional label that matches the emotion of the face. This assesses the participants' ability to process emotional information in faces. This test is scored out of 35 (5 points for each of the emotions). As this is a predominately visual test, there is very little effect of language. Therefore, virtually the same version of the test was given to all sites, thus the raw scores were used in the analysis instead of the z scores.

2.5.2 The Faux-Pas Test (FP)

The FP Test contains a series of 10 short cartoon stories describing scenarios involving social inconveniences – a faux-pas. It requires the individual to infer another's thoughts or beliefs. A structured questionnaire asks how and why the social faux-pas has occurred. Control stories are used to investigate if the participant has understood the stories. This assesses participants' ability to have a theory about another's mind (ToM). The total score is out of 40, 10 points for the control stories and the other 30 for the faux-pas questions.

As the test is language specific across the GENFI sites, slightly different versions of the test were given to difference sites. Consequently, Z Scores were created to allow for a comparison between the participants across the sites as mentioned in section 2.4.3.

2.6 Structural Brain Imaging

Participants entered a MRI scanner for approximately 50 minutes, in which a variety of scan sequences were carried out. The scan sequences were designed at the start of the projects ensuring that each participant had the same protocol. For this thesis, only the T1-weighted MRI scan sequence was used. For the GENFI scans, a variety of difference scanners were used across the sites (Siemens Trio 3T, Siemens Skyra 3T, Siemens Prisma 3T, Phillips 3T and General Electric 3T), but the MRI scans for the LIFTD and GENFI cohort at UCL, were completed on a Siemens Prisma 3T scanner. All scans were quality checked and those with movements or artefacts were removed. Furthermore, if any participants displayed moderate to severe vascular disease, or any other brain lesions such as tumours, they were also excluded from the analysis.

2.6.1 Voxel-based morphometry analysis (VBM)

VBM analysis was performed using Statistical Parametric Mapping (SPM) 12 software, version 6685 (www.fil.ion.ucl.ac.uk/spm), running under Matlab R2015a (Mathworks, USA). The T1-weighted images that had passed through the quality check, were normalized and segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) probability maps, by using standard procedures and the fast-diffeomorphic image registration algorithm (DARTEL) (Ashburner, 2007). GM segmentations were affine transformed into the Montreal Neurological Institute (MNI) space, modulated and smoothed using a Gaussian kernel with 6mm full-width, at half maximum, before analysis. Finally, a mask was applied as reported in Ridgway et al. (2009). Study-specific templates were created based on the subjects included in each analysis. At each stage, all segmentations were reviewed visually. Total intracranial volume was calculated using SPM (Malone et al., 2015).

2.6.2 Region of Interest (ROI) analysis

An automated atlas segmentation propagation and label fusion strategy – (Geodesic Information Flow: GIF) (Cardoso et al., 2015) was used on the T1-weighted volumetric MRI scans. Following the Neuromorphometrics Inc. atlas (www.neuromorphometrics.com), over 150 GM and WM regions were extracted from GIF, which were then combined to obtain the following regions of interest: the orbitofrontal cortex, dorsolateral prefrontal cortex (DLPFC) and the ventromedial prefrontal cortex (VMPFC), temporal, parietal, and occipital cortices, as well as the striatum.

In addition, GIF uses the Diedrichsen cerebellar atlas to extract subregions of the cerebellum, which were combined to generate GM volumes of the whole cerebellum (Cardoso et al., 2015; Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009; Diedrichsen et al., 2011).

All of the individual region volumes are expressed as a percentage of total intracranial volume, as computed with SPM12 (Statistical Parametric Mapping, Welcome Trust Centre for Neuroimaging, London, UK) running under Matlab R20014b (Mathworks, USA) (Malone et al., 2015).

2.7 Statistical analysis

All statistical analysis was performed using Stata/IC 14.1 for Mac (64-bit Intel). For the demographic and neuropsychometric data in Chapters 5 and 6, for data that was normally distributed (assessed by visualisation of the Quantile-Quantile [Q-Q] plot of residuals), independent sample t-tests were used to compare the patient group to the control group. This means that the data was evenly centred around the mean, with an equal distribution above and below the mean score, and thus, the parametric independent samples t-test was used. The standard deviation provides information on the spread of the data

from the mean. When visualised using the Q-Q plots, the data should display a straight line if it is normally distributed. If the data showed a material departure from a normal distribution, such as a skew or unequal variance across the range of scores, then a non-parametric Mann-Whitney U test was used. For categorical data such as gender or handedness, a chi-squared test was used to compare patients to controls.

The analysis in Chapter 3 uses a linear regression. This method was chosen as it examines the relationship between the dependant variable and one or more predictor variables. This was therefore suitable as there are multiple groups used in Chapter 3, and the effect group had on the Mini-SEA scores was being investigated, when including their age and gender as covariates. However, the data was not normally distributed as visualised by the Q-Q plot of residuals, so bootstrapping was used to calculate the confidence intervals. Normal approximation of 95% confidence intervals were calculated from 1000 bootstrap replications, sampling with a replacement from the individuals included in each analysis.

This analysis provides valid confidence intervals even when normality assumptions do not hold. After each linear regression, post-hoc pairwise comparisons were used to compare the control group, the presymptomatic mutation carriers and the symptomatic mutation carriers for each of the genetic mutations. This calculates post-estimations from the most recently fit model to assess interactions between specific independent and dependant variables, in a variety of combinations. A predicted difference score is produced, as well as *p* values and confidence intervals.

A linear regression was also used in Chapter 5, however this time the data was normally distributed for all metrics, except for the saccade latency and peak velocity. In order to overcome this violation of normality, a square root

transformation was carried out for the saccade latency and peak velocity data. Post-hoc pairwise comparisons were also carried out to compare between the patients and the control group as explained above.

For Chapter 6, a linear mixed model (LMM) was carried out to analyse the data. This method was chosen over the linear regression for this analysis as there were repeated measures on each participant. A LMM allows the correlation between scores on trials completed by the same participant to be taken into account. The LMM uses both fixed and random effects. Fixed effects are factors that are assumed to have the same impact on each observation, e.g. diagnostic group, or age. Random effects are factors that are assumed to follow a distribution and can be used to allow for clustering in the data. For example, when repeated measures on the same participant are included, the random effect is the differences between the average score for that participant and the average score of their group. Instead of estimating each of these differences as fixed effects do, they are modelled as a random effect following a normal distribution. In the model, a random intercept for participant and trial number were included. Diagnostic group was included as a fixed effect. Bootstrapping was also included as described above. Post-hoc pairwise comparisons were used to compare the patients to controls.

Chapter 7 takes a combination of approaches previously used. The linear regression in Chapter 5 is used to assess pro- and anti-saccade performance, and the linear mixed effects model from Chapter 6 to assess the emotion processing eye-tracking tests, however this data was normally distributed and so bootstrapping was not performed. Post-hoc pairwise comparisons compared performance between the controls and the presymptomatic mutation carriers.

2.8 Chapter summary

The design and set up of the LIFTD and the GENFI projects at UCL allow the two cohorts to be used interchangeably. The symptomatic participants can be used from both LIFTD and GENFI. This therefore maximises the number of symptomatic patients participating in the studies, making the results more reliable. This is further increased by the international set up of GENFI, and allows for the inclusion of very large sample sizes in what is a rare condition.

The main problem faced in this work however, is the ability for the symptomatic individuals to complete the Mini-SEA. Whilst those in the mild stages of bvFTD are typically able to understand the tests, those in the moderate to latter stages tended to struggle, particularly on the FP test with the long instructions and stories.

By carrying out this work in this way, my statistical skills have improved. I learnt to use Stata, was able to run multiple linear regressions, as well as learn how to carry out linear mixed models, something I had no previous experience of. I have felt challenged by this work and thoroughly enjoyed it.

CHAPTER 3: EMOTION PROCESSING AND THEORY OF MIND IN A FAMILIAL COHORT OF FTD: A GENFI STUDY

3.1 Chapter overview

As discussed in Chapter 1, a key symptom of frontotemporal dementia (FTD) is difficulty interacting socially with others. It is known that specific social cognitive abilities (emotion processing and theory of mind), are affected in sporadic FTD, but it is not clear if this is the case in familial FTD. This chapter uses two tests to assess emotion processing and theory of mind in individuals enrolled in GENFI. Participants are separated into non-mutation carriers (controls), presymptomatic mutation carriers and symptomatic mutation carriers. This chapter aims to identify both symptomatic deficits and presymptomatic ablities. Furthermore, it will also investigate the neural anatomical regions associated with social cognitive performance using these two tests. This therefore aims to aid our understanding of how social cognition is affected in familial FTD.

3.2 Introduction

Impairment of social cognition is one of the most prominent symptoms of FTD, particularly in bvFTD (see section 1.2.1). As discussed in Chapter 1, emotion processing refers to the ability to perceive, recognise and use emotional information from another to establish how they may be feeling, while theory of mind refers to the understanding that others have thoughts and beliefs that may be different from one's own. One task assessing social abilities is the Mini- SEA, and it is made up of two tests to assess these aspects of social cognition: the FER test (see section 2.5.1) and the FP test (see section 2.5.2). Whilst it is clear that these abilities are compromised in sporadic bvFTD (see section 1.4.1 and 1.4.2), it is not clear if they are affected in the same way in familial forms of FTD (see section 1.4.4).

Therefore, the aim of this chapter is to assess emotion processing and theory of mind in a large cohort of presymptomatic and symptomatic individuals. In order to stratify participants over time, those who are presymptomatic will be divided into an early and late group, split using the cut of off 5 years to their estimated symptom onset. Performances between the genetic mutations will be investigated. It is hypothesised that the symptomatic individuals will perform significantly worse than both the early and late presymptomatic groups, as well as the controls. There may be some differences identified in the symptomatic individuals when stratified across the genetic mutations given the different clinical and imaging phenotypes. With regards to the presymptomatic individuals, it is expected that the late group will perform worse than the controls and the early presymptomatic group. This chapter will also explore the neuroanatomical correlates associated with performance on these tasks in genetic mutation.

3.3 Methods

3.3.1 Participants

All sites gained local ethical approval for the study. Participants provided fully informed written consent and were recruited from the fourth GENFI Data Freeze (see section 2.2.1). All participants were genotyped at the local site in order to identify mutation carriers and non-mutation carriers (controls).

Together, all symptomatic mutation carriers had a mean age of onset of 57.6 (SD: 8.98). The mean age at onset in the *C9orfF72* group was 57.5 (SD: 9.09), for *GRN* group it was 60.4 (SD: 8.15) and for the *MAPT* group it was 52.4 (SD: 8.24)

Within the symptomatic mutation carriers, 75 had a diagnosis meeting Rascovsky criteria for probable bvFTD (*C9orf72* = 39, *GRN* = 19 and *MAPT* = 17) and 10 for possible bvFTD (*C9orf72* = 6, *GRN* = 2 and *MAPT* = 2). 22 participants met the Gorno-Tempini criteria for primary progressive aphasia (PPA) with 16 having a diagnosis of non-fluent variant of PPA (nfvPPA) (*C9orf72* = 2, *GRN* = 4), 1 with semantic variant PPA (*GRN* = 1) and 5 with PPA not otherwise specified (PPA-NOS) (*GRN* = 5). One individual met the Gorno-Tempini criteria for PPA-NOS but had a clinical diagnosis of bvFTD (*MAPT* = 1). Six individuals had FTD-amyotrophic lateral sclerosis (FTD-ALS: *C9orf72* = 6), 6 had ALS (*C9orf72* = 6), 1 had corticobasal syndrome (CBS: *GRN*=1), 1 had progressive supranuclear palsy (PSP: *C9orf72*=1), 1 had Alzheimer's disease (AD: *GRN*=1), 2 had Dementia - not otherwise specified (D-NOS: *C9orf72* = 1, *MAPT* = 1) and 2 were diagnosed with other disorders (*C9orf72* = 2).

Of the 127 symptomatic mutation carriers, there were no differences observed between the genetic groups for disease severity when measured using the

CDR with the NACC FTLD component (Mean (SD): *C9orf72* = 9.79 (6.26), *GRN* = 9.90 (6.50), *MAPT* = 9.71 (6.45)).

3.3.2 Experimental procedure

A standardised clinical assessment was administered to all participants which included medical history, family history and a physical examination. Information about participants was also collected from an informant who was typically a close family member, carer or friend. A blood sample was also collected. These assessments were used to classify individuals into controls and mutation carriers (see section 2.4 for more details around the study protocol). All participants underwent a general neuropsychological battery (see section 2.4.3). The Mini-SEA was the social cognitive task of interest (see section 2.5).

Mutation carriers were split into two groups, those who were symptomatic and those who were presymptomatic. The presymptomatic group were further split into two subgroups: those greater than five years to estimated onset (early) and those less than five years to estimated onset (late) (see section 2.2.1 for EYO calculations). For individuals who did not know their genetic status, researchers were also blinded to their status.

3.3.3 Statistical analysis

Using the raw scores of the control group on the FP Test, the cumulative frequency and percentile scores were calculated for each language. This was to determine if there was an influence of language across the different sites, and if the raw scores should be converted to z-scores for the analysis.

It is also possible that age and gender may influence performance on social cognitive tests, therefore the mean scores and standard deviations (SD) on

both the FP z-scores and the FER raw scores were assessed across decade (20's, 30's, 40's, 50's, 60's and over 70's). This was also done for both males and females across each decade. The influence of age was assessed using a Spearman's rank correlation for all healthy controls together, as well as for males and females individually.

To compare between the groups, mean scores were generated using the FER raw scores and the FP z-scores. A linear regression was then used to measure performance on each of the tests across the groups, and included gender and age as covariates in both models (see section 2.7). The data was bootstrapped for both tests as it was not normally distributed. Post hoc pairwise comparisons were used to assess differences in group performance.

For each emotion in the FER test, another linear regression analysis was carried out to identify differences in each of the genetic groups on the individual emotions. Age and gender were both included in the model as covariates. Bootstrapping was carried out for each as the data was not normally distributed, with post-hoc comparisons performed after to compare between the groups (see section 2.7).

3.3.4 Structural brain imaging and brain imaging analysis

Participants underwent an MRI scan as outlined in section 2.6. VBM analysis was then performed on the scans (see section 2.6.1). Out of the 421 mutation carriers involved in the study, 78 were not included in the VBM analysis: 38 did not have a scan or the scan did not pass QC, and 40 did not complete both the FP and FER test. 25 participants did not complete the FP test and so were only included for the FER VBM analysis.

In order to explore the relationship between performance on the two tests and GM volume, two flexible factorial regression models were used. Genetic

group and scanner were included as factors in the analysis. A main effect of FER/FP was included in the model and genetic group was included as an interaction. Age, TIV and gender were included as covariates in the model. Participants included in the model were mutation carriers only, both presymptomatic and symptomatic cases. Those who were mutation negative (the controls) were not included in the model. In order to investigate anatomical differences in the genetic groups, the following contrasts were set as follows:

1. *C9orf72 > GRN*: 1 -1 0 0 0 0 0 0 0
2. *C9orf72 < GRN*: -1 1 0 0 0 0 0 0 0
3. *C9orf72 > MAPT*: 1 0 -1 0 0 0 0 0 0
4. *C9orf72 < MAPT*: -1 0 1 0 0 0 0 0 0
5. *GRN > MAPT*: 0 1 -1 0 0 0 0 0 0
6. *GRN < MAPT*: 0 -1 1 0 0 0 0 0 0

As an example, the first contrast is looking for greater GM atrophy in the *GRN* group compared to the *C9orf72* group. The first 1 indicates *C9orf72* membership, -1 relates to *GRN* membership, and the third 0 relates to *MAPT* membership. The next three zeros correspond to the performance on the FER/FP tasks for each of the groups in the same order, and the final three zeros correspond to the covariates.

To investigate the GM regions that are related to the FER/FP tasks across all of the genetic groups (additive regions), the following contrast was used:

7. 0 0 0 (1/3) (1/3) (1/3) 0 0 0

In order to examine the GM correlations with the FER/FP tasks in each of the individual genetic groups, the following contrasts were used:

8. *C9orf72*: 0 0 0 1 0 0 0 0 0
9. *GRN*: 0 0 0 0 1 0 0 0 0
10. *MAPT*: 0 0 0 0 0 1 0 0 0

To determine which regions of the brain were consistent across all three of the groups, a conjunction analysis was performed. This was done by selecting all three of the FER/FP contrasts (8, 9 and 10 above) together and performing the conjunction analysis. In all of the analyses, multiple comparisons were adjusted for by using the Family-Wise Error rate set at 0.05. In the analysis, there were few regions identified after correction for multiple comparisons in the conjunction analysis, so the results were explored the results uncorrected at a threshold of $p < 0.001$. This was done as it was felt that the very small sample size in the *MAPT* group may have been influencing the results in the conjunction analysis, so much so, that no results were being found. Therefore out of interest, the threshold was reduced.

3.4 Results

3.4.1 Facial Emotion Recognition Test

Healthy controls

The cumulative frequency was calculated for the control group showing that they scored between 19 and 34 out of a possible 35 (Table 3-1). Using the percentile scores to calculate an abnormal cut off (Table 3-2), the 5th percentile was a score of 23 – this would be considered borderline abnormal, while anything below this would be considered abnormal.

When looking at the correlation between age and decade on the FER test, the mean ranged from 27.6 to 29.6, out of 35 (

Table 3-3) but the correlation was relatively weak and only a trend towards significance was observed (Rho = -0.119, p = 0.063) (Figure 3-1). It appears however that there may be an influence of gender on this test. Females ranged from 28.0 – 29.9, with a weak and non-significant correlation (Rho = -0.008, p = 0.924), but males ranged from 26.3 – 29.0 with a significant negative correlation (Rho = -0.287, p = 0.003) (Figure 3-1).

Table 3-1: Cumulative frequency of the FER in controls.

FER Score	N	Cumulative Freq.
19	3	1.2
20	3	2.4
21	1	2.8
22	2	3.7
23	7	6.5
24	9	10.2
25	15	16.3
26	16	22.8
27	16	29.3
28	29	41.1
29	36	55.7
30	33	69.1
31	28	80.5
32	24	90.2
33	16	96.7
34	8	100.0
35	0	100.0

Table 3-2: Percentile scores for the FER in controls.

Percentile	FER Raw Score
5th	23.0
10th	24.0
20th	26.0
30th	28.0
40th	28.0
50th	29.0
60th	30.0
70th	31.0
80th	31.0
90th	32.3

Table 3-3: FER score by decade in controls.

Age group	All			Females			Males		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Overall score	246	28.7	3.2	143	29.1	3.1	103	28.2	3.2
18.1-29.9	29	28.7	2.9	15	28.4	3.1	14	29.0	2.6
30.0-39.9	59	28.8	3.2	34	28.9	3.0	25	28.6	3.6
40.0-49.9	67	29.6	2.9	37	29.9	2.7	30	29.2	3.1
50.0-59.9	46	28.5	3.3	31	29.3	3.4	15	26.8	2.4
60.0-69.9	39	27.6	3.5	25	28.4	3.3	14	26.3	3.6
70.0-85.0	6	27.8	2.5	1	28.0	-	5	27.8	2.8

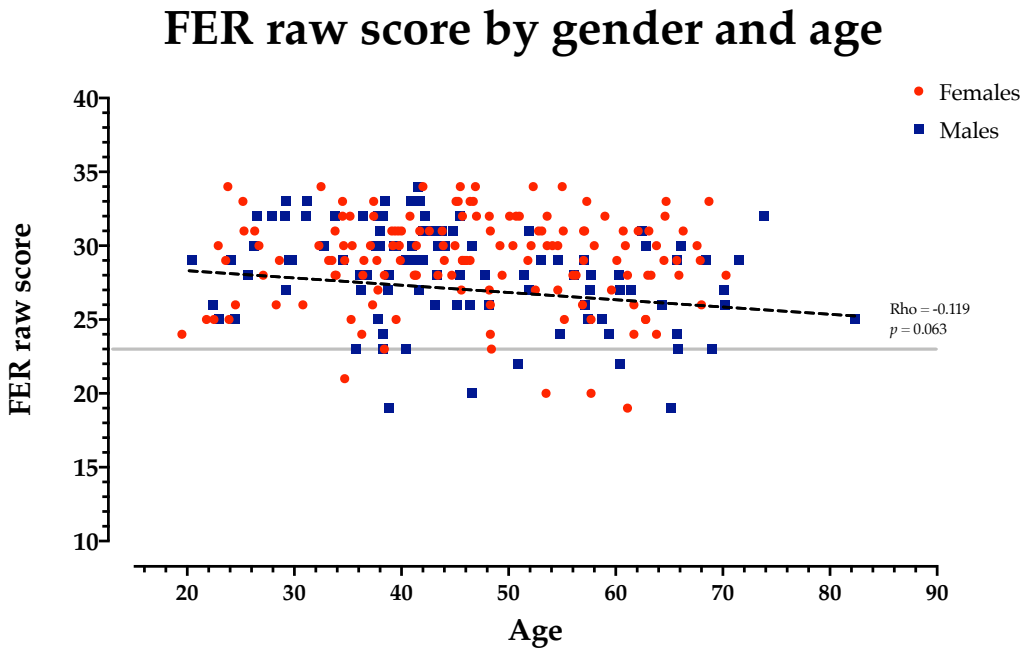

Figure 3-1: Spearman Rank Correlation between Age and FER score for controls – abnormal cut off at 23 out of 35.

Mutation carriers

When comparing FER scores between the symptomatic mutation carriers, scores were significantly lower in *C9orf72* and *GRN* when compared to *MAPT*. When comparing within each genetic mutation to the early and late presymptomatic mutation carriers, all three symptomatic groups performed significantly lower; this was also the case when comparing to controls (Table 3-4 and Table 3-5, *Figure 3-2*).

The late *C9orf72* presymptomatic mutation carriers performed significantly lower than the early and late *GRN* and *MAPT* presymptomatic mutation carriers. Furthermore, they also performed significantly lower than the early *C9orf72* presymptomatic mutation carriers and the control group (Table 3-4 and Table 3-5, *Figure 3-2*).

Table 3-4: Demographic information and FER raw and z-score means for each group – mean (SD).

FER Score - Mean (SD)		N	Age	Ed. Level	MMSE	FTDL-CDR-SOB	FER Score
Control		246	46.6 (13.1)	14.2 (3.5)	29.3 (1.2)	0.2 (0.6)	28.7 (3.2)
C9orf72	**Early PS**	81	41.5 (10.1)	14.8 (2.5)	29.3 (1.1)	0.2 (0.6)	29.0 (2.9)
	Late PS	25	56.3 (8.3)	13.2 (3.9)	28.7 (1.3)	0.4 (0.9)	26.3 (3.5)
	Symptomatic	53	62.6 (8.6)	12.9 (3.8)	23.5 (6.7)	9.8 (6.3)	18.7 (6.9)
GRN	**Early PS**	93	41.6 (9.0)	14.9 (3.6)	29.5 (0.9)	0.1 (0.2)	29.3 (3.2)
	Late PS	29	61.6 (7.1)	14.1 (3.3)	28.8 (1.8)	0.3 (0.6)	28.4 (4.2)
	Symptomatic	32	63.5 (8.0)	11.6 (3.6)	18.4 (9.3)	9.9 (6.5)	20.0 (7.2)
MAPT	**Early PS**	37	36.6 (8.1)	14.7 (2.7)	29.6 (0.8)	0.3 (0.6)	29.5 (3.0)
	Late PS	12	50.2 (10.5)	13.4 (3.9)	29.3 (1.0)	0.2 (0.6)	29.4 (2.2)
	Symptomatic	18	58.7 (9.4)	14.2 (3.8)	21.8 (8.0)	9.7 (6.4)	22.3 (6.6)

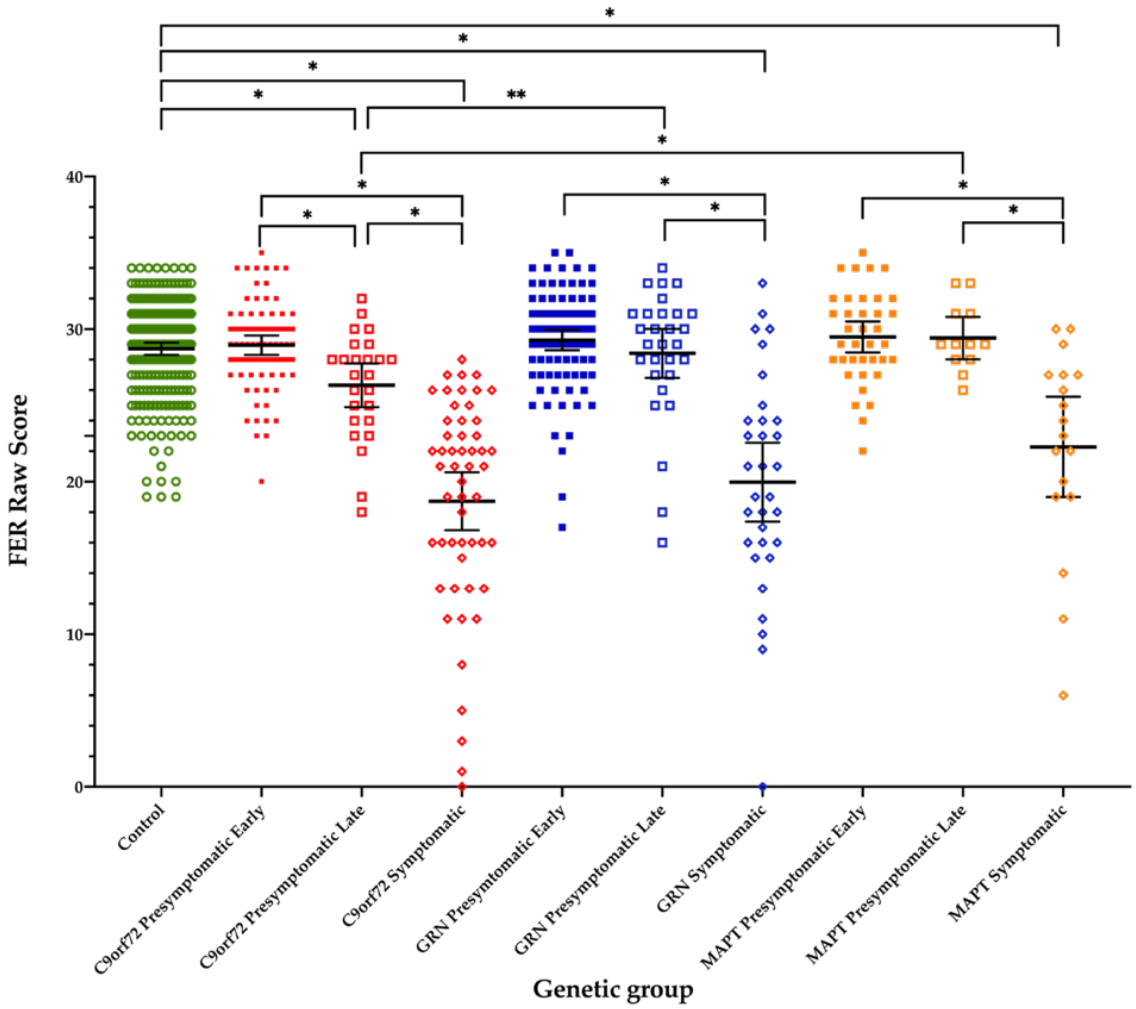

Figure 3-2: The FER scores for each genetic group with significant differences shown when compared to controls and within each genetic group.

Table 3-5: The adjusted mean differences between groups on the FER with the p values and 95% confidence intervals. *PS: Presymptomatic

		C9orf72			*GRN*			*MAPT*		
		Early PS	**Late PS**	**Symptomatic**	**Early PS**	**Late PS**	**Symptomatic**	**Early PS**	**Late PS**	**Symptomatic**
Control		0.05 0.886 -0.69 0.80	**-2.01** **0.004** **-3.39 -0.64**	**-9.20** **< 0.001** **-11.26 -7.14**	0.34 0.403 -0.45 1.12	0.32 0.684 -1.23 1.87	**-7.94** **< 0.001** **-10.45 -5.44**	0.33 0.544 -0.73 1.39	0.91 0.188 -0.44 2.26	**-5.80** **< 0.001** **-9.03 -2.56**
C9orf72	**Early PS**		**-2.07** **0.006** **-3.54 -0.60**	**-9.26** **< 0.001** **-11.44 -7.07**	0.28 0.552 -0.64 1.21	0.27 0.754 -1.41 1.94	**-8.00** **< 0.001** **-10.56 -5.43**	0.27 0.637 -0.86 1.41	0.86 0.251 -0.60 2.31	**-5.85** **< 0.001** **-9.13 -2.57**
	Late PS			**-7.19** **< 0.001** **-9.54 -4.83**	**2.35** **0.003** **0.79 3.92**	**2.34** **0.016** **0.43 4.24**	**-5.93** **< 0.001** **-8.69 -3.17**	**2.34** **0.007** **0.63 4.05**	**2.92** **0.002** **1.07 4.78**	**-3.78** **0.030** **-7.20 -0.37**
	Symptomatic				**9.54** **< 0.001** **7.35 11.73**	**9.52** **< 0.001** **7.13 11.92**	1.26 0.421 -1.81 4.32	**9.53** **< 0.001** **7.19 11.87**	**10.11** **< 0.001** **7.74 12.49**	*3.41* *0.069* *-0.27 7.08*
GRN	**Early PS**					-0.01 0.987 -1.70 1.67	**-8.28** **< 0.001** **-10.87 -5.69**	-0.01 0.990 -1.19 1.17	0.57 0.446 -0.90 2.05	**-6.13** **< 0.001** **-9.45 -2.82**
	Late PS						**-8.26** **< 0.001** **-11.05 -5.48**	0.01 0.994 -1.82 1.83	0.59 0.569 0.00 2.61	**-6.12** **0.001** **-9.59 -2.65**
	Symptomatic							**8.27** **< 0.001** **5.52 11.03**	**8.85** **< 0.001** **6.13 11.58**	2.15 0.286 -1.80 6.09
MAPT	**Early PS**								0.58 0.491 -1.07 2.23	**-6.12** **< 0.001** **-9.55 -2.70**
	Late PS									**-6.71** **< 0.001** **-10.17 -3.24**
	Symptomatic									

Neuroimaging results

The local maxima for the grey matter volume differences between the genetic groups can be found in Table 3-6. This identified the differences in GM volume between the genetic groups. There were no GM regions in which *GRN* carriers had significantly lower volume than the *C9orf72* or the *MAPT* mutation carriers.

When investigating the performance on the FER task with GM volumes in the additive analysis, it can be seen that GM regions that correlated with the task across the genetic groups were the bilateral middle temporal and superior frontal gyri, the left cingulate gyrus, insula, inferior temporal and middle frontal gyrus, and putamen, and the right fusiform gyrus, hippocampus, orbitofrontal cortex and thalamus (see Table 3-7 and Figure 3-3).

When looking at the GM regions associated with the FER task for each of the genetic mutations, there were unique neuroanatomical correlates specific to each group (see Table 3-8 and Figure 3-3) but there also appeared to be areas of overlap. To identify these overlapping regions, a conjunction analysis was carried out and found only the left putamen and left insula were common to all three genetic groups when correcting for multiple comparisons. At a reduced threshold of $p < 0.001$ uncorrected, there were a number of regions common to all three genetic mutations (see Table 3-9 and Figure 3-3) including bilateral insula and anteromedial temporal lobe and right frontal regions.

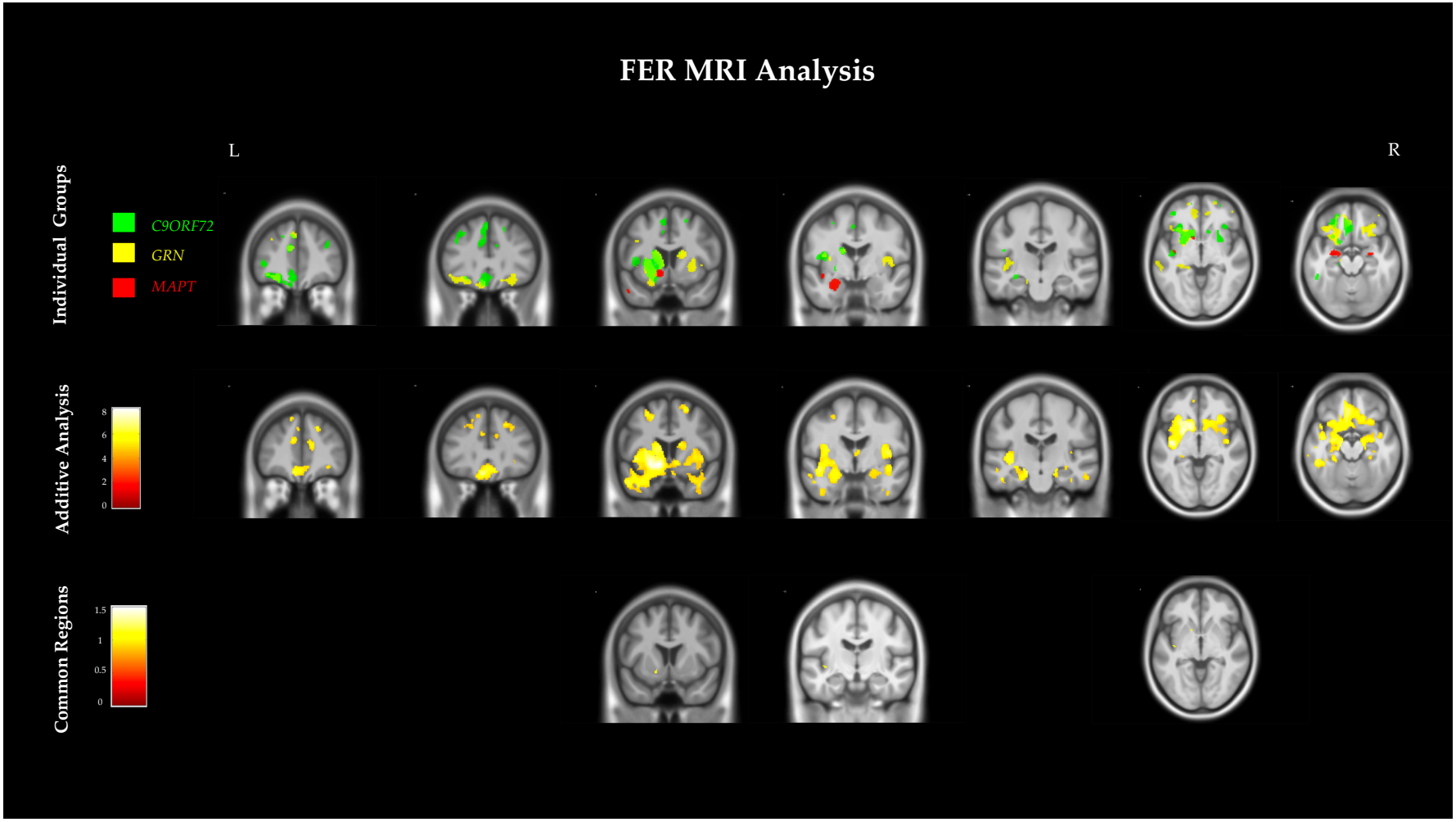

Figure 3-3: Statistical parametric maps from the voxel-based morphometry analysis of the FER test. All results displayed corrected for multiple comparisons (FWE) at $p < 0.05$.

Table 3-6: The differences in anatomical GM volume across the genetic groups. Results displayed are FWE corrected at 0.05.

Contrast	Region	cluster equivk	peak T	peak p(FWE-corr)	peak p(unc)	Coordinates (mm) x	y	z
GRN < C9orf72								
C9orf72 < GRN	Left thalamus	2477	9.77	< 0.001	< 0.001	-18	-28	2
	Right postcentral gyrus	2046	7.11	< 0.001	< 0.001	54	-8	39
	Left postcentral gyrus	764	5.94	< 0.001	< 0.001	-39	-24	51
	Right lingual gyrus	237	5.8	< 0.001	< 0.001	10	-75	-8
	Right operculum	471	5.77	< 0.001	< 0.001	40	-12	15
	Right inferior temporal gyrus	98	5.57	0.001	< 0.001	54	-54	-6
	Right middle temporal gyrus	110	5.55	0.001	< 0.001	52	-42	9
	Right cingulate gyrus	105	5.52	0.001	< 0.001	15	-50	4
	Left operculum	47	5.43	0.002	< 0.001	-54	2	0
	Right operculum	106	5.38	0.003	< 0.001	64	-27	32
	Right precuneus	33	5.36	0.003	< 0.001	9	-51	18
	Left calcarine cortex	75	5.25	0.005	< 0.001	-4	-87	-3
	Right orbitofrontal cortex	84	5.25	0.005	< 0.001	34	33	-12
	Left precuneus	29	5.22	0.006	< 0.001	-8	-62	9
	Right precuneus	43	5.03	0.013	< 0.001	6	-60	14
	Left planum polare	23	4.91	0.022	< 0.001	-58	-9	6
MAPT < C9orf72	Left amygdala	117	5.51	0.002	< 0.001	-30	-8	-20
	Right amygdala	99	5.22	0.006	< 0.001	30	-6	-20
C9orf72 < MAPT	Left thalamus	200	6.1	0	< 0.001	-16	-26	2
	Right cerebellum exterior	264	5.36	0.003	< 0.001	33	-68	-44
	Left cerebellum exterior	207	5.18	0.007	< 0.001	-33	-66	-45
	Right thalamus	81	5.11	0.01	< 0.001	16	-24	3
	Left thalamus	78	5.06	0.012	< 0.001	0	-18	6
	Cerebellar lobules VIII-X	32	4.99	0.016	< 0.001	2	-58	-34

MAPT < GRN	Left hippocampus, amygdala and temporal pole	1719	8.42	0	< 0.001	-30	-8	-20
	Right hippocampus, amygdala and temporal pole	1550	7.65	0	< 0.001	30	-4	-21
	Right inferior temporal gyrus	80	5.38	0.003	< 0.001	36	-6	-44
	Left caudate	38	5.15	0.008	< 0.001	-3	8	-3
	Right hippocampus	21	5.01	0.015	< 0.001	34	-28	-12
GRN < MAPT								

Table 3-7: The neuroanatomical GM correlates for the FER task across all of the genetic groups. All results displayed FWE corrected at 0.05.

Contrast	Region	cluster	peak	peak	peak	Coordinates (mm)		
		equivk	T	p(FWE-corr)	p(unc)	x	y	z
FER across FTD (Additive)	Left basal ganglia, orbitofrontal cortex, amygdala and hippocampus	20020	8.08	<0.001	<0.001	-12	9	-8
	Left inferior temporal gyrus	56	5.78	<0.001	<0.001	-48	-20	-24
	Left middle frontal gyrus	659	6.21	<0.001	<0.001	-28	27	40
	Left middle temporal gyrus	46	5.19	0.007	<0.001	-52	-20	-16
	Left insula	21	5	0.015	<0.001	-64	-32	-15
	Left superior frontal gyrus	225	5.51	0.002	<0.001	-10	40	22
	Left superior frontal gyrus	62	5.29	0.004	<0.001	-12	24	56
	Left superior frontal gyrus	48	5.26	0.005	<0.001	-12	39	50
	Left superior frontal gyrus	22	5.06	0.012	<0.001	-21	48	18
	Left superior frontal gyrus	19	4.91	0.023	<0.001	-8	54	18
	Right hippocampus gyrus	554	5.69	0.001	<0.001	28	-30	-22
	Right middle temporal gyrus	2168	6.37	<0.001	<0.001	54	-12	-22
	Right orbitofrontal cortex	41	4.97	0.018	<0.001	32	40	-10
	Right superior frontal gyrus	930	6.09	<0.001	<0.001	21	10	58
	Right superior frontal gyrus	40	5.64	0.001	<0.001	12	57	16
	Right superior frontal gyrus	217	5.35	0.003	<0.001	12	40	16
	Right thalamus	101	5.43	0.002	<0.001	2	-6	8

Table 3-8: Neuroanatomical GM correlates associated with the FER task in each individual genetic group. All results displayed are FWE corrected at 0.05.

Genetic group	Region	cluster equivk	peak T	peak p(FWE-corr)	peak p(unc)	Coordinates (mm) x	y	z
FER in *C9orf72*	Left basal ganglia, orbitofrontal cortex, amygdala and hippocampus	5349	6.41	<0.001	<0.001	-27	4	8
	Right orbitofrontal cortex	2731	6.24	<0.001	<0.001	26	24	-14
	Left middle frontal gyrus	430	6.05	<0.001	<0.001	-30	50	6
	Right middle frontal gyrus	204	5.63	0.001	<0.001	28	57	3
	Left middle frontal gyrus	128	5.63	0.001	<0.001	-39	44	-4
	Left insula	429	5.63	0.001	<0.001	-42	-14	-3
	Left superior frontal gyrus	95	5.57	0.001	<0.001	-16	64	12
	Right orbitofrontal cortex	165	5.56	0.001	<0.001	46	44	-9
	Right middle frontal gyrus	104	5.36	0.003	<0.001	34	40	24
	Right superior frontal gyrus	44	5.36	0.003	<0.001	15	63	18
	Right precentral gyrus	161	5.32	0.004	<0.001	45	-6	36
	Right middle frontal gyrus	24	5.22	0.006	<0.001	45	46	12
	Right hippocampus	23	5.19	0.007	<0.001	16	-12	-14
	Right fusiform gyrus	45	5.19	0.007	<0.001	26	-51	-14
	Right orbitofrontal cortex	19	5.19	0.007	<0.001	16	56	-12
	Left frontal pole	37	5.18	0.007	<0.001	-14	60	-8
	Left hippocampus	29	5.07	0.011	<0.001	-16	-20	-20
	Right inferior frontal gyrus	39	4.97	0.017	<0.001	42	42	3
	Left middle frontal gyrus	24	4.93	0.02	<0.001	-40	12	32
	Left central operculum	58	4.9	0.023	<0.001	-40	-2	15
FER in *GRN*	basal ganglia, orbitofrontal cortex, amygdala and hippocampus	8647	7.4	<0.001	<0.001	-21	6	-2
	Left middle frontal gyrus	750	6.35	<0.001	<0.001	-30	27	42
	Left inferior temporal gyrus	231	6.2	<0.001	<0.001	-50	-36	-18
	Right superior frontal gyrus	77	6.02	<0.001	<0.001	21	14	56
	Left middle temporal gyrus	132	5.95	<0.001	<0.001	-64	-28	-3

FER in *GRN* Continued	Right middle frontal gyrus	217	5.84	<0.001	<0.001	34	44	24
	Left orbitofrontal cortex	823	5.7	0.001	<0.001	-26	38	-15
	Right superior frontal gyrus	65	5.44	0.002	<0.001	20	28	46
	Right anterior cingulate	257	5.43	0.002	<0.001	10	39	15
	Left supplementary motor cortex	49	5.41	0.003	<0.001	-3	-3	48
	Left hippocampus	360	5.39	0.003	<0.001	-30	-28	-9
	Right superior frontal gyrus	73	5.36	0.003	<0.001	18	45	32
	Left hippocampus	48	5.34	0.004	<0.001	-18	-22	-18
	Left inferior frontal gyrus	28	5.29	0.004	<0.001	-50	36	-8
	Left inferior frontal gyrus	152	5.28	0.005	<0.001	-42	40	4
	Right superior frontal gyrus	45	5.24	0.006	<0.001	6	40	38
	Right superior frontal gyrus	57	5.18	0.007	<0.001	22	52	20
	Left orbitofrontal cortex	29	5.12	0.009	<0.001	-15	42	-20
	Right orbitofrontal cortex	86	5.12	0.009	<0.001	16	56	-10
	Right middle frontal gyrus	20	5.06	0.012	<0.001	46	48	-3
	Right frontal operculum	41	5.06	0.012	<0.001	40	26	4
	Right middle frontal gyrus	19	5.05	0.013	<0.001	30	24	44
	Left middle frontal gyrus	23	4.99	0.016	<0.001	-30	2	52
	Right thalamus	23	4.95	0.019	<0.001	2	-8	12
	Left orbitofrontal cortex	25	4.9	0.024	<0.001	-27	20	-16
FER in *MAPT*	Left putamen	167	6.04	<0.001	<0.001	-12	9	-8
	Left insula	162	5.88	<0.001	<0.001	-40	-6	-9
	Left amygdala and hippocampus	525	5.71	0.001	<0.001	-27	-6	-26
	Right hippocampus	84	5.37	0.003	<0.001	28	-8	-15
	Right temporal pole	26	5.05	0.013	<0.001	32	15	-30

Table 3-9: Common neuroanatomical regions to all three genetic groups after running the conjunction analysis for the FER task. Results in italics identify those uncorrected at 0.001. Those not in italics survive the FWE correction for multiple comparisons.

1	Region	cluster	peak	peak	peak	Coordinates (mm)		
		equivk	T	p(FWE-corr)	p(unc)	x	y	z
Conjunction analysis	Left putamen	18	4.89	0.025	<0.001	-16	9	-9
	Left insula	6	4.86	0.028	<0.001	-39	-14	-3
Conjunction analysis (Uncorrected at 0.001)	*Right insula*	*192*	*3.99*	*0.515*	*<0.001*	*28*	*18*	*-10*
	Right insula	*132*	*3.98*	*0.53*	*<0.001*	*39*	*0*	*9*
	Right medial frontal cortex	*338*	*3.83*	*0.709*	*<0.001*	*9*	*30*	*-15*
	Left temporal pole	*235*	*3.77*	*0.775*	*<0.001*	*-36*	*12*	*-28*
	Left inferior temporal pole	*102*	*3.76*	*0.783*	*<0.001*	*-51*	*-40*	*-15*
	Left insula	*68*	*3.7*	*0.839*	*<0.001*	*-32*	*0*	*14*
	Left parahippocampal gyrus	*54*	*3.58*	*0.927*	*<0.001*	*-26*	*-36*	*-16*
	Right parahippocampal gyrus	*38*	*3.5*	*0.964*	*<0.001*	*27*	*-28*	*-22*
	Right hippocampus	*18*	*3.5*	*0.965*	*<0.001*	*18*	*-20*	*-18*
	Right superior frontal gyrus	*17*	*3.39*	*0.989*	*<0.001*	*22*	*33*	*40*

3.4.2 Facial Emotion Recognition - Emotions

When looking at performance on the different FER emotions in the control group, individuals performed better on the positive emotions (happiness and surprise) than they did on the negative ones (disgust, fear, anger and sadness) (*Figure 3-4*).

The same pattern emerges for each of the genetic groups, with identification of negative emotions (fear, anger, sadness and disgust) being worse than recognition of positive ones (happiness and surprise). In particular, sadness and fear were the items with the poorest performance for each genetic group (see Table 3-10 and Figure 3-4).

Table 3-10: Displaying the mean and SD of the FER emotions for each group.

FER Emotions:		HAP	SUR	DIS	FEAR	ANG	SAD
Control		5.0 (0.2)	4.5 (0.9)	4.0 (1.0)	3.0 (1.4)	3.9 (0.9)	3.5 (1.3)
C9orf72	**Early PS**	5.0 (0.0)	4.6 (0.8)	3.8 (1.1)	3.1 (1.3)	3.9 (1.0)	3.8 (1.2)
	Late PS	5.0 (0.0)	4.2 (1.2)	3.6 (1.2)	**2.3 (1.2)**	3.7 (1.1)	**2.7 (1.4)**
	Symptomatic	**4.4 (1.2)**	**3.0 (1.6)**	**2.4 (1.5)**	**1.4 (1.3)**	**2.3 (1.5)**	**1.9 (1.5)**
GRN	**Early PS**	5.0 (0.0)	4.6 (0.9)	4.0 (1.0)	3.2 (1.3)	3.9 (1.0)	3.8 (1.2)
	Late PS	5.0 (0.2)	4.5 (0.7)	3.8 (1.2)	2.9 (1.3)	3.9 (1.2)	3.6 (1.1)
	Symptomatic	**4.4 (0.9)**	**3.1 (1.4)**	**3.0 (1.7)**	**2.0 (1.7)**	**2.9 (1.4)**	**1.9 (1.6)**
MAPT	**Early PS**	5.0 (0.0)	4.5 (0.9)	4.1 (0.9)	3.5 (1.6)	3.9 (1.0)	3.6 (1.3)
	Late PS	5.0 (0.0)	4.8 (0.5)	4.0 (1.2)	3.2 (1.2)	4.2 (0.7)	3.5 (0.8)
	Symptomatic	4.8 (0.5)	**3.3 (1.6)**	**2.6 (1.7)**	2.1 (1.5)	**2.6 (1.6)**	**2.7 (1.1)**

*Bold and highlighted cells indicate a significant difference compared to the control group

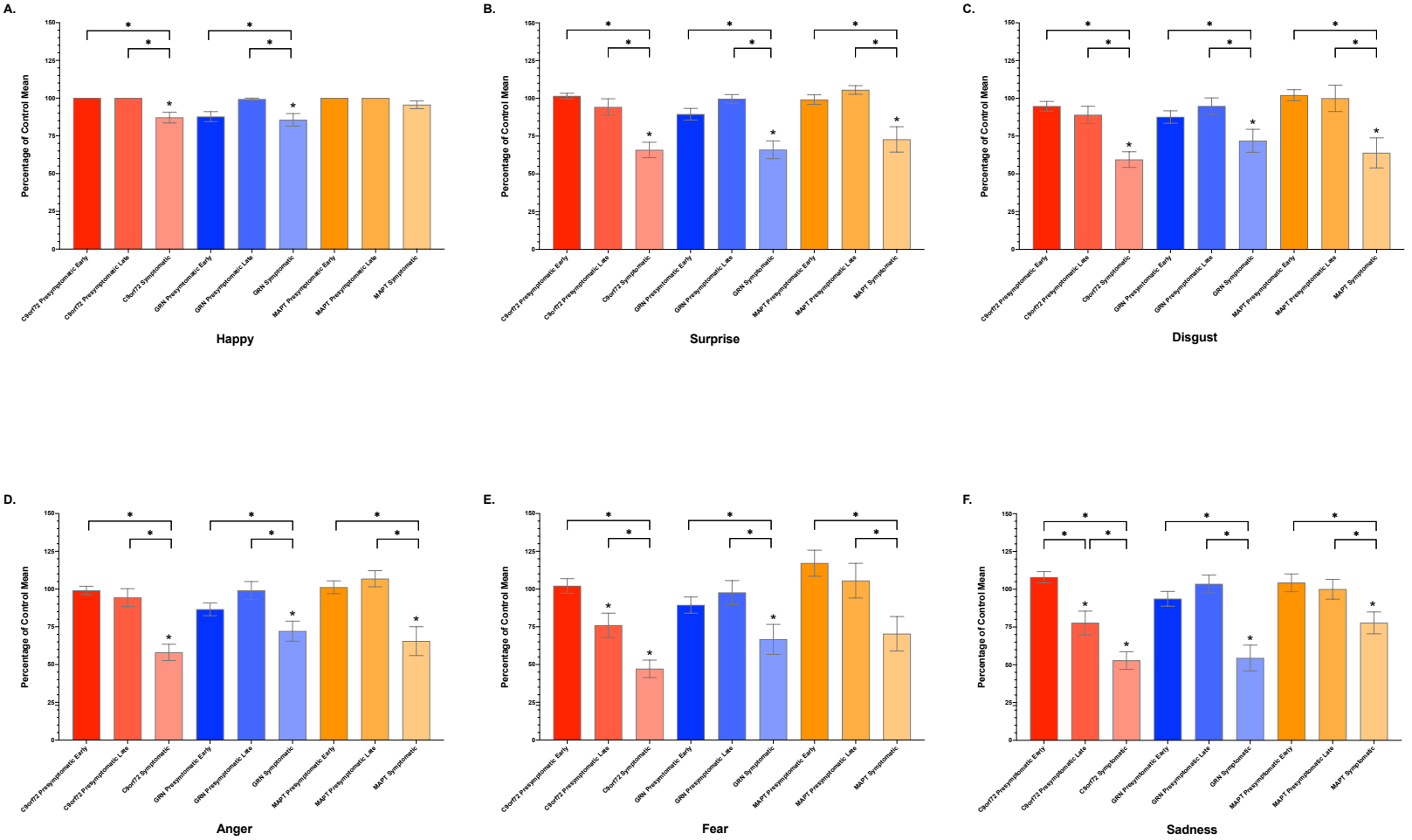

Figure 3-4: Figure displaying the percentage score of the control mean on the different emotions on the FER test across the groups. * *Above a bar indicates a significant difference from controls.*

Happiness

The *C9orf72* and *GRN* symptomatic mutation carriers performed significantly lower than their early and late presymptomatic counterparts and controls, on items of happiness. Both symptomatic groups also performed significantly lower than the *MAPT* symptomatic carriers.

Both the early *C9orf72* and *GRN* presymptomatic mutation carriers performed significantly better than the control group.

Surprise

On items of surprise, all three symptomatic groups performed significantly worse than their early and late presymptomatic counterparts and the controls.

The early *MAPT* presymptomatic mutation carriers performed significantly lower than the late *MAPT* presymptomatic group.

Anger and disgust

When looking at the negative items, on both disgust and anger, all three symptomatic groups performed significantly worse than their early and late presymptomatic counterparts and the controls.

Fear

On fearful items, both the *C9orf72* and *GRN* symptomatic carriers performed significantly lower than their early and late presymptomatic counterparts, and controls. The *MAPT* symptomatic carriers did perform significantly worse than the early *MAPT* presymptomatic carriers, but only a trend was observed for the late carriers and controls.

Additionally, the late *C9orf72* presymptomatic carriers performed significantly worse than both the late *GRN* and *MAPT* presymptomatic carriers, as well as the controls.

Sadness

Finally, on sad items, both the *C9orf72* and *GRN* symptomatic carriers performed significantly lower than their early and late presymptomatic counterparts, as well as the controls. The *MAPT* symptomatic carriers did perform significantly worse than the late *MAPT* presymptomatic carriers and controls, but not when compared to the early presymptomatic *MAPT* carriers. Furthermore, the *C9orf72* and the *GRN* symptomatic carriers both performed significantly worse than the *MAPT* symptomatic carriers.

When looking at performance in the presymptomatic groups, the late *C9orf72* carriers performed significantly lower than multiple other groups: the early *C9orf72* presymptomatic carriers, late *GRN* and late *MAPT* presymptomatic carriers as well as the control group.

3.4.3 The Faux-Pas Test

Healthy controls

The cumulative frequency in the control group fluctuated across the languages (Table 3-11). Furthermore, when looking at the percentile scores across language, the median percentile ranged from 34.0 to 39.0 out of a possible 40.0 (Table 3-12), while the mean ranged from 32.8 to 38.2 (Table 3-13). As a result, z-scores were used for the analysis on the FP Test. Any z-score of -1.65 or below was considered abnormal. This is because in standard neuropsychometric assessments, the 5th percentile is used to calculate abnormal cut-off scores; -1.65 is the equivalent of this when using a z-score. The range in performance over decade ranged from 0.4 to -0.7 (Table 3-14) and

there was a significant negative correlation (Rho = -0.195, p = 0.002). When looking at the effect of gender and age, the correlation in test performance and age was only a significant negative correlation in males (Males: Rho = -0.301, p = 0.002; Females: Rho = -0.145, p = 0.086). This implies that there may be an influence of age and gender in performance on the FP Test.

Table 3-11: Cumulative frequency of the raw FP score in controls.

Score	0: English		1: Italian		2: Dutch		3: Swedish		5: French		6: Spanish		7: German		8: Portuguese	
	N	CF	N	CF	N	CF	N	CF	N	CF	N	CF	N	CF	N	CF
19	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	6.9	0	0.0	0	0.0
20	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	6.9	0	0.0	0	0.0
21	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	6.9	0	0.0	1	8.3
22	0	0.0	0	0.0	1	1.7	0	0.0	0	0.0	1	10.3	0	0.0	1	16.7
23	1	1.7	0	0.0	0	1.7	0	0.0	0	0.0	0	10.3	0	0.0	0	16.7
24	0	1.7	0	0.0	1	3.3	0	0.0	0	0.0	0	10.3	0	0.0	0	16.7
25	1	3.4	0	0.0	1	5.0	0	0.0	0	0.0	1	13.8	0	0.0	0	16.7
26	0	3.4	0	0.0	1	6.7	0	0.0	2	6.9	0	13.8	1	12.5	0	16.7
27	1	5.1	0	0.0	1	8.3	0	0.0	1	10.3	1	17.2	0	12.5	0	16.7
28	2	8.5	1	2.7	1	10.0	0	0.0	0	10.3	0	17.2	0	12.5	1	25.0
29	0	8.5	0	2.7	4	16.7	0	0.0	0	10.3	1	20.7	0	12.5	0	25.0
30	3	13.6	0	2.7	1	18.3	0	0.0	3	20.7	1	24.1	1	25.0	0	25.0
21	2	16.9	4	13.5	4	25.0	0	0.0	1	24.1	1	27.6	0	25.0	1	33.3
32	1	18.6	1	16.2	7	36.7	0	0.0	0	24.1	2	34.5	0	25.0	1	41.7
33	2	22.0	4	27.0	5	45.0	0	0.0	1	27.6	4	48.3	2	50.0	0	41.7
34	6	32.2	2	32.4	7	56.7	1	9.1	1	31.0	2	55.2	2	75.0	0	41.7
35	4	39.0	2	37.8	2	60.0	1	18.2	3	41.4	1	58.6	0	75.0	0	41.7
36	2	42.4	0	37.8	1	61.7	0	18.2	3	51.7	2	65.5	0	75.0	1	50.0
37	3	47.5	3	45.9	6	71.7	0	18.2	6	72.4	1	69.0	1	87.5	0	50.0
38	6	57.6	4	56.8	2	75.0	2	36.4	4	86.2	2	75.9	0	87.5	1	58.3
39	5	66.1	3	64.9	4	81.7	5	81.8	2	93.1	4	89.7	1	100.0	2	75.0
40	20	100.0	13	100.0	11	100.0	2	100.0	2	100.0	3	100.0	0	100.0	3	100.0

Table 3-12: Percentile scores across language.

Percentile	ENG	ITA	NLD	SWE	FRA	ESP	DEU	PRT
5th	27	31	25	NA	26	19	NA	NA
10th	30	31	28	34	27	22	NA	21
20th	33	33	31	36	30	29	29	26
30th	34	34	32	38	34	32	32	31
40th	36	37	33	39	35	33	33	33
50th	38	38	34	39	36	34	34	37
60th	39	39	36	39	37	36	34	39
70th	40	40	37	39	37	38	35	39
80th	40	40	39	40	38	39	37	40
90th	40	40	40	40	39	40	NA	40

*ENG = English, ITA = Italian, NLD = Dutch, SWE = Swedish, FRA = French, ESP = Spanish, DEU = German, PRT = Portuguese. NA used as there were not enough participants in the group to generate all percentile scores.

Table 3-13: Mean FP raw score across language.

FP Total All	Mean	SD
0: English	36.1	(4.4)
1: Italian	36.6	(3.6)
2: Dutch	34.2	(4.6)
3: Swedish	38.2	(1.9)
5: French	34.9	(4.1)
6: Spanish	33.2	(6.0)
7: German	32.8	(1.9)
8: Portuguese	33.8	(7.0)

Table 3-14: FP mean z-score by decade.

Age group	All		Females		Males	
	N	FP Z Score	N	FP Z Score	N	FP Z Score
Overall score	**245**	**0.0 (1.0)**	**142**	**0.1 (1)**	**103**	**-0.2 (1.1)**
18.1-29.9	29	0.4 (0.7)	15	0.5 (0.8)	14	0.4 (0.7)
30.0-39.9	59	0.2 (1.0)	34	0.2 (1.0)	25	0.2 (1.1)
40.0-49.9	67	-0.1 (1.0)	37	0.1 (1.0)	30	-0.4 (1.0)
50.0-59.9	45	0.1 (0.9)	30	0.2 (0.9)	15	-0.2 (1.1)
60.0-69.9	37	-0.3 (1.3)	25	-0.1 (1.3)	14	-0.7 (1.0)
70.0-85.0	8	-0.7 (0.6)	1	-0.7 (0.0)	5	-0.6 (1.2)

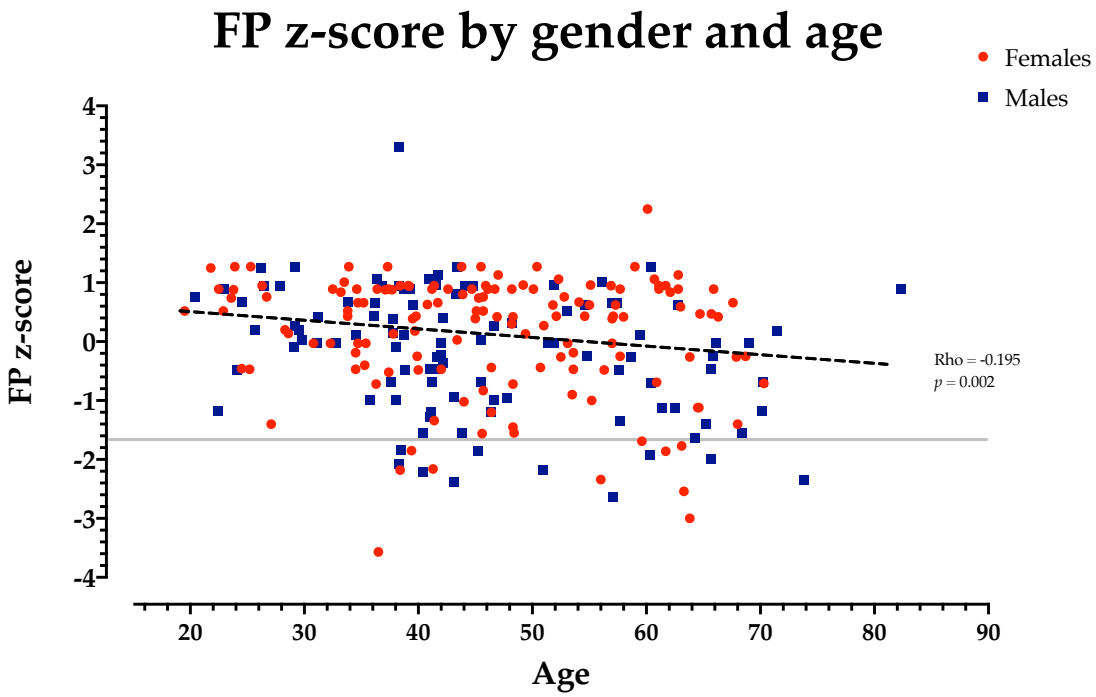

Figure 3-5: Spearman's Rank Correlation between age and performance on the FP raw scores for controls - abnormal cut off of -1.65

Mutation carriers

When comparing the FP z-scores between the symptomatic mutation carriers, scores were significantly lower in *C9orf72* and *GRN* compared to *MAPT*. When comparing within each genetic group to the early and late presymptomatic mutation carriers and to the control group, all three symptomatic groups performed significantly lower (Table 3-14 and Table 3-15, *Figure 3-6*).

Table 3-15: Demographic information and FP raw and z-score means for each group.

FP Z Score - Mean (SD)		N	Age	Ed. Level	MMSE	CDR/ NACC FTLD	FP Raw Score	FP Z Score
Control		245	46.6 (13.1)	14.2 (3.5)	29.3 (1.2)	0.2 (0.6)	35.1 (4.7)	0.0 (1.0)
C9orf72	**Early PS**	81	41.5 (10.1)	14.8 (2.5)	29.3 (1.1)	0.2 (0.6)	35.0 (5.2)	-0.2 (1.6)
	Late PS	24	56.3 (8.3)	13.2 (3.9)	28.7 (1.3)	0.4 (0.9)	31.9 (7.5)	-1.0 (2.8)
	Symp.	45	62.6 (8.6)	12.9 (3.8)	23.5 (6.7)	9.8 (6.3)	22.0 (9.9)	-4.0 (3.5)
GRN	**Early PS**	93	41.6 (9.0)	14.9 (3.6)	29.5 (0.9)	0.1 (0.2)	36.3 (4.3)	0.2 (1.0)
	Late PS	30	61.6 (7.1)	14.1 (3.3)	28.8 (1.8)	0.3 (0.6)	35.6 (3.7)	0.1 (0.8)
	Symp.	22	63.5 (8.0)	11.6 (3.6)	18.4 (9.3)	9.9 (6.5)	18.7 (12.2)	-3.7 (2.9)
MAPT	**Early PS**	37	36.6 (8.1)	14.7 (2.7)	29.6 (0.8)	0.3 (0.6)	35.2 (4.5)	0.1 (1.1)
	Late PS	12	50.2 (10.5)	13.4 (3.9)	29.3 (1.0)	0.2 (0.6)	34.7 (4.5)	0.0 (1.0)
	Symp.	12	58.7 (9.4)	14.2 (3.8)	21.8 (8.0)	9.7 (6.4)	29.2 (7.0)	-1.5 (1.6)

* Ed. Level = education level; PS = presymptomatic; Symp. = Symptomatic

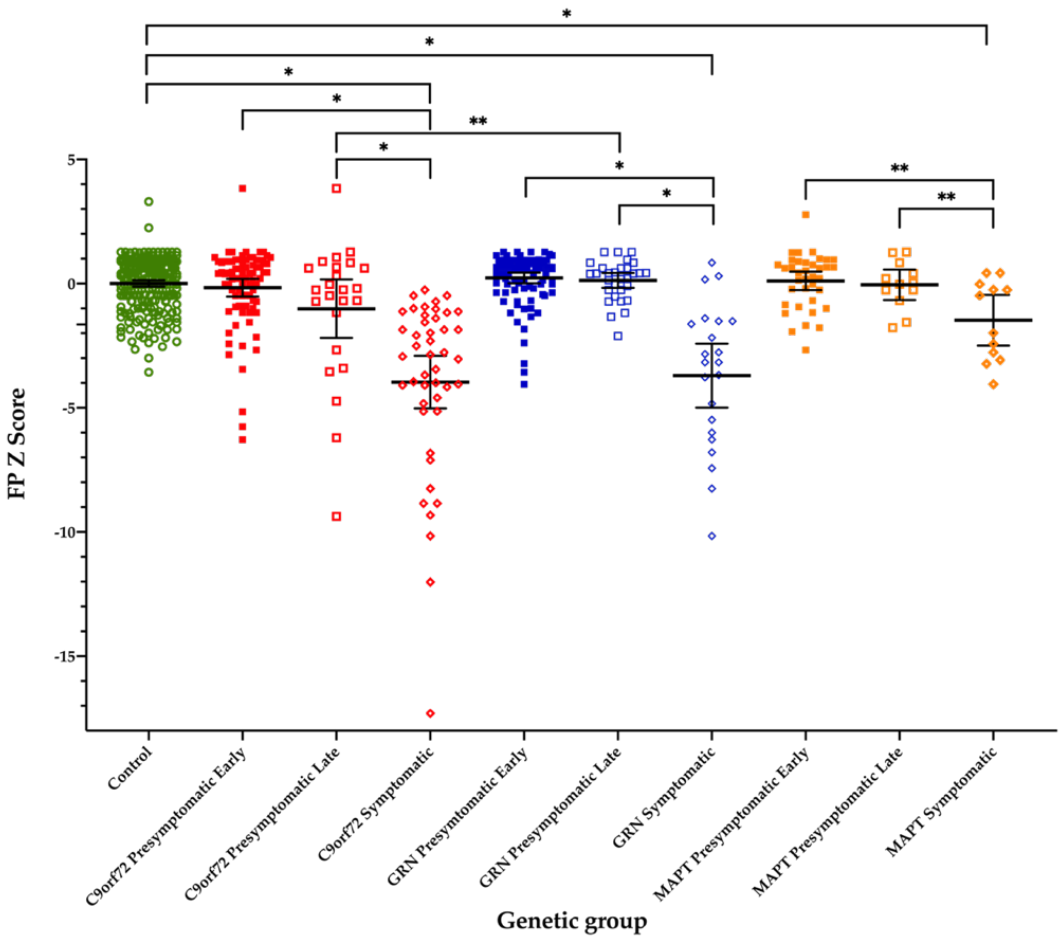

Figure 3-6: The FP mean z-scores for each genetic group with significant differences shown to controls and within each genetic group.

Table 3-16: The adjusted mean differences between groups on the FP z-scores with the p values and 95% confidence intervals shown below. *PS: Presymptomatic

		C9orf72			*GRN*			*MAPT*		
		Early PS	**Late PS**	**Symptomatic**	**Early PS**	**Late PS**	**Symptomatic**	**Early PS**	**Late PS**	**Symptomatic**
Control		-0.26 0.167 -0.62 0.11	-0.84 0.128 -1.91 0.24	**-3.60** **< 0.001** **-4.64 -2.55**	0.11 0.405 -0.15 0.37	0.41 0.013 0.09 0.74	**-3.40** **< 0.001** **-4.66 -2.15**	-0.11 0.568 -0.47 0.26	0.04 0.888 -0.53 0.62	**-1.20** **0.011** **-2.13 -0.27**
C9orf72	**Early PS**		-0.58 0.312 -1.70 0.54	**-3.34** **< 0.001** **-4.43 -2.24**	**0.37** **0.075** **-0.04 0.77**	**0.67** **0.008** **0.17 1.17**	**-3.14** **< 0.001** **-4.47 -1.82**	0.15 0.528 -0.32 0.62	0.30 0.380 -0.37 0.97	**-0.94** **0.063** **-1.94 0.05**
	Late PS			**-2.76** **< 0.001** **-4.26 -1.25**	0.95 0.085 -0.13 2.03	**1.25** **0.027** **0.14 2.36**	**-2.56** **0.002** **-4.22 -0.91**	0.73 0.206 -0.40 1.86	0.88 0.158 -0.34 2.10	-0.37 0.614 -1.78 1.05
	Symptomatic				**3.71** **< 0.001** **2.63 4.78**	**4.01** **< 0.001** **2.96 5.06**	0.19 0.811 -1.40 1.79	**3.49** **< 0.001** **2.39 4.59**	**3.64** **< 0.001** **2.48 4.79**	**2.39** **< 0.001** **1.05 3.74**
GRN	**Early PS**					0.30 0.132 -0.09 0.70	**-3.51** **< 0.001** **-4.80 -2.23**	-0.22 0.279 -0.61 0.18	-0.07 0.823 -0.67 0.53	**-1.31** **0.007** **-2.27 -0.36**
	Late PS						**-3.81** **< 0.001** **-5.08 -2.55**	**-0.52** **0.039** **-1.01 -0.03**	-0.37 0.249 0.00 0.26	**-1.62** **0.001** **-2.55 -0.68**
	Symptomatic							**3.30** **< 0.001** **1.99 4.60**	**3.44** **< 0.001** **2.07 4.81**	**2.20** **0.005** **0.67 3.73**
MAPT	**Early PS**								0.15 0.669 -0.53 0.82	**-1.10** **0.031** **-2.09 -0.10**
	Late PS									**-1.24** **0.023** **-2.31 -0.18**
	Symptomatic									

Neuroimaging results

The local maxima for the grey matter volume differences between the genetic groups can be found in Table 3-6 above.

When investigating the performance on the FP task with GM volumes in the additive analysis, it can be seen that GM regions that correlated with the task across the genetic groups were the bilateral orbitofrontal cortex, the left superior frontal gyrus, hippocampus, caudate and putamen, and the right temporal pole and insula (see Table 3-17 and *Figure 3-7*).

When looking at the GM regions associated with the FP task for each of the genetic mutations, there were unique neuroanatomical correlates specific to the *GRN* mutation group only, when correcting for multiple comparisons (see Table 3-18). To identify these overlapping regions, a conjunction analysis was carried out and found no regions common to all three genetic mutations when correcting for multiple comparisons. At a reduced threshold of $p < 0.001$ uncorrected there were two regions common to all three genetic mutations, the left amygdala and right orbitofrontal cortex (see Table 3-9).

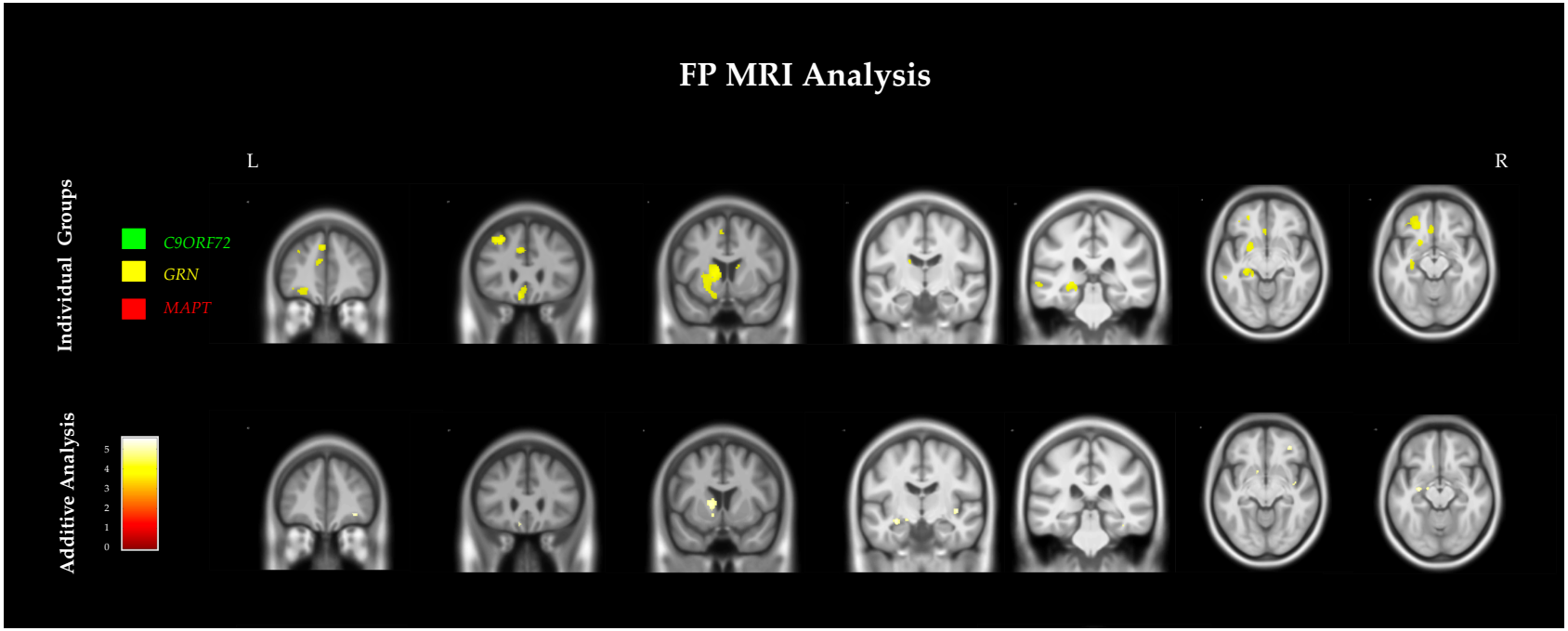

Figure 3-7: Statistical parametric maps from the voxel-based morphometry analysis of the FP test. Results the individual groups and the additive analysis are displayed corrected for multiple comparisons (FWE) at $p< 0.05$. There were no findings when corrected for multiple comparisons for the common regions and so no results are displayed.

Table 3-17: The neuroanatomical GM correlates for the FP task across all of the genetic groups. All results displayed FWE corrected at 0.05.

Contrast	Region	cluster	peak	peak	peak	Coordinates (mm)		
		equivk	T	p(FWE-corr)	p(unc)	x	y	z
FP across FTD (Additive)	Left orbitofrontal cortex	190	5.51	0.002	< 0.001	-9	21	-20
	Right temporal pole	33	5.37	0.003	< 0.001	45	20	-34
	Right insula	69	5.32	0.004	< 0.001	40	-8	-6
	Left superior frontal gyrus	23	5.28	0.005	< 0.001	-22	20	56
	Right orbitofrontal cortex	22	5.27	0.005	< 0.001	33	44	-9
	Left hippocampus	58	5.24	0.006	< 0.001	-28	-12	-14
	Left basal ganglia	349	5.17	0.008	< 0.001	-14	12	3

Table 3-18: Neuroanatomical GM correlates associated with the FP task in each individual genetic group. All results displayed are FWE corrected at 0.05.

Contrast	Region	cluster	peak	peak	peak	Coordinates (mm)		
		equivk	T	p(FWE-corr)	p(unc)	x	y	z
FP in *C9orf72*								
FP in *GRN*	Left basal ganglia, hippocampus and amygdala	2382	6.59	0	0	-15	8	6
	Left middle frontal gyrus	586	6.6	0	0	-28	26	46
	Left middle temporal gyrus	168	6.06	0	0	-64	-28	-3
	Left superior frontal gyrus	173	6.02	0	0	-4	42	36
	Left orbitofrontal cortex	461	5.96	0	0	-24	36	-15
	Left cingulate gyrus	862	5.95	0	0	-6	18	39
	Left precuneus	137	5.77	0	0	-2	-58	28
	Left hippocampus	388	5.62	0.001	0	-24	-33	-4
	Left parahippocampal gyrus	92	5.55	0.001	0	-20	-22	-21
	Left supramarginal gyrus	45	5.42	0.003	0	-60	-42	30
	Left angular gyrus	70	5.35	0.004	0	-50	-63	28
	Right middle frontal gyrus	57	5.3	0.004	0	36	45	24
	Left supplementary motor cortex	48	5.28	0.005	0	-6	10	54
	Left angular gyrus	19	5.05	0.013	0	-50	-57	44
	Left precuneus	15	4.94	0.021	0	-9	-51	38
	Left middle frontal gyrus	27	4.93	0.022	0	-33	38	33
	Right caudate	24	4.91	0.024	0	12	8	16
	Left middle temporal gyrus	21	4.91	0.025	0	-58	-51	0
FP in *MAPT*								

Table 3-19: Common neuroanatomical regions to all three genetic groups after running the conjunction analysis for the FP task. Results in italics identify those uncorrected at 0.001.

Contrast	Region	cluster	peak	peak	peak	Coordinates (mm)		
		equivk	T	p(FWE-corr)	p(unc)	x	y	z
Conjunction analysis (FWE)								
Conjunction analysis (Uncorrected at 0.001)	*Right orbitofrontal cortex*	*3*	*3.2*	*1*	*0.001*	*30*	*40*	*-9*
	Left amygdala	*1*	*3.14*	*1*	*0.001*	*-16*	*-10*	*-14*

3.5 Discussion

The aim of this study was to investigate emotion processing and theory of mind abilities in a familial cohort of FTD, specifically to investigate differences between the genetic mutations, assess performance in the presymptomatic cohort and to examine neuroanatomical regions associated with these abilities.

This study has demonstrated that both the FER and FP test are able to detect emotion processing and theory of mind deficits in symptomatic cases of familial FTD, as well as identifying emotion processing deficits in the late presymptomatic *C9orf72* mutation carriers using the FER. Furthermore, the VBM analysis revealed a left predominant basal ganglia-orbitofrontal-insula-anteromedial temporal network for the FER task. This network was observed in the FTD group as a whole, with many of the same regions observed when looking at the correlations of the tasks to the GM volumes in each of the individual genetic groups. Using the conjunction analysis however, only the left putamen and the left insula were common to all three genetic groups. A network of similar neuroanatomical regions was observed when analysing correlates of the FP task when looking at the group as a whole, although when looking at each of the groups individually, only the *GRN* genetic group withstood FWE correction. This meant that no regions were found to be common to all three genetic groups on the conjunction analysis when using an FWE correction for multiple comparisons, although the right orbitofrontal cortex and the left amygdala were significant at a threshold of $p<0.001$ uncorrected. Overall, this suggests a very similar neuroanatomical network is likely to be involved in the performance of both tasks.

By using this cohort of individuals, it has allowed for the generation of a natural control group – those in the families that are gene negative. This has

therefore given a comprehensive overview of these two tests in a large population, and generates a threshold for abnormal test scores. Given the use of these tests across the vast majority of the previous literature to assess emotion processing and theory of mind abilities in sporadic FTD, it allows for an easier comparison between the studies. Furthermore, this work also indicates that there may be an influence of age and gender on both tests, with an overall performance decreasing with age, which appears to be greatest in males. This supports previous work that has identified age related decline in emotion processing (Mill, Allik, Realo, & Valk, 2009; Sullivan, Ruffman, & Hutton, 2007; West et al., 2012) and theory of mind (Maylor, Moulson, Muncer, & Taylor, 2002; Pardini & Nichelli, 2009; Wang & Su, 2006), although some studies identify an age related decline in specific emotions i.e. anger, fear and sadness (Kessels, Montagne, Hendriks, Perrett, & de Haan, 2014). Moreover, gender differences have also previously been observed, with males performing worse than females on emotion processing tests (Hoffmann, Kessler, Eppel, Rukavina, & Traue, 2010; Kessels et al., 2014; Lee et al., 2002; Montagne, Kessels, Frigerio, de Haan, & Perrett, 2005). This therefore supports the need to adjust for age and gender in statistical analyses of tests assessing social cognition. Finally, performance on the different emotions in the control group, suggests that positive emotions (happiness and surprise) are easier to recognise than negative ones, and emotions of sadness and fear are the most difficult to identify. Other studies have suggested a similar pattern with happy faces being the easiest to identify, while negative emotions are less easily recognised i.e. sadness and fear (Kessels et al., 2014; Ruffman, Henry, Livingstone, & Phillips, 2008; Young, Perrett, Calder, Sprengelmeyer, & Ekman, 2002).

The results from the FER and FP tests in the symptomatic mutation carriers were as expected, all groups performed significantly lower than their

presymptomatic counterparts and the controls. This is in line with previous work in sporadic cases of FTD, demonstrating lower performance in bvFTD compared to controls using both the FER (Bertoux, Volle, et al., 2014; Diehl-Schmid et al., 2007; Kumfor, Hazelton, et al., 2018) and FP tests (Bertoux et al., 2013; Funkiewiez et al., 2012). When looking at performance on the emotions however, subtle differences did occur. The *C9orf72* and *GRN* symptomatic mutation carriers performed worse than the *MAPT* symptomatic mutation carriers on items of happiness and sadness. Moreover, there was no significant differences observed when comparing the symptomatic *MAPT* mutation carriers to controls and the late *MAPT* presymptomatic carriers on items of fear, as well as to the early *MAPT* presymptomatic carriers on items of sadness. It is possible that this is due to the lower number of participants in the symptomatic *MAPT* group ($N = 18$).

The main finding in the presymptomatic carriers, was that there appeared to be a decrease in emotion processing abilities in the late *C9orf72* mutation carriers (those within 5 years to symptom onset) when compared to controls, the other early and late presymptomatic carriers (*MAPT* and *GRN*) and the early *C9orf72* presymptomatic mutation carriers. This deficit was most pronounced on items of fear and sadness. Furthermore, theory of mind deficits were also observed, however there was only a trend towards significance. This therefore demonstrates that despite appearing symptom free, subtle changes in the ability to process emotional information is changing earlier in the *C9orf72* mutation carriers than the other two groups. This could therefore act as a marker for the window prior to symptom onset that may be useful in *C9orf72* clinical trials. In support of this, neuroimaging also demonstrates changes in the brain between 5 to 25 years prior to estimated onset in familial cases of FTD (Cash et al., 2018; Rohrer et al., 2015), with the

earliest anatomical changes occurring in *C9orf72* mutation carriers compared to the other two genetic mutation groups (*GRN* and *MAPT*).

When investigating these anatomical changes, differences were found between the three genetic groups. The *MAPT* mutation carriers were found to have smaller GM volume in the hippocampus, amygdala and the temporal poles when compared to the *GRN* and *C9orf72* mutation carriers. The *C9orf72* mutation carriers were found to have reduced GM volumes in the thalamus and the cerebellum compared to the *MAPT* and *GRN* mutation carriers. Furthermore, when compared to the *GRN* group, the *C9orf72* mutation carriers also had reduced GM volumes in multiple other regions including the operculum, the cingulate and the precuneus. These findings are in line with previous work investigating the neuroanatomical correlates of the individual genetic groups (Cash et al., 2018), as well as being consistent with the clinical literature and the known phenotypes of the individual conditions as discussed in section 1.3.

As previously mentioned, whilst only the left putamen and insula withstood FWE correction for multiple comparisons on the FER task, three regions did appear across the three genetic groups when looking at them independently: the basal ganglia, the insula and the orbitofrontal cortex. These regions are all highly interconnected and form part of a functional network for the social brain (Adolphs, 2002; Pessoa, 2017).

Although not classically considered a region involved in social cognition, the basal ganglia are connected with both the insula and the orbitofrontal cortex (Adolphs, 2002). The basal ganglia has been shown to have links to social processing, with particular processing of emotions such as disgust (Sprengelmeyer et al., 1997). While no study thus far has found that the basal ganglia is involved with emotion processing in sporadic bvFTD, many other

studies do suggest a link with the basal ganglia. A case study of patient MGV with a focal caudate lesion, demonstrated that he had problems with recognising negative emotions, particularly sadness and fear (Kemp et al., 2013). Furthermore, patient MGV also had problems with the affective part of theory of mind leading to problems with empathising with others (Kemp et al., 2013). Whilst the basal ganglia were found to be associated with the FP task in the additive analysis, it was clear from the individual group analysis that this was driven by the *GRN* group and thus, was not associated with the FP task in all three groups.

This work has also shown that the insula is involved in the processing of emotions. This supports previous work investigating the function of the insula as a core hub of the salience network which is involved in a wide variety of social processes (Menon & Uddin, 2010; Uddin, Nomi, Hebert-Seropian, Ghaziri, & Boucher, 2017), such as interoception, the processing of emotional experiences and the awareness of positive and negative feelings (Craig, 2002). These processes are all required when trying to identify emotions on the FER tests. The insula has been shown to be affected in sporadic bvFTD on the FER (Couto et al., 2013; Omar, Rohrer, Hailstone, & Warren, 2011b) and FP tests (Adenzato, Cavallo, & Enrici, 2010; Agustus et al., 2015), and in this study was found to be associated with both tasks on the additive analysis (although not the conjunction analysis) suggesting that its involvement may be unique to specific genetic groups.

Finally, the orbitofrontal cortex is also a known region involved in complex social and emotional behaviour (Kringelbach, 2004; Rolls, 2004). This work supports the involvement of the orbitofrontal cortex with emotion processing in all three of the genetic mutations involved in familial FTD. It was also associated with theory of mind abilities in the additive analysis. One of the main functions of the orbitofrontal cortex is stimulus-reinforcement learning,

and this can be applied to the learning of socially appropriate behaviours. When these learned behaviours are disrupted and inappropriate social behaviours occur, as in the case of sporadic bvFTD, the orbitofrontal cortex is known to be correlated with performance on the FER (Couto et al., 2013) and the FP tests (Guevara et al., 2015). Given that the orbitofrontal cortex has also been implicated in genetic FTD (Cash et al., 2018; Rohrer et al., 2015), and damage here can cause problems with insight and the inability to generate emotional helpful information (Beer, John, Scabini, & Knight, 2006), it is not surprising that this study finds deficits in emotion processing and theory of mind in genetic forms of FTD which are positively correlated to GM volume in the orbitofrontal cortex.

Whilst all of these regions have their own functions, their ability to interact with each other allows behaviours to be learned so that individuals are able to follow societal norms. Another key hub in this social network is the amygdala. Originally thought to be the key area in the brain for processing emotions, we now know it interacts with all these additional co-opted regions such as the insula and the orbitofrontal cortex, and is also involved in theory of mind abilities (Siegal & Varley, 2002). This supports the findings of this study as the amygdala was found to associated with both tasks.

A key strength of this study is down to the large sample size. Whilst familial FTD is somewhat of a rare condition, by using data collected as part of GENFI, it allows greater access to a larger cohort of individuals with familial FTD. Despite this, some groups do still have small sample sizes (i.e. symptomatic *MAPT*), and the continuation of data collection as part of GENFI will help to overcome this problem. As structural changes are happening many years prior to symptom onset, it is possible that these tests are not sensitive enough to detect early presymptomatic changes. Consequently, novel tests should be developed to be more specific and sensitive to social cognitive skills. Finally,

longitudinal analysis should be carried out to identify at what point these changes seem to be occurring throughout the disease progression. By monitoring performance over time, and identifying individuals who become converters, this will provide insight into real time changes rather than predictions of where they are in their disease process.

3.6 Chapter summary

To conclude, this study demonstrates that the FER and FP tests are able to identify deficits in emotion processing and theory of mind abilities' in familial cases of FTD, across the three main genetic mutation. Furthermore, neuroanatomical regions known to be involved with emotion processing were associated with the FER tasks and make up a basal ganglia-orbitofrontal-insula-anteromedial temporal network. Whilst there was evidence for a similar pattern on the FP task, there were no common regions that withstood FWE correction. This work was also able to identify early deficits in the late presymptomatic *C9orf72* mutation carriers and thus, these tests could be used for clinical trials as a marker of disease progression and drug effectiveness in a *C9orf72* targeted therapy. Future work should consider the longitudinal analysis of performance in these tests in a similar cohort, as well as developing novel tasks that may identify social cognitive change in the presymptomatic phases given the early neuronal loss that occurs.

CHAPTER 4: METHODS II – TEST DEVELOPMENT

4.1 Chapter overview

The aim of this project is to develop novel social cognitive tests that are more sensitive than the current standardised tests. Chapter 3 assessed the sensitivity of these tests in a familial FTD cohort; the Mini-SEA was only effective at detecting early changes in the *C9orf72* late presymptomatic mutation carriers. There are also a number of pitfalls and problems associated with the current standardised tests as discussed in section 1.4.5. In order to overcome these problems, I have designed three eye-tracking tests to assess social cognition in FTD. This chapter will therefore cover the equipment used, the development of the pilot test, and the development of the final social cognitive tests.

4.2 Eye-tracking equipment

The Eyelink 1000 plus is a highly flexible eye-tracker, with sampling of eye movements of up to 1000 Hz per second, and an accuracy of 0.15 degrees (°). For this project, a desktop mounted version will be used with the aid of a head mount, to ensure stability of the head. This will increase reliability by ensuring consistency of positioning. As previous studies have suggested that eye-movements of patients with FTD are typically normal and comparable to controls (see section 1.6.2), this method has been selected as an alternative way of measuring social cognition. Moreover, work from Primativo et al. (2017) suggest that tests of cognition such as executive function, could be designed so that the influence of language is limited (see section 1.6.1). Thus, this overcomes many of the problems associated with the standard psychological tests, allowing social cognition to be measured in a quantitative way. It removes the problem of complex instructions, and limits the amount of

language used in the tests. Thus, a short 5 minute test was designed based on the Reading the Mind in the Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001), a measure of emotion processing (see section 1.4.1 for a review of the literature) to assess whether or not this was a viable technique.

4.3 The development of a pilot eye-tracking test

4.3.1 Participants

Participants were selected from the general public at the Science Museum as part of the Live Science research project. This provided an environment in which individuals who were interested in science, of all backgrounds and ages, could participate in current research projects, of which this was one. A total of 34 participants took part in the study, but demographic details were only available for 32 (see Table 4-1). The project gained ethical approval from the University College London Research Ethics Committee (reference number 8545/001: Where Do I Look & Why?), and all participants gave fully informed consent.

Table 4-1: Demographic information for participants at the Science Museum for the RMIE pilot test. There was a total of 32 trials which were split into two sets to give rise to a set A and a set B.

	A		B	
Gender (M:F)	15	8:7	17	7:10
Handedness (R:L)	15	13:2	17	14:3
Age*	15	35.6 (18.0)	17	37.4 (14.1)
Education*	15	14.7 (2.6)	17	15.7 (2.3)
Matrix Reasoning*	15	13.6 (5.5)	17	14.2 (3.4)

*Results display number of participants and the Mean (Standard Deviation: SD) of the tests

4.3.2 Eye-tracking test development

The Reading the Mind in the Eyes Test (RMIE) is made up of 36 items that portray a complex emotion in the eye region of the face (Baron-Cohen et al., 2001). I selected this test as it measures one's ability to process complex

emotions, as opposed to the basic ones. This therefore made the test more difficult, which would be beneficial when coming to assess performance in the presymptomatic individuals. Examples of emotions include "contemplative", "decisive" and "sceptical". Furthermore, there has been much research using this test in bvFTD (see section 1.4.1).

In the original test, the participant is required to select an emotion from four options after viewing the emotive eye region of the face. In order to develop this test into an eye-tracking one, the set-up was reversed. Instead of displaying one image and four words, the experiment displays four images and one word. It was designed this way to minimise the amount of language required in the test, and allows the participant to select the image that matches the word instead of the other way around. Participants were presented with a fixation cross to which they had to look at. Once they had done this, the four images from the RMIE test appeared for 10 seconds, the target word then appeared on the screen for two seconds, followed by the four images reappearing on the screen for 5 seconds - the word was still present on the screen to prevent any memory effects (see Figure 4-1). The display timings were guided by the visual world paradigm literature (Huettig, Rommers, & Meyer, 2011).

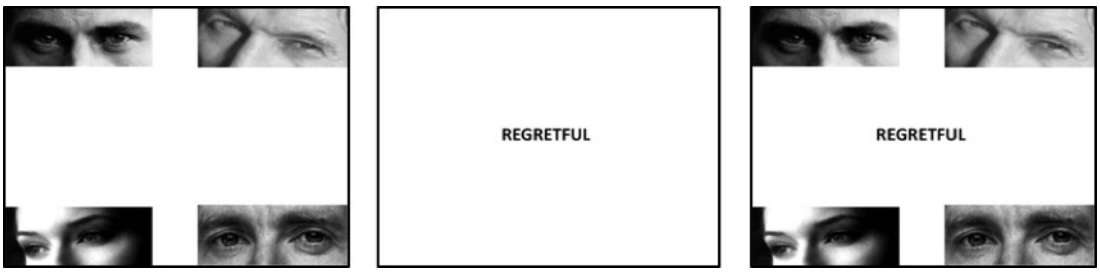

Figure 4-1: Example of a trial in the modified RMIE eye-tracking test

The frequency of the words in the RMIE test, were checked using N-watch software. 32 items were selected from the original test. These were then split

into positive and negative words (see Table 4-2), and randomised to generate the order for presentation of the images. Furthermore, the target image was randomised to each of the four corners, ensuring that there was an equal distribution in each corner across the test. A distractor item of a similar valence was used, for example, if the target image was displaying a positive emotion, the distractor was also positive; this was known as the similar distractor. The other two items were of the opposite valence, i.e. negative if the target was positive; these are referred to as distractor 1 (D1) and distractor 2 (D2). In order to cut down the test duration due to the time constraints at the Science Museum, the trials were randomly split into two sets (16 in set A and 16 in set B), ensuring an equal split of positive and negative target items in both.

Table 4-2: A list of the emotions used in the RMIE test that were modified for use in the pilot EP test.

Positive	Negative
Desire	Regretful
Fantasizing	Serious
Tentative	Hostile
Insisting	Preoccupied
Interested	Distrustful
Flirtatious	Sceptical
Confident	Accusing
Contemplative	Panicked
Playful	Upset
Friendly	Concerned
Decisive	Suspicious
Reflective	Doubtful
Thoughtful	Uneasy
Fantasizing*	Cautious
Interested*	Nervous

** Items of fantasizing and interested had two different images used in the original RMIE test*

4.3.3 Apparatus

An Eyelink 1000 plus was used to measure eye movements and sampled at 1000 Hz per second. The experiment was designed using SR research software

- Experiment Builder. Viewing was binocular but only the right eye was tracked. The eye-tracker and 18" display screen (resolution of 1920 x 1080 pixels) were positioned 70 cm from the participant. These were both connected to the host PC, which is provided by SR research (see *Figure 4-2*). The host PC is used to control the experiment, and monitors the position of the eye throughout the tests. A 9-point calibration was used to set up the camera, allowing for accurate recordings of the eyes.

4.3.4 Experimental procedure

Participants were asked to sit on the chair in front of the display screen, and place their chin on the head mount. Participants were instructed to follow the grey dot inside the black circle, with only their eyes, as it moved around the screen in order to calibrate the camera. Once an accurate calibration had been carried out, participants were instructed to look at the images as they appeared on the screen – no other instructions were given. A drift correct procedure was carried out between each trial in order to maintain accuracy. If there had been a large head movement from the initial set up and calibration, then recalibration was carried out as and when needed. Participants also completed the Ravens Matrix Reasoning test as a global measure of IQ.

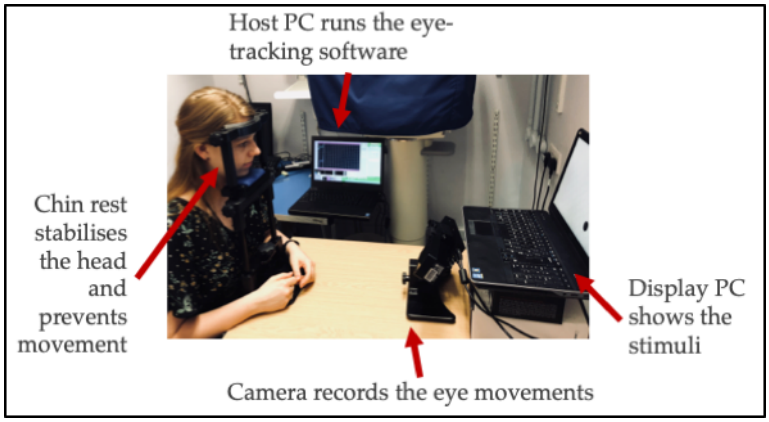

Figure 4-2: An example of the experiment set up for the social cognition eye-tracking battery.

4.3.5 Statistical analysis

As this was a pilot study to test the viability of an eye-tracking test with limited instructions, the analysis was used to determine items that worked over those that did not. Interest areas (IAs) were created in the SR research analysis programme, Data Viewer. These represented the target, similar and D1 and D2 images, and are referred to respectively as: the target IA, the similar IA and the distractor IAs. The percentage of dwell time was used as the measure of interest; this eliminated the differences in time of exposure to the images in the pre-and-post conditions. Greater time spent looking at a particular IA is assumed to show identification of the probe word.

Initially, the IAs were compared to see if there were any obvious differences before the presentation of the word. If there were any differences across participants, it indicated that there were problems with the images, as they were not being looked at evenly to start with. Next, paired t-tests were used on each trial to assess percentage of dwell time in each of the four corners, before and after the probe word. Items were selected, if there was a trend in the increase in time spent looking at the target after the probe word appeared compared to before.

4.3.6 Pilot Results

The initial analysis of the data revealed that two participants should be removed due to a large amount of missing data. This was because there were problems with the recording and saving of the experiment. After the removal of these two participants, it was clear that some of the trials worked very well, with the participants looking significantly longer at the target IA than the other IAs ($N = 10$), however this effect was not seen in all trials ($N = 22$).

In order to further investigate this, an analysis of the mean percentage dwell time in the pre-and-post conditions were compared across each of the target interest areas. Furthermore, a qualitative comparison of the images was carried out. In seven of the trials, it appeared that looking time was greatest for the similar IA. For these seven trials, the images were visually compared; it was apparent that it was very difficult to distinguish between the target and similar image. These images were therefore changed to ones that were more distinct from the target. In addition to this, on three of the trials, one of the distractor items showed a greater percentage dwell time in the post condition. Again, these images were very similar to the target item and were changed. Finally, there was also one item in which the intensity of the image seemed to be different to the rest, and so this was visually adjusted to match the others to prevent it from standing out and drawing the participants' attention. Consequently, a total of 18 items were selected for use in the total data set after these changes were made.

4.3.7 Pilot discussion

The aim of this pilot study was to investigate the viability of eye-tracking tests to assess social cognition with as little language as possible. The results suggested that over half of the items were suitable to use after a few changes were made. Two additional items were added to the data set and were manually generated in line with the items that worked. This created a data set of 20 items for the final complex emotion processing test.

The results from this pilot suggested that eye-tracking, and this test in particular, could be a viable method to analyse social cognition in FTD. Despite the data from two participants not included, it was felt that the method was accessible and easy to use, and with some practice, would be a

reliable method of assessment in an FTD cohort, despite the behaviour and language problems.

4.4 The development of other eye-tracking tests

4.4.1 Introduction

With the success of the modified version of the RMIE test, the development of other eye-tracking tasks began. As the development of the modified RMIE test used Experiment Builder software, this was also used in the development of the other tests. The same equipment and set up was also used (see 4.3.3 and 4.3.4).

4.4.2 Oculomotor functioning

It is important to know if differences between the control group and the patient group are not due to problems with oculomotor function (see section 1.6.2.). In order to assess the current cohort of participants eye-movements, a battery of tests was developed based on the work by Shakespeare et al. (2015). Fixation stability, pro-saccades, anti-saccades and smooth pursuit tests were developed using Experiment Builder. All stimuli were presented on a grey background (Colour in RBG: 128, 128, 128).

Fixation test

A red cross (Colour in RGB = 128, 128, 128; Size = 0.5 degrees of visual angle - ° VA) was presented in the middle of the screen after the drift correct procedure was carried out. It appeared on the screen for 10 seconds and individuals were instructed as follows: "A red cross will appear on the screen. Look as closely as you can at the red cross without blinking for 10 seconds. The first one will be a practice" (Crossland, Rubin, & Gary, 2002; Shakespeare et al., 2015). There was a total of four trials, the first of which was classed as a practice trial.

Smooth Pursuit

A smooth pursuit is when the eye follows a moving object. It is a moving fixation upon an object, rather than a saccade. The participant was required to follow a red dot as it moved across the screen. The red target (RGB = 255, 0, 0; Size = 0.5° VA) appeared in the centre of the screen after the drift correct procedure was completed. The target moved 10° either side of the centre (20° total amplitude) in both horizontal and vertical directions. Each trial lasted 10 seconds with the sinusoidal target frequency set at 0.25Hz. There were two practice trials and two active trials one in each direction. The participants were told to "Follow the red dot as it moves across the screen".

Pro-saccade test

For the pro-saccade test, a red cross (RGB = 255, 0, 0; Size = 0.5° VA) appeared in the middle of the screen. Once the participants had fixated on the cross, a green dot (RGB = 0, 200, 0; Diameter = 0.5° VA) appeared at 8 ° VA in the horizontal direction and 5° VA in the vertical directions either side of the target fixation cross. The difference in visual angle was chosen in order to reflect a naturally wider horizontal viewing plane. Participants were asked to "Look as quickly and as accurately as they could to the new green dot when it appeared". There were two conditions, an overlap and a gap condition. In the overlap condition, when the dot appeared on the screen, it was 500ms until the cross disappeared, i.e. they were both on the screen at the same time. In the gap condition, the cross had disappeared from the screen for 200 ms before the dot appeared, i.e. they were not on the screen at the same time. There were 16 trials in total (8 overlap, 8 gap) (Garbutt et al., 2008; Shakespeare et al., 2015). A drift correct procedure occurred between each. If there was a large head movement detected, the calibration was performed again.

Anti-saccade test

This test forms the same structure as the pro-saccade test, however the dot is red (RGB = 255, 0, 0; Size = 0.5° VA), and participants are told to "Look in the opposite direction to the dot when it appears. For example, if the dot appeared on the right, you should look left, and if it appeared at the top, you should look at the bottom". The test included the same number of trials and locations as the pro-saccade test, however only the gap condition was administered.

4.4.3 Emotion processing – simple and complex emotions

Given that the social cognitive test piloted at the science museum used emotions that were more complex than the six basic emotions (see section 1.4.1 and section 4.3.2), the pilot, plus the two additional trials, were named as the Complex Emotion Processing Test. An additional test was designed using the six universal basic emotions. It used the same format as the complex test but was referred to as the Simple Emotion Processing Test. As Ekman, Ellsworth, Friesen, Goldstein, and Krasner (1972) suggested the six basic emotions were cross culturally recognised, it was hypothesised that symptomatic bvFTD patients may not be able to understand the complex emotions, but may be able to recognise the basic emotions in the simple test. This is supported by the work in Chapter 3 (see section 3.4.1 and 3.4.2), as all of the symptomatic groups were able to identify some of the emotions displayed in the FER test; no symptomatic group performed at floor on the test or on the individual emotions.

Stimuli selection

Images were selected from the NimStim Face Stimuli Set (https://www.macbrain.org/resources.htm). The images in this database were selected over the Ekman Faces as the images are of a higher quality, are more

recent, and thus, have a higher ecological validity. All the images contained in this data set have been validated. There is a total of 43 individuals each displaying the six basic emotions. The 43 individuals were stratified based on ethnicity and selected to match the majority of the cohort. After removing these, 24 items (six emotions viewed four times) were selected based on the clarity and lighting of the images. This maintained consistency and prevented any items from standing out. Half of the images were male and the other half were female.

Stimuli structure

The images were grouped together based on gender, so the four images were all male or all female. The emotions displayed consisted of two positive emotions (happy; surprise) and two of the negative emotions (fear, sadness, anger or disgust) (see *Figure 4-3*). This was decided so that the test was equally as difficult across all trials – four negative items was believed to be more difficult than two positive and two negative items. This also maintained consistency across trials. The target image was equally distributed across all positions, and the rest of the images were randomly selected to the remaining positions.

Figure 4-3: Image displaying an example of the simple EP test.

Experiment builder programming

The images appeared on the screen for 10 seconds, before being replaced by a probe word for 2 seconds. Then the images reappeared again for a further 5

seconds, with the probe word remaining on the screen. This was done in order to minimise any memory effects. After the 5 seconds, a blank screen appeared, and the next trial began.

Analysis

The analysis in both tests will use target, similar and distractor interest areas, in order to assess the percentage of dwell time before and after the probe word. This will be compared both within and between the groups. A mixed effects model will be used to analyse the data as outlined in section 2.7.

4.4.4 Theory of Mind

As previously mentioned, individuals with bvFTD have a deficit with their theory of mind abilities (section 1.4). The main problem with the current ToM tests is that the individuals with bvFTD find it difficult to understand the test instructions, especially in tests such as the Faux-Pas. This therefore made it difficult to develop a test that would tap into these abilities, whilst removing the need for language. When looking at the developmental psychology literature, the Sally-Anne test is a popular tool for assessing first and second order false beliefs (Perner & Lang, 1999; Perner & Wimmer, 1985). It is often used to assess the development of ToM during childhood, with younger children able to complete the first order test but not the second (Wenxin, Jingxin, Yiwen, & Yueping, 2004). In addition to this, the literature surrounding eye-tracking paradigms was assessed and provided some inspiration for the development of the test (Roux, Brunet-Gouet, Passerieux, & Ramus, 2016; Schneider, Slaughter, Becker, & Dux, 2014; Schuwerk, Jarvers, Vuori, & Sodian, 2016; Senju, Southgate, White, & Frith, 2009). Consequently, a modified version of the Sally-Anne test was developed.

Stimuli selection

Images were selected from google images; all were licensed under the non-commercial reuse with modification. The images selected were pictures of a male and female cartoon character, and four items of furniture: a set of drawers, a bookshelf, a chair, a table, a rug, a door and a book. All images were saved as PNG files with the background removed.

Stimuli structure

The four items of furniture were placed in the corners of the screen. Walls were drawn in to create the look of a room, with a door opening inwards. The rug was used as a centre piece and reference point which the first character stood on (see *Figure 4-4*). The book, the characters and the drawers were animated to simulate movement.

The idea of the test was to show a short video, creating a first order false belief. The male cartoon character stood holding a book in the middle of the room. He then moved to put the book behind the cushion on the chair and left the room. The female character then appeared, and took the book from the chair and moved it to the set of drawers. She then exited the room. The male character reappeared and had to decide where to look for the book. This was implied when a speech bubble appeared from his head displaying the book, as if he was thinking of it. All the stimuli disappeared except for the four items of furniture in the corners, with the idea of monitoring where individuals would look.

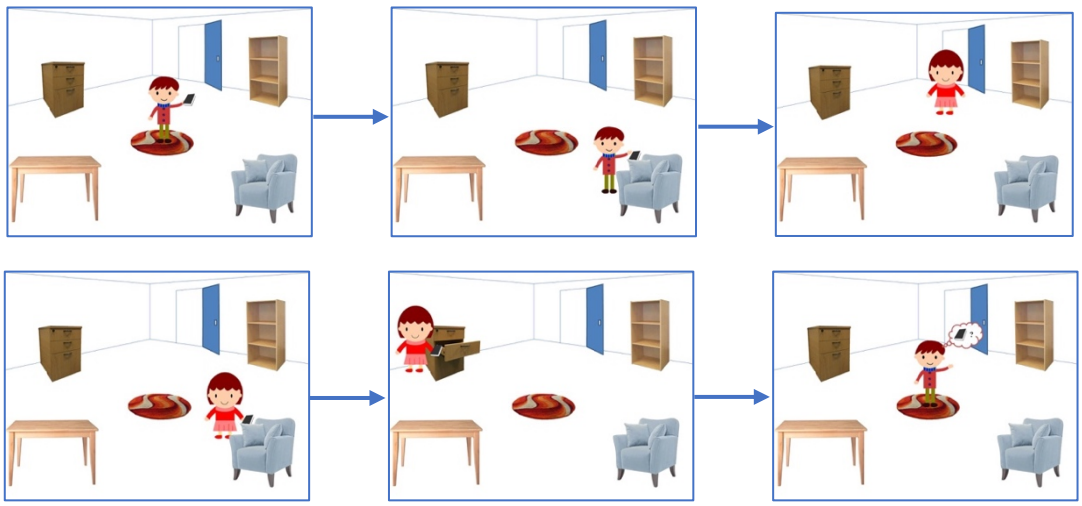

Figure 4-4: Image displaying an example of the ToM processing test.

Experiment builder programming

An initial fixation cross appeared on the screen that the participants had to fixate on. Once this occurred, the video began to run. There was only one trial.

Analysis

As this is a novel test, the analysis will be purely exploratory in the first instance. Time spent looking at the four items of furniture will be compared at the end of the video when only these items remain on the screen. Performance will then be compared across the groups using a linear regression analysis as there was only one trial.

4.4.5 Participant cohort and additional tests

Participants who took part in this novel eye-tracking battery of tests, were recruited from the LIFTD and GENFI studies. They completed all the standard procedures associated with the projects (see Chapter 2), as well as the eye-tracking tests. One other psychometric test was included to act as a validation for the simple and complex eye-tracking tasks: the novel social cognitive synonyms test (see Appendix 6). This was to ensure that the individuals understood the emotional labels used in the tasks. The entire battery takes

approximately 25 minutes to run, with approximately 20 minutes of the time being dedicated to the eye-tracking tests, and the other 5 minutes to completing the additional social cognitive test. All tests were piloted on 10 older healthy adults to ensure that no errors were made in the programming of the experiments, to check that the design and set up run smoothly, and the experiments were collecting the desired data.

4.5 Chapter summary

The aim of the development of these three tests, is to increase accessibility of social cognitive tests to the whole of the FTD spectrum. By removing the majority of the test instructions, keeping the tests simple and straightforward, hopefully more individuals with FTD will be able to complete the tests.

The greatest problem I had with developing this battery however, was the program crashing midway through testing. The test was tolerated very well by all participants, but crashed on over a third of testing sessions. I tried multiple things to correct this, turning off the internet, changing Ethernet cables and ensuring that the power was connected at all times, but I was unable to fix the problem. I am still unsure why this happened, and the staff at SR research are also unclear. I believe it may have something to do with the connection to our server at the DRC, or the virus software installed on the computer. Whilst this is frustrating, the data was not lost as it saves to the host PC automatically. However, a significant amount of the data was lost as multiple people were using the eye-tracking computer with the same participants. Unbeknown to us at the time, if the programs crashed but were started up with the same code name, the most recent experiment overwrote the original. Eight participants lost some of their data due to this, and thus were not included in the analysis. Once this was identified, the code names were changed at the start of the experiment, so that no two researchers were

using the same identifiable code for the same participant. This resolved the problem.

Whilst the tests were designed to reduce the amount of language required in the test, something I overlooked when designing them was the impact of how passive the eye-tracking tests were. As the participants were not required to engage with the test, other than to watch the screen as if it was a TV, some individuals did find them rather monotonous and somewhat boring, particularly in the presymptomatic group. Furthermore, in some cases, if the participants were scheduled to complete the tests after lunch, they became very tired and sleepy, particularly as the room was dark and rather warm. This is problematic as their eyes would droop and cause the data to become very messy. In order to overcome these problems, I moved all testing to the morning, and split up the eye-tracking tests by putting the additional pen and paper task in the middle. I found this was effective and prevented people from losing interest.

Consequently, these problems have caused me to lose a large amount of data (28/90 participants). While this seems a lot, I feel like this is not too bad given this is the first attempt at designing eye-tracking tasks. If I were to redo the work, I feel that I would have a better understanding of the software and programs used, to prevent such a large loss of data.

I have thoroughly enjoyed developing these tests. The ability to be creative in the test design, and then see it come together, has been something I have not done before. I have learnt how to use new software, developed my programming and analytical skills, and improved my problem-solving abilities. Overall, the eye-tracking tasks caused less distress to the symptomatic participants compared to the standardised tests, and the

majority came away feeling much more positive about the work. This in turn made it much easier and more relaxing for me as the researcher to carry it out.

To conclude, I feel that the tests developed here give an alternative to the standard psychology tests, and Chapters 5, 6 and 7 go some way to validating the use of alternative testing paradigms in FTD, and will hopefully be more sensitive to earlier changes in the disease.

CHAPTER 5: BASIC OCULOMOTOR FUNCTION IN FTD

5.1 Chapter overview

This chapter aims to comprehensively assess the oculomotor functioning in individuals with bvFTD and to understand if there are any deficits that may influence the cognitive eye-tracking tasks. Individuals with bvFTD will be compared to a control group, and multiple metrics will be assessed using four tasks: fixation stability, smooth pursuit, pro-saccade and anti-saccade tests. A test of predictive power using an area under the receiver operating characteristic (ROC) curve will be performed. Performance on all of these tests will be correlated with neuroanatomical regions of interest that include the orbitofrontal cortex, the dorsolateral prefrontal cortex, the ventromedial prefrontal cortex, the temporal, parietal and occipital lobes, as well as the striatum, cingulate, and cerebellum. The anti-saccade task has previously been demonstrated as a task of executive function. Therefore, performance on this test will be correlated with the executive function/speed of processing neuropsychometric tasks that are included in the standard psychometric battery (see section 2.4.3).

5.3 Introduction

Currently, standardised pen and paper neuropsychometric tests are used to assess social cognition in bvFTD. While these have been used for many years, and indicate clear deficits (see section 1.4), there are a number of problems with these tests (see section 1.4.5). In addition, as has been demonstrated in Chapter 3, some are not sensitive enough to detect early presymptomatic change. This is problematic as we move towards clinical trials as reliable, validated and robust measures are needed to assess the effectiveness of potential therapeutic treatments (Sabbagh, Hendrix, & Harrison, 2019). Recently there has been a move towards using eye-tracking to improve the sensitivity of these tests, without the use of test instructions (Primativo et al., 2017). This is beneficial for those with FTD as it can minimise a number of problems. Firstly, the time spent on the test reduces which overcomes attentional problems, secondly it may decrease problems with apathy as it requires much less active engagement than traditional tests, and finally, it does not require a comprehensive understanding of a story or complex test instructions, as they can be made very simple. However, the use of eye-tracking equipment assumes that the individual does not have any problems with their eye movements. Whilst this can be assumed in a healthy control population, this may not be the case in those with bvFTD.

There have been a number of studies investigating eye-movements in bvFTD. The focus has been around pro-saccades (eye-movements towards a target), anti-saccades (eye-movements in the opposite direction to the target) and smooth pursuit (ability to follow a target as it moves across the screen). A number of studies have suggested that saccadic latency (time to generate the saccade towards the target) on the pro-saccade test, is significantly delayed in patients with bvFTD when compared to healthy controls (Burrell et al., 2012; Douglass et al., 2018; Meyniel et al., 2005). However, in another study, this

difference was only found in the vertical direction (Garbutt et al., 2008). In others, no difference in saccadic latency was found at all (Boxer et al., 2006). Peak velocity (how quickly the eye is moving) and accuracy of saccades to the target has also been found to be impaired in patients with bvFTD when compared to controls (Douglass et al., 2018; Garbutt et al., 2008). Despite this, some studies have found no such deficits on the peak velocity or the accuracy of the saccades (Boxer et al., 2006; Burrell et al., 2012). In contrast to these conflicting results, performance on anti-saccade tests indicate that individuals with FTD have difficulties with correctly completing the anti-saccade task (Boxer et al., 2006; Boxer et al., 2012; Burrell et al., 2012; Douglass et al., 2018; Garbutt et al., 2008; Meyniel et al., 2005), but have no difficulties in correcting themselves once they realise they have committed an error, with the exception of one study (Boxer et al., 2012). Finally, it is also understood that the ability to follow a smooth pursuit target is also impaired in bvFTD (Boxer et al., 2006; Garbutt et al., 2008). It is possible that the different results seen in the pro-saccade tests are due to the heterogeneity of FTD. It is also possible that they may be due to differences in the equipment used (only three out of the six studies used the same eye-tracking equipment), or in differences in design and set up of the trials. It is for this reason that basic eye movements should be considered as a pre-screen before completing any neuropsychology tests that use eye-tracking as its main metric.

Therefore, the aim of this study is to assess oculomotor function in the cohort of individuals who will be participating in the novel eye-tracking tasks. It aims to go further than the previous work, by pulling all areas of oculomotor research in FTD together, to give a comprehensive overview of functioning in bvFTD. In addition to this, the understanding of neural correlates associated with oculomotor function will be explored. This work will therefore identify if individuals with bvFTD have significant oculomotor impairments that

would affect their ability to complete the novel eye-tracking tests. Pro-saccade, anti-saccade and smooth pursuit measures will be analysed. An additional test investigating the ability to fixate on a target has also been included in line with Shakespeare et al. (2015). Given the attentional deficits observed in bvFTD (Stopford, Thompson, Neary, Richardson, & Snowden, 2012), it is hypothesized that fixation may not be stable over a long period of time. Furthermore, as many of the brain regions affected in FTD are also associated with these eye-tracking metrics (Boxer et al., 2006; Burrell et al., 2012), an analysis of the brain regions correlated with these tests, will be carried out in a ROI analysis.

5.4 Methods

5.4.1 Participants

Participants were recruited from the LIFTD and GENFI projects at the DRC, UCL. All participants gave fully informed consent in line with the Declaration of Helsinki. A total of 19 bvFTD patients and 22 healthy controls took part in the study. All participants with bvFTD had been given a clinical diagnosis of probable bvFTD in line with the current Rascovsky criteria (Rascovsky et al., 2011), 10 of which were genetically confirmed (*C9orf72* = 5, *GRN* = 3 and *MAPT* = 2). The mean disease duration was 8.1 years (SD = 5.9).

All participants were seen by a clinician, and underwent a neurological examination to confirm the diagnosis or identify that the individual was a healthy control (see section 2.4). All participants had normal visual acuity (or was corrected to normal by glasses/contact lenses). Participants completed all four of the eye-tracking tests, as well as an extensive neuropsychological battery (see section 2.4.3) which was administered by a trained psychologist and lasted approximately 2 hours.

5.4.2 Equipment

The test stimuli were presented on a Dell Latitude E6540 Laptop from a fixed viewing distance of 70 cm, and was set up with the Eyelink 1000 plus eye-tracker as described in section 4.3.3. A chin rest provided by SR research was used on all participants to reduce the amount of head movement, and increase eye gaze stability throughout the tests. The gaze data was parsed automatically by the Eyelink system. If velocity was greater than 30 degrees per second (°/sec), and acceleration was greater than 8000°/sec^2, it was parsed as a saccade. Blinks were detected by identifying three or more missing samples in a period of saccadic activity. All other data that was not defined as a saccade or blink, was classed as fixation data.

Before starting the experiment, a calibration procedure was carried out (a random nine-point calibration procedure provided by the in-built software, Experiment Builder, that accompanies the Eyelink 1000 Plus). This procedure could be repeated through the experiment either at the start of each test or in-between each trial. This was done if the participant needed a break or moved away from the head mount for any reason. Furthermore, a slip in the calibration sometimes occurred, for example if the individual's glasses moved or they tilted their head slightly. In order to identify this, a drift correct procedure occurred at the start of each trial. This is where the individual had to fixate on a single target in the middle of the screen. It was made up of a grey inner circle with a black outer circle (0.1° and 0.4° visual angle respectively). When the experimenter felt that the participant was looking at the target, they started the experiment. Any discrepancies observed between the target location and the position of the eye gaze during this process, was corrected by repeating the calibration procedure above.

5.4.3 Procedure

The experiment took place in a dark quiet room. Participants were sat facing the laptop displaying the stimuli, while the experimenter sat out of the participants' eye view to run the experiment. The experiment took a maximum of 10 minutes to complete. Participants completed the fixation stability, smooth pursuit, pro-saccade and anti-saccade tasks as outlined in sections 4.4.2.

5.4.4 Structural brain imaging

All participants underwent volumetric T1-weighted MRI. All scans were quality checked (QC), and those with movements or artefacts were removed. Furthermore, if any participants displayed moderate to severe vascular disease or any other brain lesions, they were also excluded from the analysis. A ROI analysis was carried out as described in section 2.6.2. In order to establish any relationships between the ROIs and the eye-tracking measures, a Pearson's correlation analysis was carried out. To understand if any correlations that occurred were due to disease severity (as measured using the CDR with the NACC FTLD component), partial correlations were carried out.

5.4.5 Statistical analysis

Demographic and psychometric data

Demographic and psychometric data was analysed using independent t-tests on normally distributed data, or Mann Whitney U tests for data that was not normally distributed (see section 2.7). A Spearman's Rank correlation analysis was also carried out between the executive function/speed of processing neuropsychometric tests with the anti-saccade correct metric. This was to investigate the relationship between them, as previous work has demonstrated a correlation (Mirsky et al., 2011).

Eye-tracking data

All gaze data was loaded into Data Viewer for pre-processing. This is the software provided by SR Research that accompanies the Eyelink 1000. After this, the data was exported to Stata/IC 14.1 for statistical analysis. Fixation and saccade reports were generated (Appendix 7).

Multiple linear regression models (see section 2.7) were run for each of the measures below, comparing the measure of interest with the diagnostic group while co-varying for age. For the peak velocity, current saccade amplitude was also included as a covariate as this was highly correlated with the peak amplitude ($r = 0.837$, $p < 0.001$). For the saccade latency and peak velocity measures on the pro-saccade tests, square root transformations were carried out, before running the regression analysis, as the data was not normally distributed. For the anti-saccade tests on both the correct and self-corrected measures, bootstrapping was performed on the data as it was also not normally distributed.

One individual with bvFTD did not have sufficient data to be included in the fixation, smooth pursuit and pro-saccade analysis, and one other was not included in the fixation analysis.

Fixation stability

The Reaction Time Manager tool in Data Viewer was used to zero all values to the onset of the cross. A saccade and fixation report were output. All practice trials were removed for the analysis.

Small square wave jerks: The saccade report was used for this analysis. A small square wave jerk was counted in a predefined algorithm for each individual on each trial. It was defined as a saccade that moved away from the central fixation cross, and was followed by another saccade which moved

back towards the fixation cross in the direction that it had come from. The first saccade had to be < 2° in amplitude, while the second saccade had to be less than 300ms later with a similar amplitude (< 0.75° difference) to the first.

Large square wave jerks: The large square wave jerks followed the same algorithm as small square wave jerks, however the first saccade must be between 2° and 6° in amplitude. The number of large square wave jerks were then counted for each individual on each trial.

Number of large intrusive saccades: A saccade was classed as a large intrusive saccade if the current amplitude was greater than 2°, and it did not contain a blink. These were then counted for each individual on each trial. The data was used from the saccade report.

Longest period of fixation: Using the fixation report, the maximum time period spent looking at the fixation cross (time between saccades) without blinking, was classed as the longest period of fixation for each individual on each trial.

Predictive power

As this task has not been carried out in the bvFTD population before, a receiver operating characteristic curve (ROC) was generated and the area under the curve (AUC) calculated for each of the individual metrics to identify the predictive power of separating cases from controls. A non-parametric analysis was carried out accounting for the ties in the data. Using a Youden index, a cut point was selected to determine the sensitivity (the probability that a diseased person correctly characterised) and specificity (the probability that a healthy person has a negative test outcome) of the fixation measure. The Youden index is defined as:

$$J_c = SE_c + SP_c - 1$$

where J = Youden index, SE = sensitivity, SP = specificity and $_c$ = cut point.

Smooth pursuit

A sample report was generated by Data Viewer, and any saccade or a blink data was removed.

Pursuit gain: In order to calculate the pursuit gain (the ratio between the eye and the target velocity), the eye velocity was divided by the target velocity. Then each of those samples was averaged across each segment of pursuit. The number of segments of pursuit an individual had carried out, was then assigned a gain value. An overall weighted average of pursuit gain was calculated for each individual. This was done by using the length of each section of pursuit to take into consideration how long they maintained the pursuit for. This weighted average for each individual was then used in the group analysis.

Pro-saccades

The Reaction Time Manager tool in Data Viewer was used to zero all values to the onset of the target in both the overlap and the gap condition. A saccade report was generated, and the first saccade that met the following criteria was used for the analysis: the first saccade that did not contain a blink, did not start before the onset of the target, went in the same direction as the target and started at the fixation cross. If this first saccade happened to be greater than the 6th saccade in the trial, it was not included in the analysis.

Amplitude error: The amplitude error is how close to the target the initial saccade amplitude was. It was calculated by taking the visual angle of the current target away from the saccade amplitude of the current saccade. It is measured in degrees of visual angle.

Saccade latency: The saccade latency is the time taken for the individual to generate the first saccade after the target has appeared. This is output in Data Viewer as the current saccade start time. This can be used as the Reaction Time Manager tool zeroes the target onset, and all events are calculated from this time.

Peak velocity: The peak velocity is calculated in degrees per second and is the maximum velocity reached for the saccade of interest.

Anti-saccades

The Reaction Time Manager tool in Data Viewer was used to zero all values to the onset of the target in both conditions. A saccade report was generated.

Correct anti-saccades: An anti-saccade was defined as the first saccade that did not contain a blink, did not start before the onset of the target, started at the fixation cross, was greater than 2° in amplitude and went in the opposite direction to the target. It was not greater than the 6th saccade. The first saccade that met this criterion for each individual on each trial was counted.

Self-corrected anti-saccades: Self-corrected anti-saccades occur when the individual makes a small eye movement towards the target but then realises that they should look in the other direction. In order to calculate this, those trials that contained correct anti-saccades were removed from the data. The remaining trials then contained all data that was not a correct anti-saccade. A similar algorithm that was used for the correct metric, was then applied but specified the correction. It was the first saccade that did not contain a blink, did not start before the target onset, was greater than 2° in amplitude and went towards the target. This saccade was then followed by another saccade that went away from the target, back in the direction it had come from, and

was within 500ms of the first saccade. The first saccade that met this criterion was kept, as long as it was less than the 6th saccade in the trial.

5.5 Results

5.5.1 Demographics and neuropsychometric data

The demographic and neuropsychometric mean scores and standard deviations (SD) can be found in Table 5-1. The control group were matched on age and gender to the patients with bvFTD. However, the bvFTD group had significantly lower education levels ($p = 0.040$), and MMSE scores ($p < 0.001$), as well as a significantly higher disease severity score, as measured using the CDR with the NACC FLTD component ($p < 0.001$). For the neuropsychometric tests, the bvFTD group performed significantly worse on all tests compared to controls (see Table 5-1).

5.5.2 Oculomotor functioning

The mean and standard deviations for the basic eye movements are summarised in Table 5-2 for each of the measures in the four tasks.

Fixation stability

The mean eye position for each group is shown in *Figure* 5-1 and the individual performance on each of the metrics is displayed in *Figure* 5-2. Significant differences were observed between the bvFTD and controls on the number of small square wave jerks and the length of fixations. Those with bvFTD had significantly higher numbers of small square wave jerks ($p = 0.028$) and shorter periods of fixation ($p = 0.001$). No significant differences were observed on the number of large square wave jerks, although there was a trend towards a higher number of large intrusive saccades ($p = 0.055$) in bvFTD.

When looking at the predictive power of the fixation metrics to discriminate the patients from controls, the AUC for the length of the fixation was 0.79 (CI: 0.64 - 0.95) which indicates an acceptable level of discrimination. This was higher than the other three fixation metrics: small square wave jerks has an AUC of 0.71; (CI: 0.56 - 0.87), large intrusive saccades had an AUC of 0.67 (CI: 0.53 - 0.81) and large square wave jerks had an AUC of 0.56 (CI: 0.48 - 0.63). The ROC curves can be found in *Figure* 5-3. For maximum accuracy (Youden index), the optimal cut points with the associated specificity and sensitivity values can be found in Table 5-3 for each of the four fixation metrics.

Smooth pursuit

There were no significant differences observed between the two groups on the ability to pursue a target in either the horizontal or vertical direction. However, there was a trend towards the bvFTD group being less accurate than controls in the horizontal condition (p = 0.063) (see *Figure 5-4* for the pursuit traces).

Pro-saccades

Very few differences were observed on the pro-saccade tests (see *Figure 5-5*). No significant group differences were observed except for amplitude error and peak velocity in the vertical overlap conditions, which were worse in bvFTD than controls (amplitude error: p = 0.008; peak velocity, p = 0.012).

Anti-saccades

The bvFTD group were significantly impaired at performing correct anti-saccades relative to controls on the horizontal (p < 0.001) and vertical (p = 0.016) conditions (see *Figure 5-6*). No differences were observed between the two groups on the self-corrected anti-saccades measure

Table 5-1: Demographic and neuropsychometric data for the control and bvFTD participants.

	HC (N = 22)		bvFTD (N = 19)		*p* value
	Mean	SD	Mean	SD	
Demographics					
Gender (F : M)	9 : 13		5 : 14		0.326
Age	64.2	5.7	63.7	6.2	0.821
Education	16.8	2.3	13.6	3.0	0.004
MMSE	29.5	0.7	24.8	4.0	< 0.001
CDR with NACC FTLD	0.80	0.78	10.3	3.70	< 0.001
Disease duration	-	-	8.1	5.9	-
General Intellect					
WASI Visual IQ	123.7	7.9	83.7	3.7	< 0.001
WASI Performance IQ	119.7	14.7	93.6	17.2	< 0.001
Episodic memory					
RMT Faces	42.7	5.3	34.6	7.6	0.001
RMT Words	48.4	1.9	36.6	8.4	< 0.001
Digit Span – Forward Total	9.0	2.2	6.8	0.5	0.005
Executive function/Speed of processing					
Digit Span – Backwards	8.3	2.6	4.8	1.9	< 0.001
Fluency – Letter	15.1	5.7	8.2	4.9	< 0.001
Fluency – Category	24.2	3.9	12.1	6.5	< 0.001
D-KEFS Colour Inference*	29.8	4.3	49.7	18.0	< 0.001
D-KEFS Word Inference*	22.7	4.6	30.1	9.1	0.009
D-KEFS Colour Word Inference*	56.5	17.3	93.3	36.4	< 0.001
Trails Making Test A*	30.3	11.2	52.0	29.1	0.001
Trails Making Test B *	69.2	24.7	171.5	90.9	< 0.001
Digit Symbol	55.5	13.9	31.6	13.0	< 0.001
Language					
NART	40.0	6.4	27.1	14.1	0.006
BPVS	147.9	1.3	119.4	35.5	< 0.001
GNT	25.9	2.9	14.3	8.8	< 0.001
Posterior cortical skills					
Arithmetic	14.8	4.9	8.3	6.8	0.002
VOSP	18.2	1.2	15.5	3.2	0.005
Social cognition					
Mini-SEA	25.7	1.5	17.4	6.3	< 0.001
Facial Emotion Recognition Test	29.7	3.2	22.75	4.5	< 0.001
Faux-Pas Test	34.3	3.2	26.5	5.0	<0.001
Emotional Synonyms Test	24.9	0.3	23.3	1.7	<0.001
mIRI	53.7	11.3	32.7	10.1	< 0.001
RSMS	42.3	9.7	19.2	9.1	< 0.001

WASI, Wechsler Abbreviated Scale of Intelligence; D-KEFS, Delis Kaplan Executive System; NART, National Adult Reading Test; BPVS, British Picture Vocabulary Scale; VOSP, Visual Object and Space Perception Test; Mini-SEA, Mini-Social and Emotional Assessment; mIRI: modified Interpersonal; Reactivity Index; RSMS: Revised Self-Monitoring Scale. *Indicates tests scored in seconds

Table 5-2: Table displays the means and standard deviations for the fixation, pursuit, pro-saccade and anti-saccade metrics for the control and bvFTD groups.

Test	Analysis	Direction	Gap / Overlap	Visual angle	Control		bvFTD		Significant difference: p =	Confidence intervals	
					Mean	SD	Mean	SD			
Fixation	Small SQWJ frequency	NA	NA	NA	**0.75**	**1.65**	**3.06**	**4.16**	**0.028**	**0.26**	**4.32**
	Large SQWJ frequency	NA	NA	NA	0.00	0.00	0.44	0.97	0.129	-0.09	0.67
	Large intrusive saccades	NA	NA	NA	*0.10*	*0.30*	*1.47*	*3.11*	*0.055*	*-0.03*	*2.77*
	Long. Period of fix (ms)	NA	NA	NA	**6140.8**	**2527.0**	**3322.6**	**2135.8**	**0.001**	**-4417.2**	**-1281.8**
Pursuit	Gain (0.25Hz)	Horizontal	NA	NA	*0.81*	*0.15*	*0.71*	*0.17*	*0.063*	*-0.21*	*0.01*
		Vertical	NA	NA	0.70	0.19	0.61	0.17	0.167	-0.21	0.04
Pro-Saccades	Amplitude error	Horizontal	Gap	8	-4.70	0.45	-4.87	0.72	0.440	-0.55	.25
		Horizontal	Overlap	8	-4.59	0.45	-4.77	0.57	0.297	-0.53	0.17
		Vertical	Gap	5	-2.61	0.38	-2.69	0.40	0.529	-0.35	0.18
		Vertical	Overlap	5	**-2.65**	**0.38**	**-3.07**	**0.52**	**0.008**	**-0.73**	**-0.12**
	Saccade latency	Horizontal	Gap	8	201.56	49.19	249.55	196.19	0.308	-0.97	2.98
		Horizontal	Overlap	8	258.67	89.26	380.72	307.69	0.158	-0.84	0.39
		Vertical	Gap	5	255.63	59.50	312.81	334.69	0.708	-2.14	3.12
		Vertical	Overlap	5	287.09	53.29	331.33	183.18	0.351	-1.02	2.80
	Peak velocity	Horizontal	Gap	8	199.44	29.44	207.02	40.71	0.220	-0.25	1.04
		Horizontal	Overlap	8	176.19	23.14	180.74	30.25	0.096	-0.09	1.02
		Vertical	Gap	5	150.79	32.35	165.49	34.10	0.127	-0.18	1.38
		Vertical	Overlap	5	**144.00**	**26.51**	**137.62**	**36.35**	**0.035**	**0.05**	**1.30**
Anti-Saccades	Number of correct anti-saccades	Horizontal	Gap	8	**1.27**	**0.94**	**0.37**	**0.60**	**< 0.001**	**-1.39**	**-0.40**
		Vertical	Gap	5	**0.73**	**0.88**	**0.21**	**0.42**	**0.016**	**-0.93**	**-0.09**
	Number of self-corrected anti-saccades	Horizontal	Gap	8	2.00	0.89	2.21	0.97	0.517	-0.44	0.88
		Vertical	Gap	5	2.05	0.92	2.75	1.04	0.111	-0.16	1.52

Abbreviations: SQWJ – Square wave jerks; Long. Period of fix – Longest period of fixation.

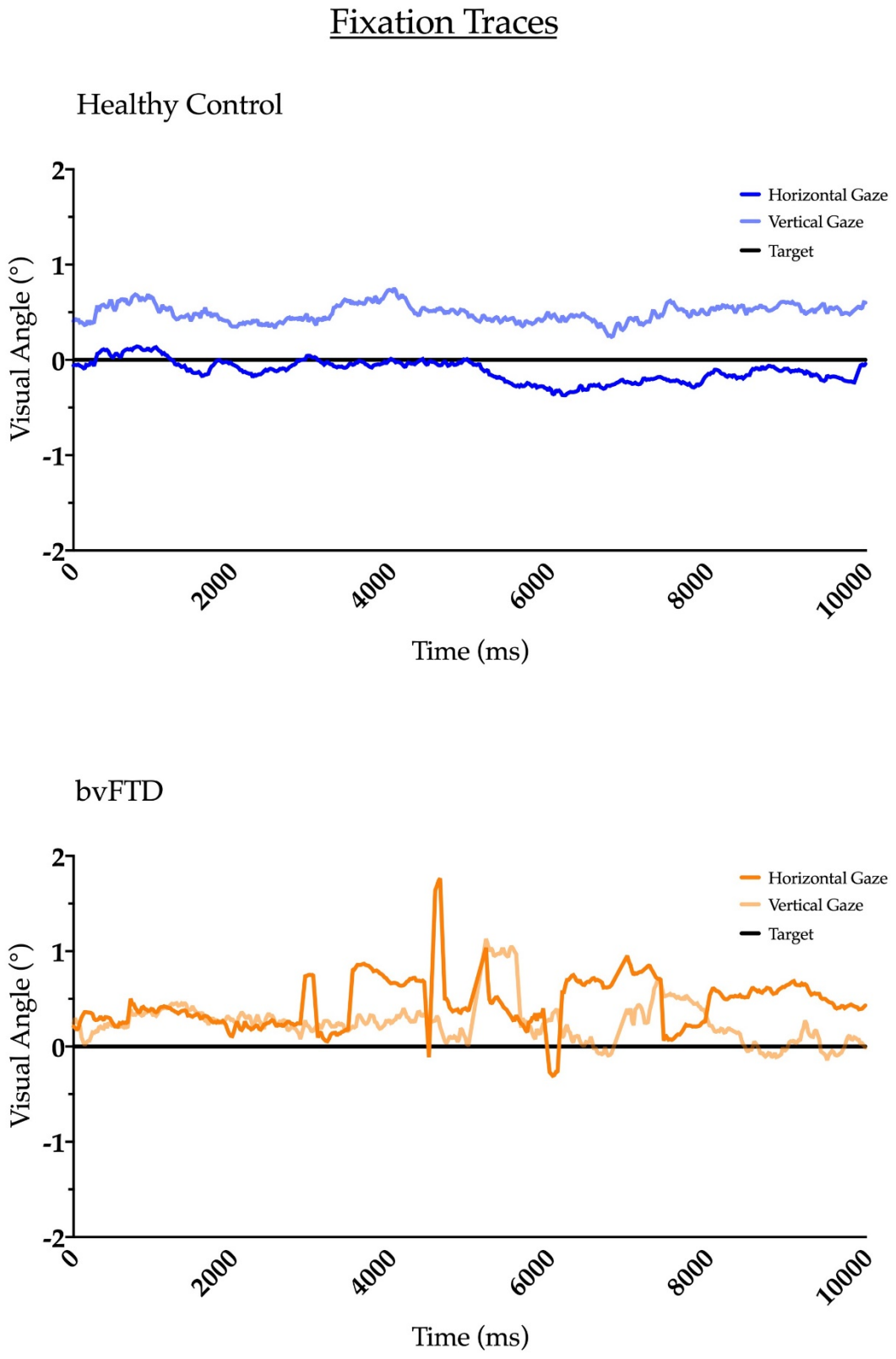

Figure 5-1: The mean fixation traces across all trials for each group is represented above. The darker line represents the horizontal gaze position on the screen, whilst the lighter line represents the vertical gaze position. The solid black line represents the position of the target throughout the trials.

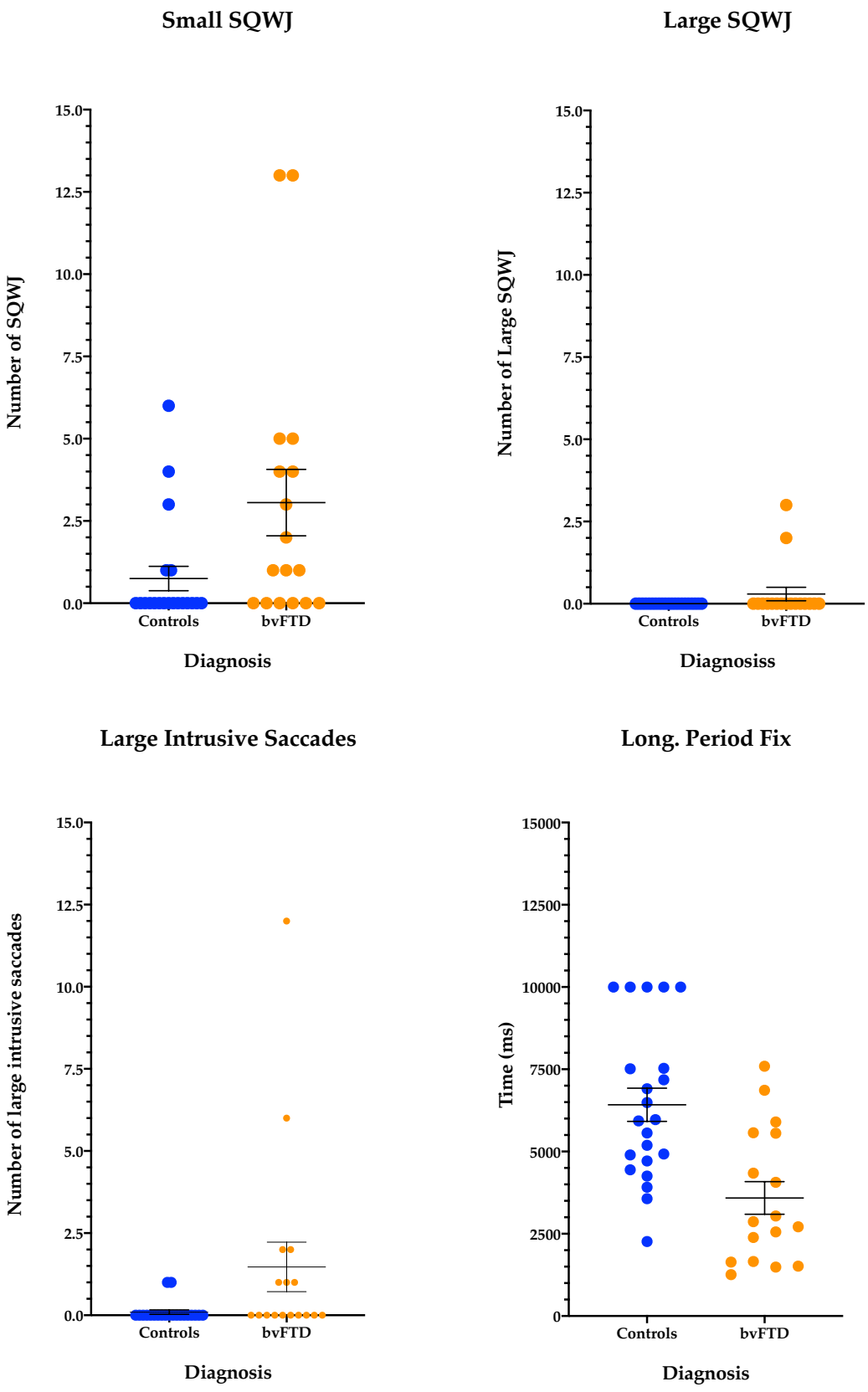

Figure 5-2: Individuals performance on each of the fixation metrics for the control and the bvFTD groups. Bars represent the mean and SE.

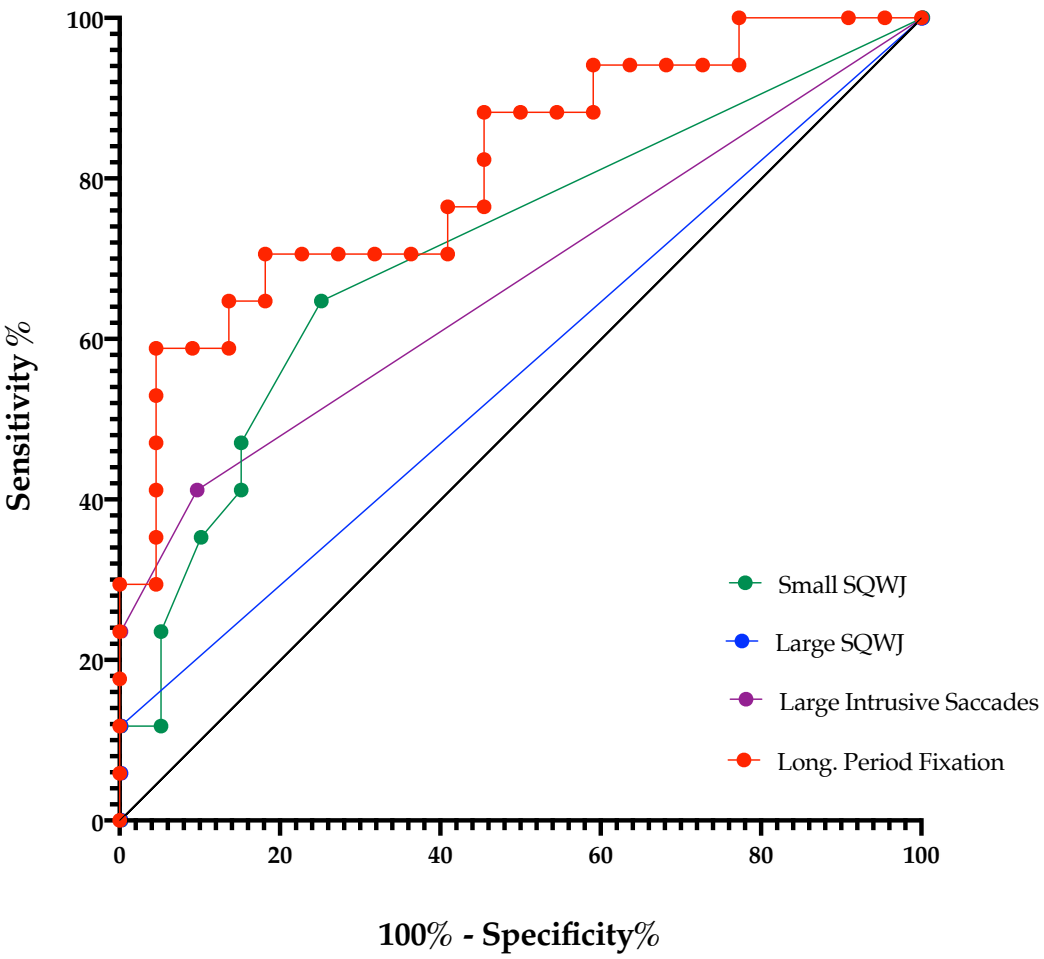

Figure 5-3: The ROC curve for each of the fixation metrics. Each line depicts a different metric as specified in the legend.

Table 5-3: The sensitivity and specificity for the individual fixation metrics for a cut off specified by the Youden index.

	Cut Off (ms)	Youden Index	SE	Sensitivity	Specificity	AUC at ROC cut point
Longest period of fixation	3813.5	0.6	807.3	0.86	0.71	0.78
Small Square Wave Jerks	0.5	0.4	1.5	0.65	0.75	0.70
Large Square Wave Jerks	1.0	0.1	0.2	0.12	1.00	0.56
Large Intrusive Saccades	0.5	0.3	0.8	0.41	0.90	0.66

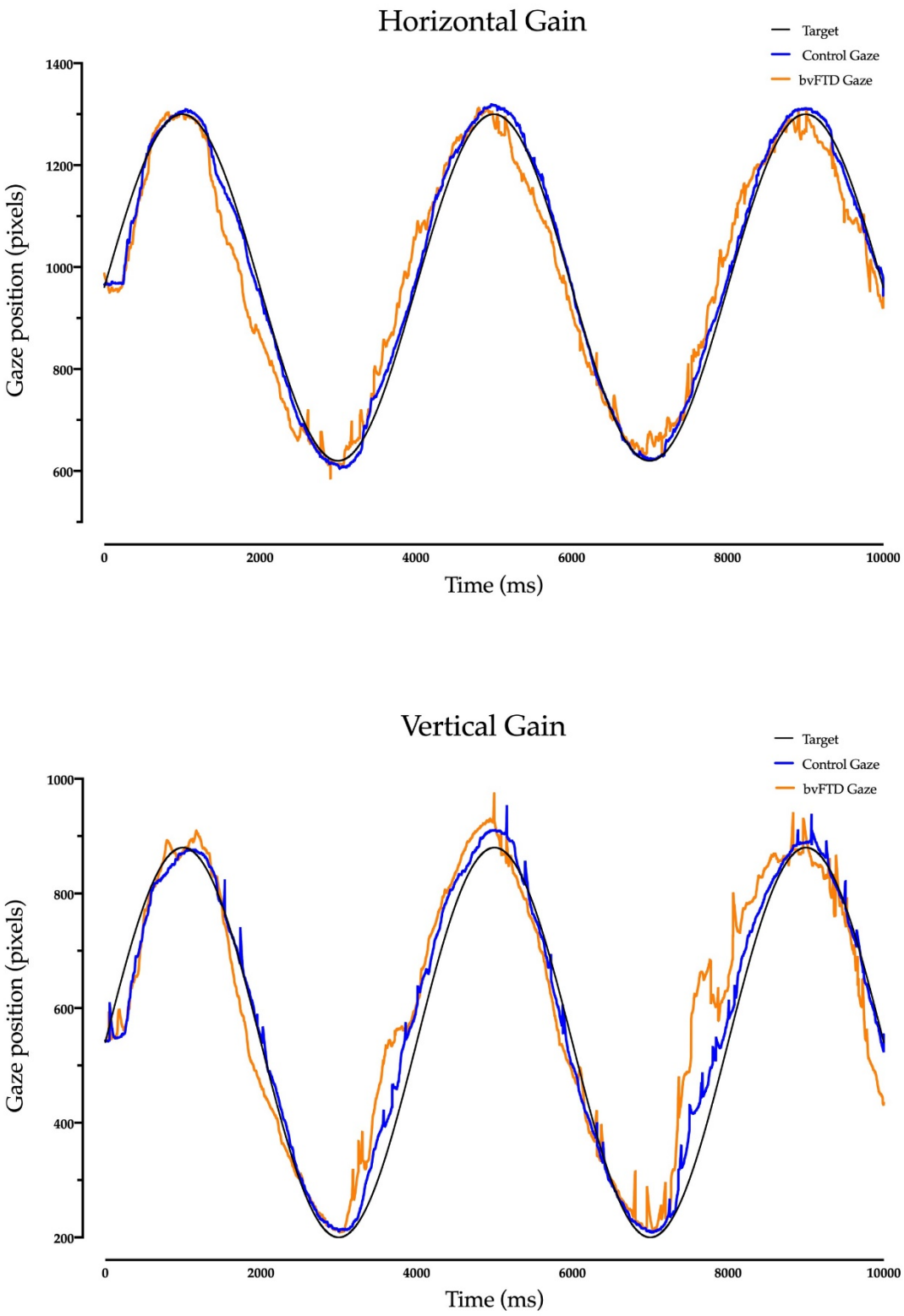

Figure 5-4: The pursuit traces are shown for each group in each condition. The lines represent the mean eye position across the trials for each group whilst pursuing the target as it moves across the screen. Controls are represented by the blue line, the bvFTD by the orange line and the target by the black line. The top image represents the horizontal condition and the bottom image represents the vertical condition.

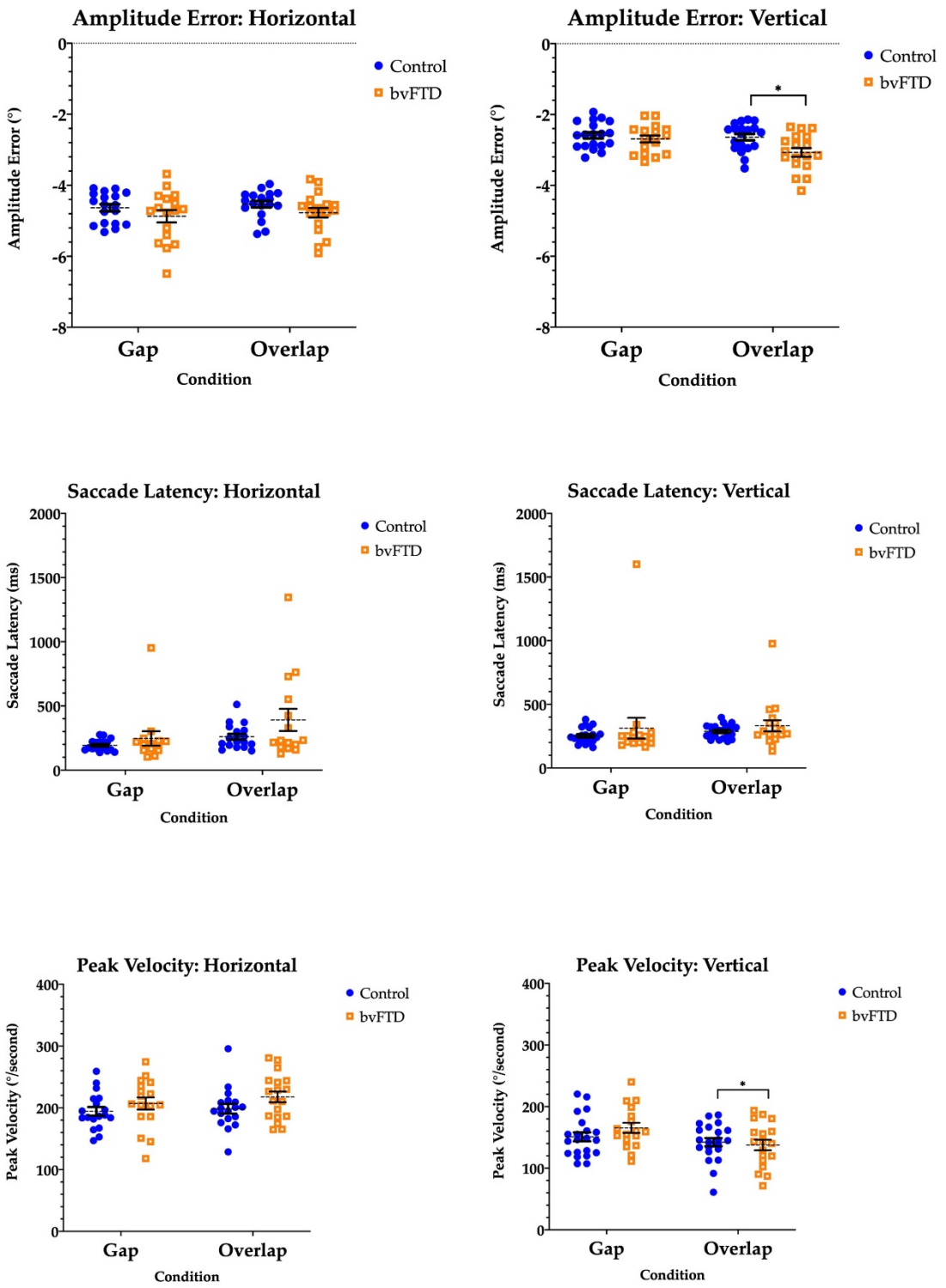

Figure 5-5: Individual performance on the pro-saccade tests on each of the metrics. Both direction and condition are displayed.

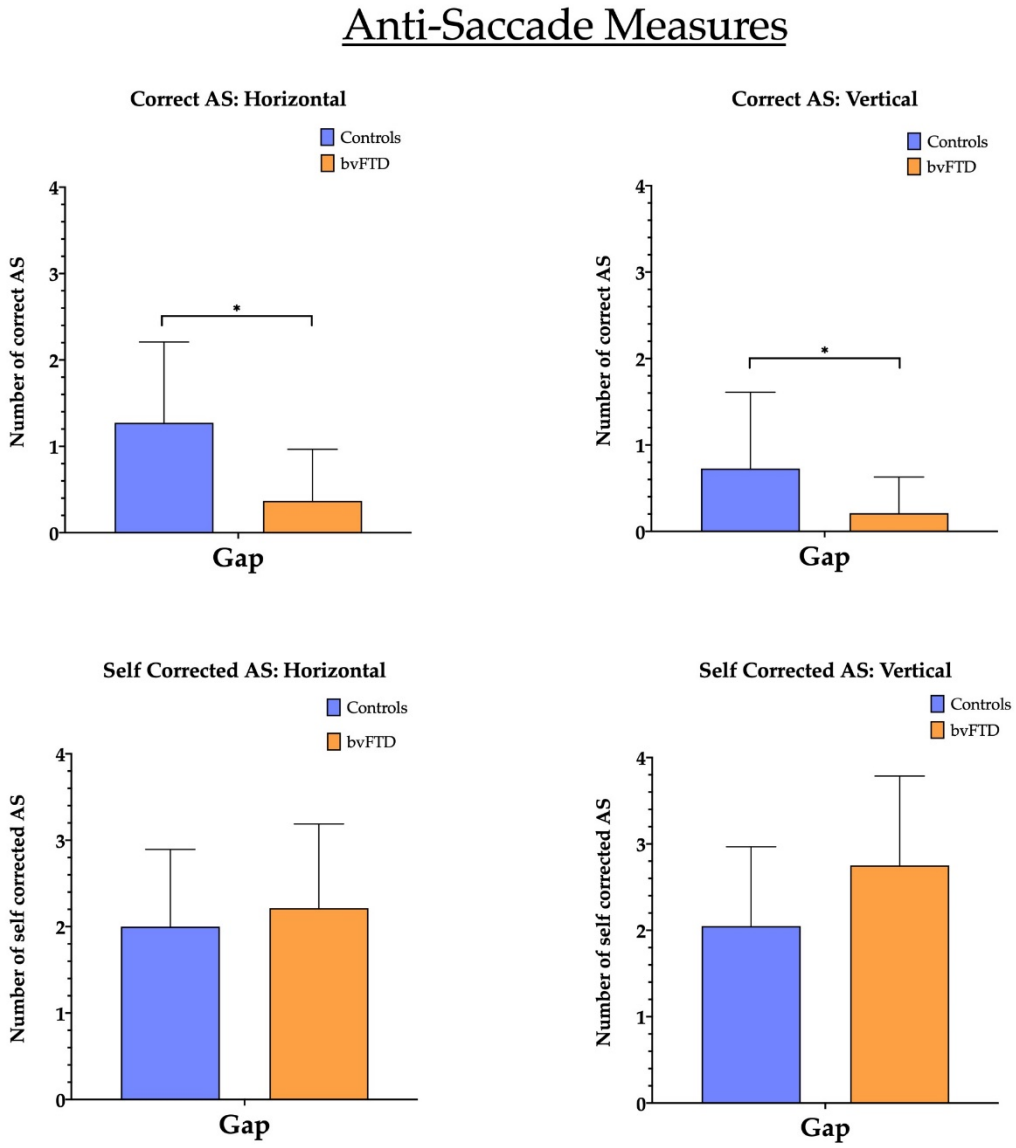

Figure 5-6: Mean number of correct and self-corrected anti-saccades made, with error bars, for each direction and each condition between the groups.

5.5.3 Region of interest analysis

Table 5-4 demonstrates the correlations between the oculomotor tests and ROI.

Fixation stability

Small square wave jerks negatively correlated with the orbitofrontal cortex (r = -0.39, p = 0.015), the ventral medial prefrontal cortex (VMPFC: r = -0.48, p = 0.002), the striatum (r = -0.39, p = 0.014) and the cerebellum (r = -0.33, p = 0.044). The longest period of fixation positively correlated with the orbitofrontal cortex (r = 0.42, p = 0.009).

Smooth pursuit

The VMPFC (r = 0.36, p = 0.026) and the occipital lobe (r = 0.37, p = 0.023) positively correlated with performance on the vertical gain.

Pro-saccade

No correlations were found with any of the pro-saccade tests and the ROI.

Anti-saccade

The number of correct anti-saccades made on both the horizontal and vertical conditions, positively correlated with dorsolateral prefrontal cortex (DLPFC: Hor.: r = 0.35, p = 0.026; Ver.: r = 0.38, p = 0.015), the temporal (Hor.: r = 0.42, p = 0.006; Ver.: r = 0.49, p= 0.001) and parietal lobes (Hor.: r = 0.34, p = 0.029; Ver.: r = 0.36, p = 0.021). The striatum also positively correlated with the horizontal condition (r = 0.47, p= 0.002). Negative correlations were found in the horizontal condition on the self-corrected anti-saccades, in the temporal (r = -0.43, p = 0.009) and parietal lobes (r = -0.43, p = 0.011). A negative correlation

was found on the vertical condition with the temporal lobe (r = 0.046, p = 0.012).

5.5.4 Disease severity

Disease severity correlated with performance on the longest period of fixation (r = -0.47, p = 0.003), and the number of correct anti-saccades made in the horizontal condition (r = -0.52, $p < 0.001$).

When investigating the influence of disease severity on the ROI using partial correlations, there were a few correlations that did not remain significant (see Table 5-5). Small square wave jerks no longer correlated with the striatum and the cerebellum. The anti-saccade correct test in the horizontal condition, no longer correlated with the striatum. The remaining correlations remained significant and thus, were not influenced by disease severity.

5.5.5 Psychology correlations

The correlations between the anti-saccade test and EF/speed of processing neuropsychometric tests are displayed in Table 5-6. On the horizontal condition of the number of correct anti-saccades made, positive correlations were found between the length of the digit span, letter fluency, category fluency and the digit symbol test. Negative correlations were also found on the time taken to complete both Trails Making Test A and B, and the D-KEFS colour and colour/word inference times. Only a trend towards a negative correlation was found on the D-KEFS word inference test in the horizontal condition. Positive correlations were only found on the digit span backwards and the digit symbol test on the vertical correct anti-saccade condition. Negative correlations were found on the Trails Making Test A, and all three of the D-KEFS inference tests (colour, word and colour/word).

Table 5-4: Correlations between the ROIs and the oculomotor eye-tracking tests are presented in the table below. The r value is presented at the top, followed by the *p* value below.

	Fixation				Pursuit		Pro-saccade: Amplitude Error				Pro-saccade: Saccade latency				Pro-saccade: Peak Velocity				Anti-saccade: Correct		Anti-saccade: Self-Corrected	
	Small SQWJ	Large SQWJ	Large intrusive saccades	Longest period fixation	Horizontal	Vertical	H8 Gap	H8 Overlap	V5 Gap	V5 Overlap	H8 Gap	H8 Overlap	V5 Gap	V5 Overlap	H8 Gap	H8 Overlap	V5 Gap	V5 Overlap	H8 Gap	V5 Gap	H8 Gap	V5 Gap
Orbitofrontal Cortex	-0.39	-0.23	-0.29	0.42	0.08	*0.29*	0.13	0.14	-0.07	*0.18*	-0.10	-0.03	-0.13	-0.06	0.08	0.12	0.10	0.24	-0.06	-0.25	0.28	0.22
	0.015	0.154	0.075	0.009	0.640	*0.076*	0.418	0.399	0.679	*0.258*	0.534	0.852	0.448	0.693	0.623	0.443	0.538	0.129	0.717	0.120	0.102	0.247
DLPFC	0.03	0.09	0.05	0.00	0.08	-0.08	-0.03	-0.04	0.04	-0.08	0.15	-0.02	0.12	0.28	-0.03	-0.23	-0.19	-0.23	0.35	0.38	-0.18	-0.28
	0.864	0.598	0.758	0.999	0.643	0.617	0.850	0.790	0.810	0.633	0.360	0.885	0.483	0.085	0.857	0.161	0.251	0.145	0.026	0.015	0.288	0.144
VMPFC	-0.48	-0.22	-0.30	*0.30*	0.09	0.36	0.09	0.14	-0.02	0.14	-0.15	0.02	-0.10	-0.16	0.09	0.23	0.20	0.22	-0.10	-0.18	0.31	0.31
	0.002	0.178	0.068	*0.061*	0.584	0.026	0.600	0.375	0.902	0.406	0.373	0.919	0.544	0.310	0.606	0.157	0.218	0.166	0.521	0.251	0.074	0.100
Temporal lobe volume	-0.08	0.12	0.06	-0.06	-0.09	0.23	-0.20	-0.09	0.02	0.11	-0.02	0.01	0.01	0.05	-0.20	-0.21	-0.11	-0.04	0.42	0.49	-0.43	-0.46
	0.625	0.485	0.721	0.719	0.567	0.165	0.215	0.584	0.922	0.498	0.922	0.975	0.973	0.742	0.222	0.189	0.512	0.813	0.006	0.001	0.009	0.012
Parietal lobe volume	-0.12	0.14	0.14	-0.05	-0.16	0.24	-0.12	-0.02	-0.08	0.08	0.02	0.06	-0.02	0.14	-0.13	-0.16	-0.10	-0.04	0.34	0.36	-0.43	-0.37
	0.468	0.385	0.403	0.759	0.311	0.139	0.450	0.906	0.613	0.65	0.904	0.735	0.901	0.376	0.419	0.310	0.554	0.792	0.029	0.021	0.011	0.051
Occipital lobe volume	*-0.30*	-0.11	-0.08	0.12	-0.23	0.37	-0.04	-0.09	-0.12	0.09	0.00	0.00	-0.08	0.06	-0.10	-0.06	0.08	0.08	0.07	-0.03	-0.27	-0.20
	0.066	0.517	0.650	0.449	0.160	0.023	0.812	0.561	0.479	0.571	0.984	0.997	0.630	0.719	0.531	0.724	0.623	0.638	0.675	0.850	0.115	0.291
Striatum	-0.39	0.14	-0.02	0.22	0.20	0.08	-0.03	0.06	-0.05	-0.05	0.07	-0.02	0.09	0.22	-0.08	-0.14	-0.10	-0.17	0.47	0.17	-0.14	-0.17
	0.014	0.384	0.902	0.180	0.209	0.625	0.871	0.697	0.758	0.747	0.657	0.925	0.583	0.179	0.624	0.406	0.540	0.304	0.002	0.283	0.436	0.369
Cerebellum	-0.33	0.12	0.04	0.08	0.19	0.12	-0.20	0.12	0.10	-0.15	-0.05	0.16	0.09	0.05	-0.21	0.11	-0.06	-0.23	0.09	0.08	0.01	0.06
	0.044	0.384	0.810	0.643	0.232	0.469	0.213	0.445	0.57	0.345	0.748	0.319	0.586	0.776	0.192	0.520	0.734	0.152	0.567	0.639	0.970	0.760

Table 5-5: The partial correlations for those tests that significant correlational with the ROI. The partial correlations in this table is to take into consideration the effect of disease severity. The top line of each result in the table represents the Pearson's r correlation value, while the bottom line represents the statistical significance of the *p* value.

	Fixation		Pursuit	Anti-Saccade – Correct		Anti-Saccade – Self Corrected	
	Small SQWJ	Longest period fixation	Vertical	H8 Gap	V5 Gap	H8 Gap	V5 Gap
Orbitofrontal Cortex	-0.35 0.029	0.38 0.019					
DLPFC				0.36 0.024	0.37 0.019		
VMPFC	-0.46 0.004		0.39 0.019				
Temporal lobe volume				0.44 0.005	0.48 0.002	-0.45 0.008	-0.43 0.023
Parietal lobe volume				0.42 0.007	0.39 0.013	-0.43 0.011	
Occipital lobe volume			0.38 0.019				
Striatum	-0.28 0.088			0.28 0.079			
Cerebellum	-0.32 0.051						

Table 5-6: Executive function and speed of processing correlations with the correct number of anti-saccades performed on the eye-tracking test for each of the conditions.

	Anti-Saccade – Correct	
	H8 Gap	V5 Gap
Digit Span Backward	0.54 < 0.000	0.45 0.003
Fluency – Letter	0.44 0.005	0.27 0.094
Fluency – Category	0.38 0.015	0.19 0.252
Trails Making Test A	-0.44 0.005	-0.35 0.025
Digit Symbol	0.50 0.001	0.35 0.028
D-KEFS Colour Inference	-0.43 0.006	-0.38 0.018
D-KEFS Word Inference	-0.29 0.077	-0.37 0.019
D-KEFS Colour/Word Inference	-0.45 0.006	-0.37 0.024
Trails Making Test B	-0.41 0.016	-0.27 0.113

5.6 Discussion

The aim of this study was to investigate basic oculomotor functions in the individuals completing the novel emotion processing and theory of mind eye-tracking tests. This was to ensure that problems on the novel tests would not be a consequence of abnormal eye movements. Fixation stability, smooth pursuit, pro-saccades and anti-saccades were assessed in bvFTD and compared to a control group.

The findings demonstrate problems with fixation stability and anti-saccades in bvFTD. There were also some deficits in amplitude error and peak velocity on the pro-saccade test; these deficits however, were only found in the vertical overlap condition. No significant differences were observed on the pursuit test, however there was a trend towards less accurate horizontal pursuit; lower gain values observed in bvFTD.

5.6.1 Horizontal vs vertical movements

Throughout the different oculomotor tests, participants were presented with two conditions: horizontal vs vertical. A clear pattern emerges, the vertical condition was much harder than the horizontal condition, in both bvFTD and controls. This is because much of the visual information we see on a daily basis, is processed in the horizontal plane, for example when reading, it is much easier to read when it is displayed horizontally than it is vertically (Schmidt, Ullrich, & Rossner, 1993; Yu, Park, Gerold, & Legge, 2010). As a result, we have much less need, and therefore less practice, at moving our eyes in the vertical direction, and this is reflected in the results shown here across the tests.

5.6.2 Fixation stability

There was an increase in the number of small square wave jerks made, and lower maximum periods of fixation in the bvFTD group relative to controls. It is possible that this is due to oculomotor disinhibition which is driven by the frontal lobes.

In order to see continuously, our visual system consistently makes microsaccades in order to prevent foveal fixation on a particular point (Martinez-Conde, Macknik, Troncoso, & Dyar, 2006). Small square wave jerks are a malfunction of this process in which the micro saccades are exaggerated. This is because saccadic intrusions occur which take the eye away from the target and then back again towards it in a corrective manner (Otero-Millan, Schneider, Leigh, Macknik, & Martinez-Conde, 2013). Whilst small square wave jerks do occur in the healthy population, they are more common in brainstem and cerebellar disorders, such as PSP (Phokaewvarangkul & Bhidayasiri, 2019; Pinnock, McGivern, Forbes, & Gibson, 2010; Rascol et al., 1991). They are also observed in other cortical disorders such as AD and posterior cortical atrophy (Nakamagoe, Yamada, Kawakami, Koganezawa, & Tamaoka, 2019; Shakespeare et al., 2015). Consequently, as square wave jerks increase in frequency in multiple neuro-degenerative disorders, including bvFTD as demonstrated here, it is perhaps a non-specific measure of neurodegeneration, rather than particular to certain disorders. Our findings suggest the involvement of the orbitofrontal cortex and the VMPFC, with the number of square wave jerks produced. In support of this, previous findings have demonstrated a link between the thickness of the frontal lobe in AD patients, with the number of small square wave jerks produced (Shakespeare et al., 2015). These results also suggest the involvement of the striatum and cerebellum, which are also supported by findings in PSP and PD (Shaikh, Xu-

Wilson, Grill, & Zee, 2011). These areas however, did not remain significant after the disease severity was taken into consideration, thus suggesting that these areas are more strongly affected later in the disease course, rather than to the square wave jerks.

With regard to the length of fixation, those with bvFTD fixated on the target for a shorter period of time than the control group did. It indicates that individuals with bvFTD are struggling to maintain a fixation for very long, and their eyes are wanting to move. This is the first study (to my knowledge) that has investigated this in bvFTD. It is possible that this is due to inhibitory problems, especially given the correlation with the orbitofrontal cortex in FTD (Hornberger, Geng, & Hodges, 2011; Peters et al., 2006). This is further supported by a trend towards an increased number of large intrusive saccades in the bvFTD group relative to controls, and its trend in correlation with the orbitofrontal cortex.

When determining the predictive power of the fixation metrics, both the length of the fixation and the number of small square wave jerks were best at distinguishing cases from controls out of the four metrics. Both metrics fell between 0.7 and 0.8 suggesting that they are fair predictors of disease. The remaining two metrics, large intrusive saccades and large square wave jerks, were below 0.7 suggesting that they are poor predictors and an unreliable test for discriminating between the groups. Using the Youden index to determine the cut point, the longest period of fixation had the best specificity and sensitivity, and thus would produce fewer false positives and negatives than the remaining three fixation metrics. This therefore suggests that out of the four metrics, the longest period of fixation may be the best predictor of disease. That being said, when comparing the performance of this task to others already in use, it is either comparable or falls behind others in

distinguishing those with bvFTD from controls. When looking at global measures of neurodegeneration, the Montreal Cognitive Assessment (MoCA) has a AUC of 0.93 (CI: 0.87 - 0.97; cut point: <17; SE: 78; SP: 98) and the Mini Mental State Examination (MMSE) of 0.77 (CI: 0.68-0.85; cut point: <26; SE: 58; SP: 88) (Freitas, Simões, Alves, Duro, & Santana, 2012), while another social cognitive test had an AUC of 0.97 at a cut off of 46 out of 60 (SE: 94; SP: 100) (Diehl-Schmid et al., 2007). This suggests that while the longest period of fixation may be a fair predictor of disease and the best out of those used here, there are others that may be better at distinguishing cases from controls.

A further point to note, in this analysis the Youden index was used to determine the cut point for the task to establish the specificity and sensitivity. This assumes that false positives are as equally undesirable as false negatives and that it is independent of the control and disease group size, as well as the prevalence of the disease (Smits, 2010). Whilst for this analysis it was suitable to use this method to give an understanding of the tasks cut points, it is worth noting that it may not always be desirable to give equal weighting to false positive and false negatives and the prevalence of the disease should also be considered (Smits, 2010).

Overall there is a clear deficit in fixation stability in bvFTD. The ability for individuals with bvFTD to focus on a particular target, without deviating away, is impaired. It is possible that this is a result of oculomotor disinhibition cause by atrophy in the frontal regions, such as the orbitofrontal cortex and VMPFC, rather than a striatal-cerebellum problem. This is an important finding when it comes to task design. In order to prevent problems on novel cognitive eye-tracking tests being a result of fixation difficulties, participants should not be required to focus on a specific stimulus for a given period of time.

5.6.3 Smooth pursuit

Overall, participants with bvFTD did not show any difficulties pursuing a moving target when compared to controls. There was a trend towards a significant difference in the horizontal condition, but this is most likely because it is an easier test than the vertical one, therefore the control group performed better. It is interesting that no significant differences were observed, given that the previous literature showed a deficit (Boxer et al., 2006; Garbutt et al., 2008). However, these previous studies used a ramp-step pursuit test. This is where an individual is required to make an initial saccade to identify the location of the target, and then track it as it moves (Rashbass, 1961). This is a much more difficult test than the smooth pursuit test in this study, and is reflected in the gain values.

In order to pursue a target, the frontal eye fields pass information down to the oculomotor centres throughout cortical (Tanabe, Tregellas, Miller, Ross, & Freedman, 2002) and subcortical regions (Gaymard & Pierrot-Deseilligny, 1999), and they are involved in the higher order processing of visual information. The cerebellum on the other hand, is also involved in the ability to carry out pursuit, particularly the flocculus and the para-flocculus, by processing the velocity of stimuli and the prediction of the movement (Thier & Ilg, 2005). Our findings are consistent with frontal lobe correlations with vertical pursuit, however no significant correlations were found with the cerebellum on horizontal pursuit. This is somewhat surprising, especially given that the cerebellum can be affected in bvFTD (Bocchetta et al., 2016). No correlations were found with disease severity on this test. It is possible that these correlations would have emerged should a more severe group have been tested, or that a more difficult test, like the ramp-step test, had been used.

However, for the purpose of this thesis, there would be no case in the novel eye-tracking tests in which participants would have been presented with a ramp-step type pursuit. All stimuli are available prior to moving in the ToM test. Thus, this would not have been a beneficial check of eye-movements. Furthermore, whilst the target stimuli in the smooth pursuit test was very small, the one in the ToM test is much larger. This should make this much easier for the participants to follow. Consequently, I feel that the ability to make a smooth pursuit in the individuals with bvFTD in this cohort, will not affect their performance on the novel tests.

5.6.4 Pro-saccades

On a whole, performance on the pro-saccade tests remained relatively intact. Differences only emerged on the vertical overlap condition for the amplitude error and peak velocity, in which the patients were less accurate, and had slower saccades. In addition to differences being seen on the vertical condition, the overlap condition is also much harder than the gap condition. This is because it requires individuals to shift their attention away from the current target which has remained on the screen, to a new target – this is known as set shifting. The gap condition is much easier, as we naturally look to new things as they appear on the screen if nothing else is holding our attention. It is therefore not surprising that deficits on the vertical overlap in bvFTD are observed, while there are no differences on the other conditions.

Whilst the amplitude error and the peak velocity was affected by the type of condition, saccade latency seemed to be unaffected. This is a somewhat unusual finding, especially as some individuals with bvFTD go on to develop an oculomotor apraxia (Ogaki et al., 2012). This may therefore again link back to the severity of the patient group, and if carried out in individuals who are moderate or severe, a deficit here may also be seen.

These results are promising however, as they indicate that this group of individuals with bvFTD, in general, do not have problems with their saccadic eye movements. While the emotion processing tests do have multiple images on the screen at once, they are given sufficient time to explore the images so this should not be a problem.

5.6.5 Anti-saccades

As part of the bvFTD diagnostic criteria, the individual commonly presents with executive function problems. Our findings are in line with this, as fewer anti-saccades were made in the bvFTD group across all conditions. The anti-saccade test is an extremely difficult test for both the bvFTD and control group. It requires individuals to go against their instincts to look at the new stimulus (Munoz & Everling, 2004).

In order to complete the test, the tendency to look at the new stimuli must be inhibited (Hutton & Ettinger, 2006). This is reflected in the psychology correlations, as well as in the ROI analysis, as the anti-saccade test correlates with the psychology assessments of executive function. The test also correlates with known anatomical regions (orbitofrontal cortex, DLPFC, and the VMPFC) which are associated with executive function and inhibition (Jurado & Rosselli, 2007). Executive function tests have also been known to correlate with the parietal lobes (Lynch, Mountcastle, Talbot, & Yin, 1977), even in FTD (Roca et al., 2013; Rohrer et al., 2008), and this is also found in these results.

Despite generating fewer correct anti-saccades than the control group, no significant differences were observed between the number of self-corrected anti-saccades. This demonstrates that the individuals with bvFTD were able to understand the test, as they recognised that they had not correctly carried

out the anti-saccade test, and corrected themselves to look away from the stimuli. This result is encouraging for the deployment of the novel eye-tracking test. It suggests that while their executive function abilities are impaired, they are able to follow instructions and tolerate the eye-tracking well. Furthermore, the results suggest the use of anti-saccades in a clinical setting. These findings very clearly demonstrate that anti-saccades correlate very well with psychological measures of executive function. The implementation of this type of test in clinic is extremely easy to do, requiring the clinician to generate anti-saccades using their hands. It is possible that this type of test could be useful in aiding the diagnosis of bvFTD, and may be able to distinguish it from other neurological and psychological disorders.

5.6.6 Limitations and future work

Despite using reliable and accurate equipment and software, there were a limited number of trials in each condition. This was to ensure that the combination of these measures, plus the novel tests, did not take too long. Future work should aim to increase the number of trials in each condition, to increase power and thus, provide more confidence in the results. Furthermore, while the sample size was sufficient for a cross sectional study in bvFTD, the work coming out of ALLFTD and GENFI provide much more informative data; it would be beneficial to continue to increase the sample size. Finally, work on oculomotor function should be carried out in a more severe patient group. Whilst they may not be able to complete the standardised psychology assessments, or perhaps even the novel cognitive eye-tracking tests, it is likely that they would be able to complete these basic measures as they are very short and simple. Given this work carried out here, and the neuroimaging research in FTD, it is possible that some of these measures will be affected later in the disease.

5.7 Chapter summary

This work gives a comprehensive overview of oculomotor functioning in bvFTD. While there are some deficits observed on fixations and anti-saccades, I feel we can be confident that the results from the novel eye-tracking tests will not be influenced by these deficits, as the ability to pursue stimuli and generate saccades towards the images remain intact. The fixation task also showed promise as a predictive test when using the length of fixation and number of small square wave jerks as measures of performance. The anti-saccade test demonstrated very strong evidence of EF deficits in bvFTD, and it is possible that this type of test could be used in a clinical setting to help aid diagnosis, as well as in clinical trials.

CHAPTER 6: NOVEL SOCIAL COGNITIVE EYE-TRACKING TESTS

6.1 Chapter overview

In this chapter, the two emotion processing eye-tracking tasks, and the theory of mind eye-tracking test developed in Chapter 4, are assessed in symptomatic individuals with bvFTD, from both the LIFTD and GENFI cohorts. They will be compared to a control group, and performance on the standardised psychometric tests will be correlated with the eye-tracking tasks. Performance over the five second post period will be analysed to see if there is an optimal timeframe in which the post images should be displayed for in the simple task. Neural correlates will also be investigated using a ROI analysis, specifically looking at the orbitofrontal cortex, the dorsolateral prefrontal cortex, the ventromedial prefrontal cortex, the temporal, parietal and occipital lobes, as well as the striatum, cingulate, and cerebellum. In addition, neural correlates of the eye-tracking tasks will also be investigated using a VBM analysis. The work in this chapter aims to overcome some of the problems associated with the current psychometric tests, and to see if eye-tracking is a viable tool in cognitive bvFTD research.

6.2 Introduction

As humans, our social skills have evolved over thousands of years. In the outset, those who were best at cooperating and communicating with others, had protection from predators and other human beings. Through working together, they had increased access to food, and there were a wider range of potential mates available. These social skills continued to develop, and it now allows us to understand what others may be thinking and feeling, to predict the outcomes of social scenarios, and try to understand why others do the things they do. In an ever-increasing complex world, with the role of social media redefining what it means to be social, we are forever required to keep up with new ways of staying in touch and communicating with others.

There are a multitude of different disorders and diseases that cause this innate and robust ability to break down, such as Autism Spectrum Disorders (ASD), mental health disorders such as psychosis and schizophrenia, and dementia. BvFTD is no exception to this, and it is a clear hallmark feature (see section 1.4), despite not being included as part of the diagnostic criteria (see section 1.2.1). Life becomes extremely difficult when you are unable to process social information, and it is a devastating feature for the carers and loved ones, who watch and experience the individual deteriorate.

Current tests to monitor the changes in social cognition have a whole variety of problems, from being subjective, to relying on the consistency of the examiners, and having complex tests with difficult instructions to follow. This makes it very difficult to use these tests as a reliable tool to assess the progression of social cognitive deficits in this cohort of individuals; they continue to progressively decline, not only in their social abilities, but also in a multitude of other areas as well. This is problematic when it comes to the design of outcome measures for clinical trials. It is hard to know if a potential

therapeutic treatment is working if the outcome measure, i.e. the social cognitive test, is not good enough at detecting these changes. This is even more problematic in bvFTD, as many of the trials will focus on familial FTD (Greaves & Rohrer, 2019). The majority of the trials are likely to be in those prior to onset or in the very early stages of the illness. If the tests are not reliable enough, it is not likely to detect any positive changes after the drugs have been administered. It is therefore crucial that reliable and valid tests are designed and used as we move forward into the realms of therapeutic trials.

Even though there have been very few tests assessing cognition through eye-tracking in FTD (Primativo et al., 2017), it is a metric that has been used reliably in many other conditions (see section 1.6). The work suggests that eye-tracking is a viable tool, as it is well tolerated by many individuals, the design of the test can be very simple, and minimal effort is required by the participant. Furthermore, as outlined in Chapter 5, it is unlikely that oculomotor deficits will affect performance in individuals with FTD, although it is advisable to check this prior to interpretation of the results.

Consequently, this chapter therefore aims to assess whether the novel tests developed in Chapter 4, can be used in individuals with a diagnosis of bvFTD. This study will pilot the tests to see if they can be completed, assess if they are measuring emotion processing, and ensure that there is a variety in complexity of the stimuli which may eventually pick up earlier changes in a presymptomatic cohort.

6.3 Methods

6.3.1 Participants

Participants were recruited from the LIFTD and GENFI projects. A total of 18 bvFTD patients and 22 healthy controls took part. This is the same set of participants that were included in Chapter 5, except for one individual with bvFTD who was not included in this chapter. All participants with bvFTD had been given a clinical diagnosis of probable bvFTD in line with the current Rascovsky criteria (Rascovsky et al., 2011), 9 of which were genetically confirmed (*C9orf72* = 5, *GRN* = 2 and *MAPT* = 2). The mean disease duration was 8.2 years (SD = 6.1). All participants followed the study protocol with the clinical examination and psychology assessments as mentioned in section 2.4.

6.3.2 Procedure

The same equipment and set up was used as in Chapter 5, and described in section 4.3.3 and 4.3.4. The experiment took around 10 minutes to complete.

The simple and complex emotion processing tasks were completed as described in section 4.3.2 and 4.4.3. In addition, the theory of mind eye-tracking task was also carried out as described in section 4.4.4.

6.3.3 Structural brain imaging

All participants underwent volumetric T1-weighted MRI. All scans were quality checked (QC) and those with movements or artefacts were removed. Furthermore, if any participants displayed moderate to severe vascular disease or any other brain lesions, they were also excluded from the analysis. A ROI and VBM analysis was carried out as described in section 2.6.1 and 2.6.2.

In order to establish any relationships between the ROI and the eye-tracking tests, a Pearson's correlation analysis was carried out. To understand if any correlations that occurred were due to disease severity (as measured using the CDR with the NACC FTLD component – see section 2.4.2), partial correlations were also carried out.

In order to explore the relationship between performance on the eye-tracking tests and GM density, two multiple regression models were used to correlate the GM tissue maps to the complex and simple tests. Control participants were not included in the analysis. Age, gender and total intracranial volume were entered as covariates. The Family-Wise Error rate for multiple comparisons correction was set at 0.05.

6.3.4 Statistical analysis

Demographic and psychometric data

Demographic and psychometric data was analysed using independent t-tests on normally distributed data, or Mann Whitney U tests for data that was not normally distributed (see section 2.7). A Spearman's Rank correlation was also carried out between the neuropsychological tests of interest, with the target image on the simple and complex emotion processing tasks. This was done in the bvFTD group only to investigate which cognitive domains were impacting on their performance.

Pre-processing of the eye-tracking data

All gaze data was loaded into Data Viewer for pre-processing. This software is provided by SR Research to accompany the Eyelink 1000 Plus to analyse the data. After this, the data was exported to Stata/IC 14.2 for statistical analysis. An interest area report was generated (Appendix 7).

Simple and complex eye-tracking tests

A difference score was calculated for the amount of time spent looking at each of the four images/interest areas: the target image, the similar image and the two distractor images. The time spent looking at the images before the probe word appeared (the pre-score), was subtracted from the time spent looking at the images after the probe word appeared (the post-score). This generated four dwell time difference scores for each of the images for every individual on all trials – one for each of the corners. The two distractor difference scores were combined together to give one total distractor score. This was done by adding the two together and dividing by two. As there were differences in the presentation time (10 seconds for the pre-score vs 5 seconds for the post score), the percentage of time spent looking at the images was used.

Interest area analysis: In order to compare performance on each of the tests, a mixed effects model was carried out for both the simple and complex emotion processing tests. Age and gender were not included in the model as participants were equally matched. As the data was not normally distributed, bootstrapping was used (see section 2.7). Participant and trial number were included as clusters in the analysis. Diagnosis (bvFTD or control) and image type (target, similar, and distractor) were included in the model, with the dwell time difference score included as the variable of interest. One individual with bvFTD did not have sufficient data to be included in the complex analysis.

Pairwise comparisons were carried out (see section 2.7) to compare performance within the groups on each of the three interest areas: target, similar and distractor, as well as between group comparisons for each of the interest areas. For both tasks this was done for the whole duration of the post condition (percentage dwell time in the post condition over five seconds: 0-5

seconds), but in the simple condition, this was also done over four other conditions as well. The percentage of dwell time was recalculated over the first (0-1 second), second (0-2 seconds), third (0-3 seconds) and fourth (0-4 seconds) second of the post display time. The dwell time difference score was then calculated for each of the four new time conditions, and both the between and within group analyses carried out. This was to establish whether a shorter time period could be used in the post condition. The different time periods were generated in Data Viewer.

Simple emotion analysis: Mixed effects models were run to look at the differences between the emotions. The dwell time difference score for the target interest area was only used as this was the main measure of interest. The data was again not normally distributed and so bootstrapping was performed. Pairwise post hoc comparisons were carried out to look at the effect of emotion type in controls. This was then assessed in the bvFTD group, but was calculated as a percentage of the control score. A percentage was calculated because there are differences observed in the literature across emotions in the control population. This was calculated by dividing the bvFTD individuals raw score, by the mean control score for that emotion, and multiplying by 100:

(INDIVIDUAL RAW SCORE (HAPPINESS) / MEAN CONTROL SCORE (HAPPINESS)) * 100

The same process was carried out when grouping the emotions into positive and negative valence. Positive combined happiness and surprise whilst negative included sadness, disgust, fear and anger. Performance in the control group was calculated, followed by the bvFTD as presented as a percentage of the control score.

Age and Gender: Despite the two groups being matched on age and gender, to ensure these were not having an effect on performance, a correlational

analysis was performed using the target dwell time difference score. Overall correlations for both groups, as well as for each group independently, was carried out with age.

A gender analysis was also carried out and used a linear regression. This again focused only on the target dwell time difference score. An overall model was run for both groups, as well as each group independently.

Theory of mind eye-tracking test

As this is a novel test, performance in the control group needed to be assessed to establish how the it was working. A linear regression model was carried out for the analysis. As the data was not normally distributed, bootstrapping was performed on the data. A mixed effects model was not used in this scenario as there was only one trial per person. The dwell time was calculated for each of the four interest areas (Chair, Drawers, Table and Wardrobe) after the cartoon character disappeared from the screen at the end of the trial.

Once the performance was established in the control group, another linear regression was carried out to assess performance between the groups.

6.4 Results

6.4.1 Demographics and Neuropsychometry

The demographic and neuropsychometric mean scores and standard deviations (SD) can be found in Chapter 5 (see Table 5-1). In comparison to the participants in Chapter 5, one individual with bvFTD was not included in this analysis due to missing data. The control group were matched on age and gender to the patients with bvFTD. However, there were significant differences in education level ($p = 0.04$), MMSE score ($p < 0.001$) and disease severity ($p < 0.001$).

For the neuropsychometric tests, significant differences were observed between the controls and the patients with bvFTD on all tests (see Table 5-1).

6.4.2 Complex

IA analysis

Figure 6-1 summarises the complex emotion processing results. When looking at the dwell time difference scores for the amount of time spent looking at the images after the probe word appeared compared to before, control participants looked 17% more at the target image than the similar image, and 18% more at the target compared to the distractor images (see Table 6-1). There were no differences seen between the similar and distractor images. The same pattern emerged in the bvFTD participants, but to a lesser extent: 4 % more at the target image than the similar one, and 5% more at the target image than the distractor one (see Table 6-1). No significant differences were found between the similar and distractor images.

Table 6-1: The mean dwell time difference scores for each of the interest areas for the controls and bvFTD patients.

	Mean difference	CI	
Controls			
Target vs Similar	17%	0.13	0.23
Target vs Distractor	18%	0.14	0.23
Similar vs Distractor	0%	-0.02	0.02
bvFTD			
Target vs Similar	4%	0.00	0.08
Target vs Distractor	5%	0.01	0.10
Similar vs Distractor	1%	-0.01	0.03

When comparing between the groups, the bvFTD participants looked 13% less at the target image than the controls (Table 6-2). No differences were found on the amount of time spent looking at the similar and distractor images.

Table 6-2: Differences between the bvFTD and control group on the complex EP test.

	Control		bvFTD		% difference	CI	
	Mean	SD	Mean	SD			
Distractor	-2.4%	18.3%	-2.7%	13.7%	-0.2%	-0.02	0.02
Similar	-2.2%	19.0%	-1.2%	14.7%	1.1%	-0.02	0.04
Target	15.2%	25.6%	2.1%	17.5%	-13.1%	-0.18	-0.07

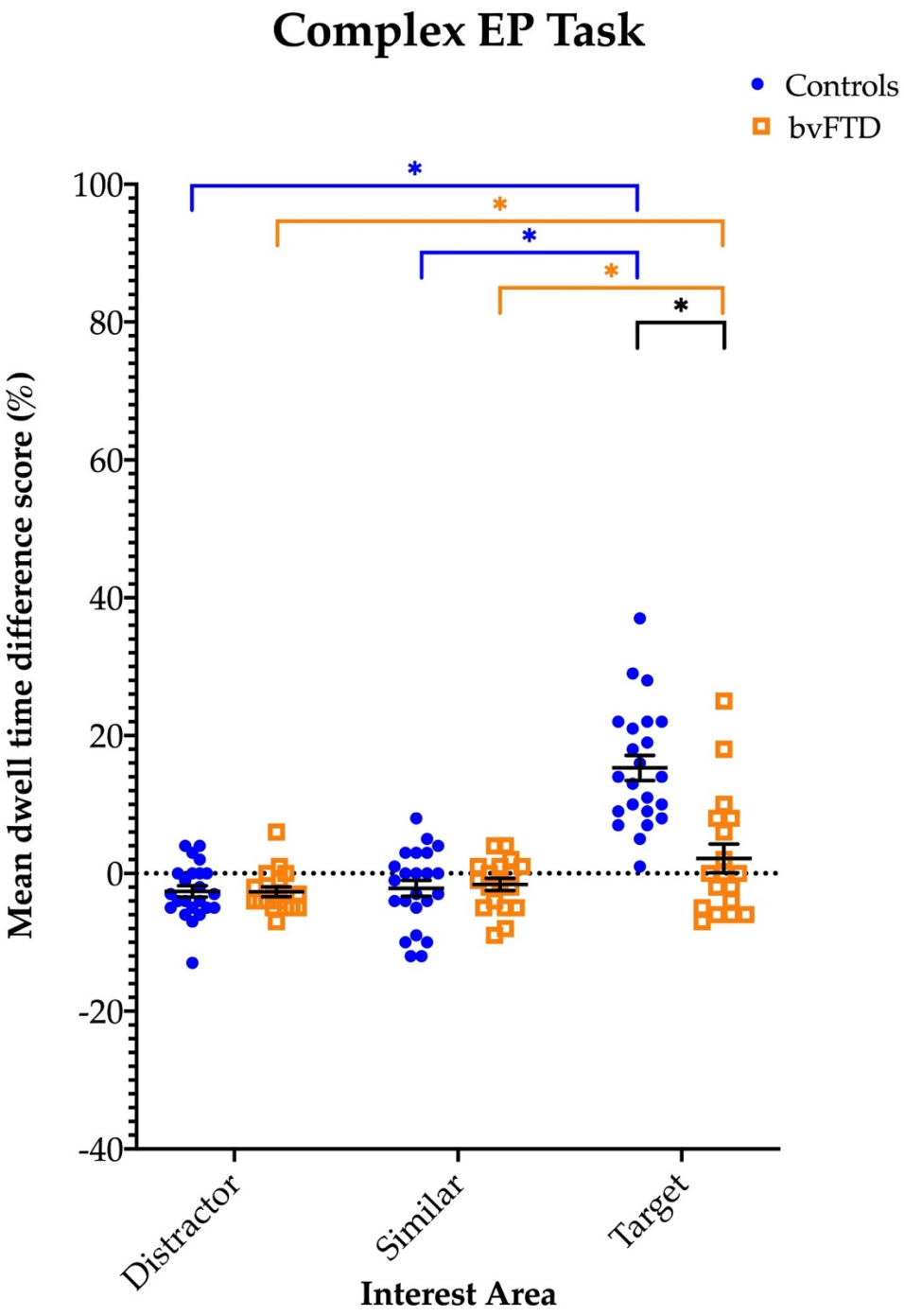

Figure 6-1: Displays the complex EP data for the bvFTD patients and the controls. Orange and blue significance lines indicate within group differences (bvFTD and controls respectively), black significance lines indicate between group differences.

Age, gender and disease severity

The correlation analysis between performance on the target interest area and age did not find a significant correlation overall (r = -0.01, p = 0.800), for controls (r = -0.06, p = 0.212) or for bvFTD (r = 0.05, p = 0.406). The same pattern emerged for gender, with no significant differences between males and females overall (p = 0.293), in the control group (p = 0.436) or in the bvFTD group (p = 0.836). A significant negative correlation was found between the dwell time difference score for the target interest area and disease severity (r = -0.63, p = 0.006) (see *Figure 6-2*).

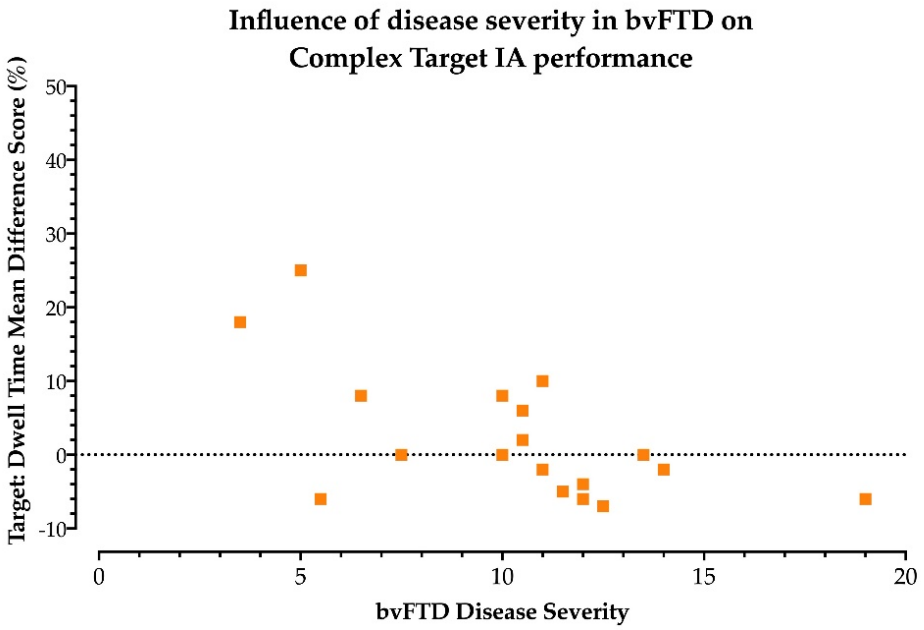

Figure 6-2: Scatter plot of the dwell time difference score for the target interest area on the complex EP test and disease severity as measured using the CDR with the NACC FTLD component.

Psychology correlations

No psychology test significantly correlated with the dwell time difference score for the target interest area (see Table 6-3). There were a few tests that did approach significance after controlling for disease severity: WASI performance IQ, D-KEFS colour/word inference and the arithmetic test (see Table 6-3).

Table 6-3: Psychology correlations for the complex EP test for the dwell time difference score in the target interest area. Bold indicates a significant correlation whilst italics highlights a trend. The partial correlations take into consideration the impact that disease severity.

	Correlation		Partial Correlation	
	r	*p*	*r*	*p*
General intellect				
WASI Visual IQ	-0.10	0.668	0.22	0.394
WASI Performance IQ	0.14	0.523	*0.48*	*0.054*
Episodic memory				
RMT Faces	-0.31	0.166	-0.08	0.784
RMT Words	-0.14	0.526	-0.03	0.916
Digit Span - Forward Total	0.26	0.260	0.32	0.205
Executive function/speed of processing				
Digit Span - Backwards	0.25	0.264	0.36	0.162
Fluency – Letter	0.07	0.759	-0.14	0.605
Fluency – Category	0.01	0.964	0.08	0.765
D-KEFS Colour Inference	-0.28	0.222	-0.16	0.556
D-KEFS Word Inference	*-0.37*	*0.098*	-0.29	0.269
D-KEFS Colour/Word Inference	-0.24	0.290	*-0.53*	*0.051*
Trails Making Test A – Time	-0.03	0.882	-0.28	0.287
Trails Making Test B – Time	-0.32	0.149	-0.36	0.248
Digit Symbol	*0.41*	*0.056*	-0.35	0.205
Language				
NART	-0.03	0.887	0.32	0.283
BPVS	-0.20	0.385	-0.10	0.702
GNT	0.05	0.821	-0.31	0.243
Parietal cortical skills				
Arithmetic	*0.39*	*0.072*	*0.53*	*0.065*
VOSP	0.36	0.362	0.24	0.408
Social cognition				
Mini-SEA Score	-0.24	0.373	-0.36	0.195
Facial Emotion Recognition Test	0.18	0.494	-0.05	0.847
Faux-Pas Test	-0.11	0.700	0.06	0.488
mIRI	0.11	0.694	-0.25	0.377
RSMS	0.18	0.500	0.14	0.500
Synonyms	0.27	0.282	0.15	0.569

WASI, Wechsler Abbreviated Scale of Intelligence; D-KEFS, Delis Kaplan Executive System; NART, National Adult Reading Test; BPVS, British Picture Vocabulary Scale; VOSP, Visual Object and Space Perception Test; Mini-SEA, Mini-Social and Emotional Assessment; mIRI, Modified Interpersonal Reactivity Index; RSMS, Revised Self-Monitoring Scale. *Indicates tests scored in seconds

ROI analysis

Performance on the target interest area positively correlated with volume in the right temporal lobe (r = 0.51, p = 0.030). After controlling for disease severity, only the left and right dorsolateral prefrontal cortex (r = 0.60, p = 0.010; r = 0.59, p = 0.013 respectively) positively correlated with the dwell time difference score for the target interest area. There were a number of regions that displayed a trend towards significance: the left and right temporal lobe, the left and right occipital lobe, and the left and right cingulate, (see Table 6-4).

Table 6-4: Correlations between the ROI and the dwell time difference score for the target interest area. Bold indicates a significant correlation whilst italics indicates a trend. The partial correlations take into consideration the impact of disease severity on the correlation between test performance and the ROI.

	Correlation		Partial Correlation	
	r	*p*	r	*p*
Orbitofrontal cortex				
Left	-0.26	0.290	-0.38	0.135
Right	-0.05	0.854	-0.18	0.495
Dorsolateral prefrontal cortex				
Left	*0.41*	*0.089*	***0.60***	***0.010***
Right	*0.42*	*0.082*	***0.59***	***0.013***
Ventromedial prefrontal cortex				
Left	-0.17	0.493	-0.34	0.189
Right	-0.07	0.800	-0.24	0.354
Temporal lobe				
Left	0.40	0.097	*0.43*	*0.082*
Right	**0.51**	**0.030**	*0.44*	*0.078*
Parietal lobe				
Left	-0.15	0.553	-0.02	0.932
Right	-0.06	0.815	0.04	0.874
Occipital lobe				
Left	-0.47	0.050	*-0.45*	*0.068*
Right	*-0.34*	*0.164*	*-0.43*	*0.087*
Striatum				
Left	0.11	0.663	0.06	0.431
Right	0.41	0.095	0.28	0.814
Cingulate				
Left	-0.36	0.142	*-0.44*	*0.080*
Right	-0.38	0.118	*-0.45*	*0.072*
Cerebellum				
	0.17	0.496	0.26	0.314

VBM analysis

In the VBM analysis, the dwell time difference score for the complex target interest area was not associated with grey matter volume in the bvFTD group, even after adjusting for disease severity.

6.4.3 Simple

IA analysis

Figure 6-3 summarises the simple emotion processing results over the five second post period. Figure 6-4 displays the dwell time difference score over the five time bins for the target interest area only. When looking at the dwell time difference scores for the amount of time spent looking at the images in the five seconds after the probe word appeared compared to before, control participants looked 45.4% more at the target image than the similar image, and 45.1% more at the target compared to the distractor images (see Table 6-5); these were both significantly different to one another. There were no significant differences seen between the similar and distractor images. The same pattern emerged in the bvFTD participants but to a lesser extent: 7.9% more at the target image than the similar one, and 6.9% more at the target image than the distractor one (see Table 6-5); these were both significantly different from one another. No differences were found between the similar and distractor images.

The same pattern emerged over all of the time bins for the control group (see Table 6-5) with significant differences between the target and distractor, and target and similar images. This was the same in the bvFTD group, except for over the first second of the post condition, in which there was no significant difference between the target and the similar images (see Table 6-5).

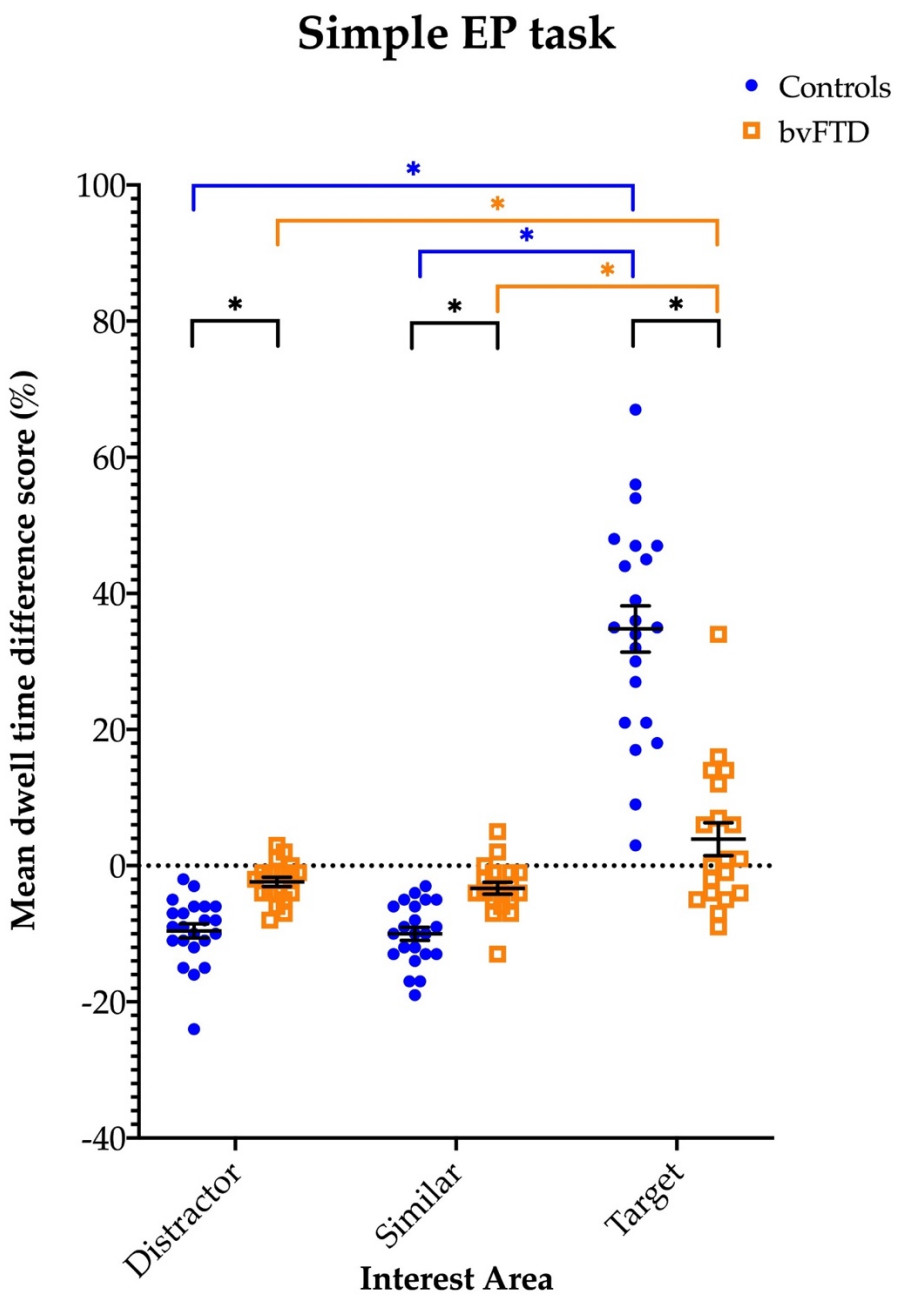

Figure 6-3: Displays the simple EP data for the bvFTD patients and the controls with the post time period of 5 seconds. Orange and blue significance lines indicate within group differences (bvFTD and controls respectively), black significance lines indicate between group differences.

Table 6-5: Within group differences across the four interest areas and the confidence intervals.

Time Bin	IA	Mean difference	CI	
Controls				
< 1 second	Similar vs Distractor	-0.3%	-2.9%	1.9%
	Target vs Distractor	**22.9%**	**17.6%**	**32.5%**
	Target vs Similar	**23.3%**	**17.7%**	**31.4%**
< 2 seconds	Similar vs Distractor	-0.8%	-2.5%	0.8%
	Target vs Distractor	**31.1%**	**25.0%**	**41.2%**
	Target vs Similar	**32.0%**	**25.5%**	**39.8%**
< 3 seconds	Similar vs Distractor	0.0%	-1.1%	1.3%
	Target vs Distractor	**37.9%**	**30.8%**	**45.7%**
	Target vs Similar	**37.9%**	**30.0%**	**44.9%**
< 4 seconds	Similar vs Distractor	-0.3%	-1.6%	0.7%
	Target vs Distractor	**42.7%**	**34.1%**	**50.2%**
	Target vs Similar	**43.1%**	**34.2%**	**50.3%**
< 5 seconds	Similar vs Distractor	-0.3%	-1.4%	0.8%
	Target vs Distractor	**45.1%**	**37.1%**	**53.7%**
	Target vs Similar	**45.4%**	**37.6%**	**53.7%**
bvFTD				
< 1 second	Similar vs Distractor	2.8%	-0.6%	5.2%
	Target vs Distractor	**5.2%**	**2.0%**	**10.3%**
	Target vs Similar	2.5%	-1.7%	6.7%
< 2 seconds	Similar vs Distractor	0.6%	-2.0%	2.8%
	Target vs Distractor	**4.5%**	**1.2%**	**10.1%**
	Target vs Similar	**3.8%**	**0.7%**	**8.8%**
< 3 seconds	Similar vs Distractor	-0.7%	-3.2%	1.1%
	Target vs Distractor	**5.4%**	**1.1%**	**11.5%**
	Target vs Similar	**6.1%**	**2.4%**	**11.7%**
< 4 seconds	Similar vs Distractor	-1.0%	-3.6%	0.7%
	Target vs Distractor	**5.9%**	**1.6%**	**12.9%**
	Target vs Similar	**7.0%**	**3.0%**	**13.9%**
< 5 seconds	Similar vs Distractor	-1.1%	-3.4%	0.6%
	Target vs Distractor	**6.9%**	**2.7%**	**14.3%**
	Target vs Similar	**7.9%**	**4.0%**	**15.3%**

When comparing between the groups across the 5 seconds post period, the bvFTD participants looked 30.7% less at the target image, 6.8% more at the similar image and 7.6% more at the distractor images than the control group did, all of which were significantly different (see Table 6-6).

The same pattern emerged at all time bins, except for when comparing the distractor images between the two groups over the first second, where there was no significant difference between them (see Table 6-6).

Table 6-6: Between group differences across the interest areas with their mean scores, difference and confidence intervals.

Time Bin	IA	Control		bvFTD		% difference	CI	
		Mean	SD	Mean	SD			
< 1 second	Distractor	-7.1%	4.4%	-5.7%	4.0%	1.3%	-0.9%	4.1%
	Similar	**-7.4%**	**5.3%**	**-3.0%**	**4.8%**	**4.5%**	**1.2%**	**7.4%**
	Target	**15.8%**	**14.0%**	**-0.5%**	**8.5%**	**-16.3%**	**-23.9%**	**-10.2%**
< 2 seconds	**Distractor**	**-7.0%**	**4.4%**	**-2.4%**	**3.5%**	**4.6%**	**2.6%**	**7.5%**
	Similar	**-7.8%**	**5.3%**	**-1.7%**	**4.9%**	**6.1%**	**3.6%**	**9.2%**
	Target	**24.2%**	**14.0%**	**2.1%**	**8.3%**	**-22.0%**	**-29.2%**	**-15.2%**
< 3 seconds	**Distractor**	**-8.2%**	**4.5%**	**-1.6%**	**3.2%**	**6.6%**	**4.6%**	**9.3%**
	Similar	**-8.1%**	**4.6%**	**-2.3%**	**4.2%**	**5.9%**	**3.3%**	**8.5%**
	Target	**29.8%**	**15.1%**	**3.8%**	**9.8%**	**-26.0%**	**-33.3%**	**-17.7%**
< 4 seconds	**Distractor**	**-9.1%**	**4.7%**	**-1.8%**	**3.3%**	**7.3%**	**5.0%**	**9.8%**
	Similar	**-9.4%**	**4.6%**	**-2.8%**	**3.8%**	**6.6%**	**3.9%**	**9.2%**
	Target	**33.6%**	**15.5%**	**4.2%**	**10.8%**	**-29.5%**	**-36.5%**	**-20.4%**
< 5 seconds	**Distractor**	**-9.8%**	**4.9%**	**-2.3%**	**3.0%**	**7.6%**	**5.3%**	**10.4%**
	Similar	**-10.1%**	**4.4%**	**-3.3%**	**4.0%**	**6.8%**	**4.5%**	**9.5%**
	Target	**35.3%**	**16.3%**	**4.6%**	**10.5%**	**-30.7%**	**-38.3%**	**-22.6%**

The time bin analysis of the target interest area revealed significant differences between all the time bins, except for between the 4 and 5 second period in the control group (Table 6-7). In the bvFTD group however, significant differences were only found up to two seconds with the remaining time groups; no significant differences were observed at three, four and five seconds (Table 6-8).

Table 6-7: Estimated difference scores and confidence intervals between the time bins in the control group for the target interest area. Items in bold represent a significant difference between the time bins.

Controls					
Time Bin	< 1 second	< 2 seconds	< 3 seconds	< 4 seconds	< 5 seconds
< 1 second		**8.3%**	**13.9%**	**17.8%**	**19.5%**
		5.8% **10.8%**	**11.4%** **16.5%**	**15.3%** **20.3%**	**16.9%** **22.0%**
< 2 seconds			**5.6%**	**9.5%**	**11.2%**
			3.1% **8.1%**	**7.0%** **12.0%**	**8.6%** **13.7%**
< 3 seconds				**3.9%**	**5.5%**
				1.4% **6.4%**	**3.0%** **8.1%**
< 4 seconds					1.7%
					-0.9% 4.2%
< 5 seconds					

Table 6-8: Estimated difference scores and confidence intervals between the time bins in the bvFTD group for the target interest area. Items in bold represent a significant difference between the time bins.

bvFTD					
Time Bin	< 1 second	< 2 seconds	< 3 seconds	< 4 seconds	< 5 seconds
< 1 second		**2.6%**	**4.3%**	**4.7%**	**5.1%**
		0.3% **4.9%**	**2.0%** **6.6%**	**2.4%** **6.9%**	**2.8%** **7.4%**
< 2 seconds			**1.7%**	**2.1%**	**2.5%**
			-0.6% **3.9%**	**-0.2%** **4.3%**	**0.2%** **4.7%**
< 3 seconds				0.4%	0.8%
				-1.9% 2.6%	-1.5% 3.1%
< 4 seconds					0.4%
					-1.8% 2.7%
< 5 seconds					

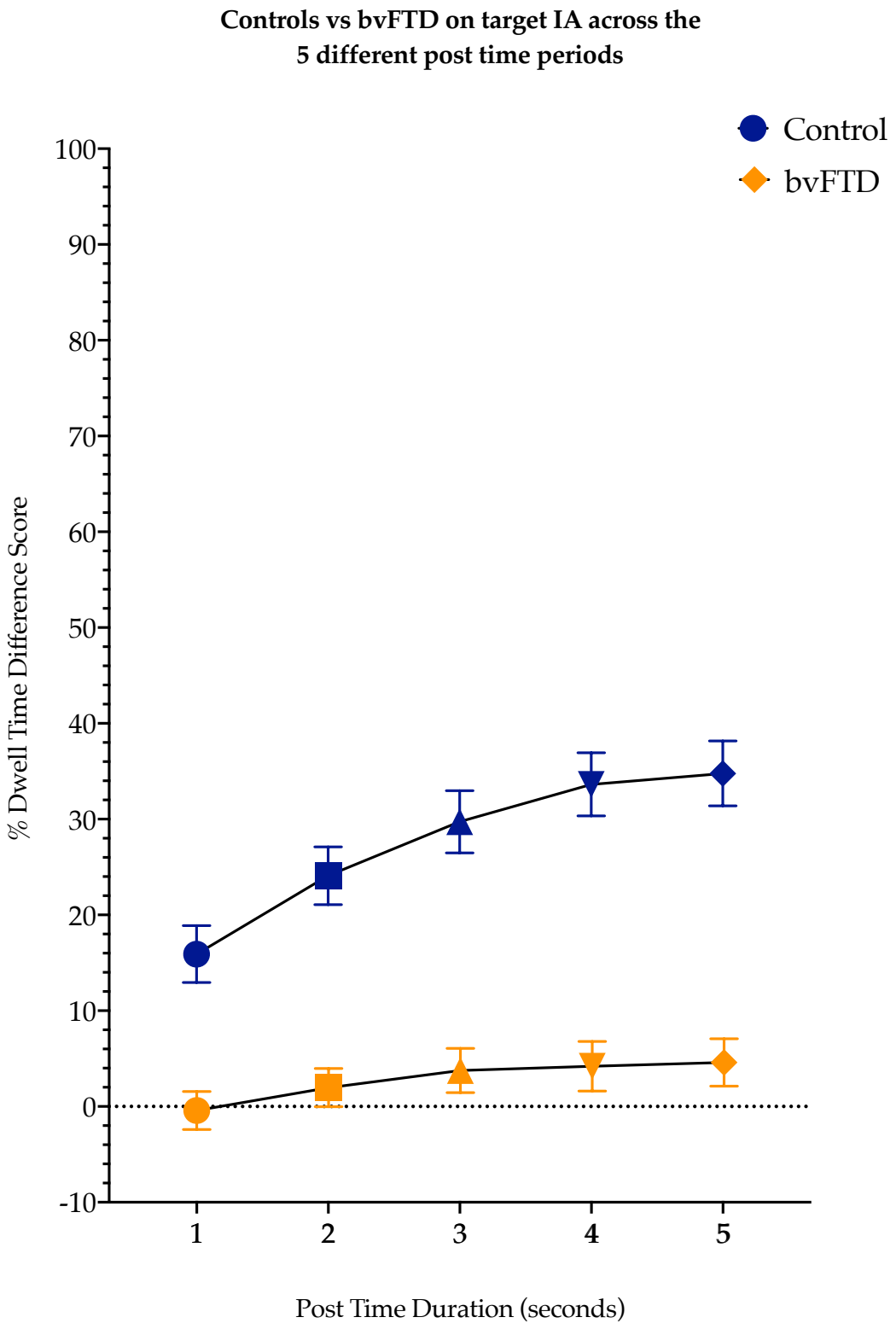

Figure 6-4: The dwell time difference score has been calculated for the five different post time bins for both the control and bvFTD group.

Age, gender and disease severity

A significant negative correlation was found between performance on the target interest area and age overall (r = -0.13, $p < 0.001$); this was driven by the control group (r = -0.32, $p < 0.001$), as the correlation was not significant in the bvFTD group (r = 0.03, $p = 0.484$). There was no significant effect of gender overall ($p = 0.547$), in the control group ($p = 0.328$) or in the bvFTD group ($p = 0.182$). A significant negative correlation was found between the dwell time difference score for the target interest area and disease severity (r = -0.53, $p = 0.023$) (see *Figure 6-5*).

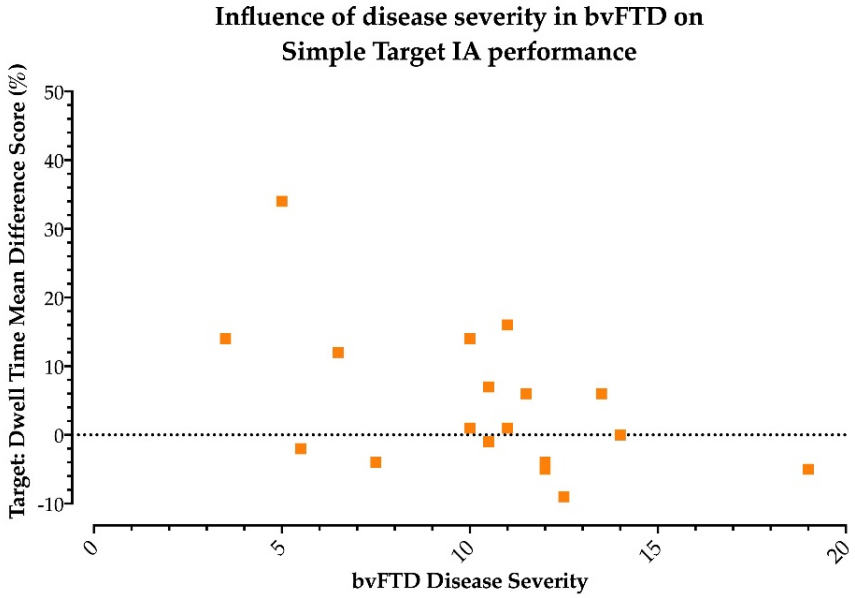

Figure 6-5: Scatter plot of the dwell time difference score for the target interest area on the simple EP test and disease severity (CDR with the NACC FTLD component).

Psychology correlations

Performance on the target interest area dwell time difference score on the simple test, only correlated with the RMT Faces (r = -0.55, $p = 0.008$). After controlling for disease severity, only the WASI performance IQ was significantly correlated with the dwell time difference score (r = 0.57, $p = 0.016$). A trend was found on the arithmetic test (see Table 6-9).

Table 6-9: Psychology correlations for the simple EP eye-tracking test for the dwell time difference score in the target interest area.

	Correlation		Partial Correlation	
	r	*p*	r	*p*
General intellect				
WASI Visual IQ	-0.22	0.335	0.22	0.405
WASI Performance IQ	-0.12	0.593	**0.57**	**0.016**
Episodic memory-				
RMT Faces	**-0.55**	**0.008**	-0.02	0.955
RMT Words	-0.12	0.610	0.19	0.529
Digit Span - Forward Total	-0.23	0.301	0.19	0.472
Executive function/speed of processing				
Digit Span - Backwards	-0.09	0.706	0.36	0.157
Fluency – Letter	*-0.37*	*0.092*	-0.05	0.867
Fluency – Category	0.04	0.847	0.14	0.607
D-KEFS Colour Inference*	-0.33	0.150	-0.16	0.556
D-KEFS Word Inference*	*-0.43*	*0.054*	-0.14	0.616
D-KEFS Colour/Word Inference*	0.18	0.443	-0.40	0.155
Trails Making Test A*	-0.01	0.952	-0.36	0.167
Trails Making Test B*	-0.12	0.612	-0.17	0.595
Digit Symbol	0.20	0.376	0.23	0.412
Language				
NART	*-0.39*	*0.072*	0.16	0.596
BPVS	-0.21	0.351	-0.27	0.318
GNT	-0.17	0.443	-0.16	0.566
Parietal tests				
Arithmetic	0.08	0.735	*0.53*	*0.063*
VOSP	-0.24	0.273	0.32	0.263
Social cognition				
Mini-SEA Score	-0.27	0.320	-0.34	0.217
Facial Emotion Recognition Test	0.04	0.873	-0.15	0.593
Faux-Pas Test	*0.06*	*0.083*	0.22	0.463
mIRI	-0.13	0.629	-0.44	0.104
RSMS	0.11	0.682	0.07	0.815
Synonyms	0.19	0.441	0.08	0.776

WASI, Wechsler Abbreviated Scale of Intelligence; D-KEFS, Delis Kaplan Executive System; NART, National Adult Reading Test; BPVS, British Picture Vocabulary Scale; VOSP, Visual Object and Space Perception Test; Mini-SEA, Mini-Social and Emotional Assessment; mIRI, Modified Interpersonal Reactivity Index; RSMS, Revised Self-Monitoring Scale. *Indicates tests scored in seconds.

ROI analysis

A positive correlation was found between performance on the target interest area and the right temporal lobe (r = 0.57, p = 0.013), and a negative correlation between performance and the left occipital lobe (r = -0.52, p = 0.027). After controlling for disease severity, a significant positive correlation was found with the dwell time difference score for the target interest area and the left and right dorsolateral prefrontal cortex (r = 0.54, p = 0.024; r = 0.55, p = 0.022 respectively), and the right temporal lobe (r = 0.52, p = 0.035). A significant negative correlation was found with the left and right cingulate (r = -0.49, p = 0.049; r = -0.51, p = 0.038 respectively) and left occipital lobe (r = -0.50, p = 0.035).

Table 6-10: Correlations for the dwell time difference score for the target interest area and the ROIs on the simple EP test. Bold indicates a significant correlation, whilst italics indicate a trend towards significance. The partial correlations consider the impact disease severity.

	Correlation		Partial Correlation	
	r	*P*	r	*p*
Orbitofrontal cortex				
Left	-0.29	0.239	-0.38	0.137
Right	0.00	0.987	-0.18	0.483
Dorsolateral prefrontal cortex				
Left	*0.41*	*0.090*	***0.54***	***0.024***
Right	*0.43*	*0.072*	***0.55***	***0.022***
Ventromedial prefrontal cortex				
Left	-0.22	0.382	-0.35	0.171
Right	-0.11	0.665	-0.25	0.326
Temporal lobe				
Left	*0.46*	*0.054*	*0.48*	*0.051*
Right	**0.57**	**0.013**	**0.52**	**0.035**
Parietal lobe				
Left	-0.19	0.451	-0.09	0.722
Right	-0.11	0.065	-0.04	0.872
Occipital lobe				
Left	**-0.52**	**0.027**	**-0.50**	**0.035**
Right	*-0.40*	*0.400*	*-0.46*	*0.062*
Striatum				
Left	0.17	0.505	0.14	0.601
Right	*0.42*	*0.079*	0.32	0.213
Cingulate				
Left	-0.43	0.076	**-0.49**	**0.049**
Right	*-0.46*	*0.057*	**-0.51**	**0.038**

VBM analysis

In the VBM analysis the dwell time difference score for the simple target interest area was not associated with grey matter volume in the bvFTD group, even after adjusting for disease severity.

6.4.4 Simple emotions

Figure 6-6 summarises the impact of emotion type on performance across the two groups, for the target interest area. Performance in the control group on the simple test when a fearful emotion was shown, was significantly worse than all other emotions (see Table 6-11). No significant differences were seen in the bvFTD group across the emotions (see Table 6-12). The bvFTD group had a significant deficit on all emotions relative to the controls (see Table 6-13).

Table 6-11: Performance in the control group across the emotions on the simple test for the target interest area only.

	Control											
	Anger	Disgust		Fear		Happy		Sadness		Surprise	
Anger		0.04	0.382	**-0.08**	**0.02**	*0.06*	*0.083*	0.00	0.967	0.01	0.697
Disgust				**-0.12**	**< 0.001**	0.03	0.456	-0.04	0.361	-0.03	0.464
Fear						**0.15**	**< 0.001**	**0.08**	**0.032**	**0.95**	**0.002**
Happy								*-0.06*	*0.089*	-0.05	0.114
Sadness										0.01	0.748
Surprise											

Table 6-12: Performance in the bvFTD group across the emotions on the simple test for the target interest area only.

	bvFTD											
	Anger	Disgust		Fear		Happy		Sadness		Surprise	
Anger		-0.04	0.154	-0.01	0.456	0.02	0.533	-0.02	0.180	0.00	0.974
Disgust				0.03	0.231	*0.06*	*0.065*	0.02	0.485	0.04	0.162
Fear						0.03	0.353	-0.01	0.427	0.01	0.558
Happy								-0.04	0.106	-0.02	0.522
Sadness										0.03	0.237
Surprise											

Table 6-13: Between group differences on the individual emotions on the simple test for the target interest area only.

	Control		bvFTD		P value	CI	
	Mean	SD	Mean	SD			
Happy	40%	29%	7%	20%	< 0.001	-0.45	-0.22
Surprise	35%	25%	5%	19%	< 0.001	-0.39	-0.21
Disgust	37%	27%	1%	16%	< 0.001	-0.45	-0.29
Fear	26%	29%	4%	19%	< 0.001	-0.36	-0.14
Anger	35%	26%	5%	16%	< 0.001	-0.38	-0.20
Sadness	24%	25%	3%	18%	< 0.001	-0.42	-0.22

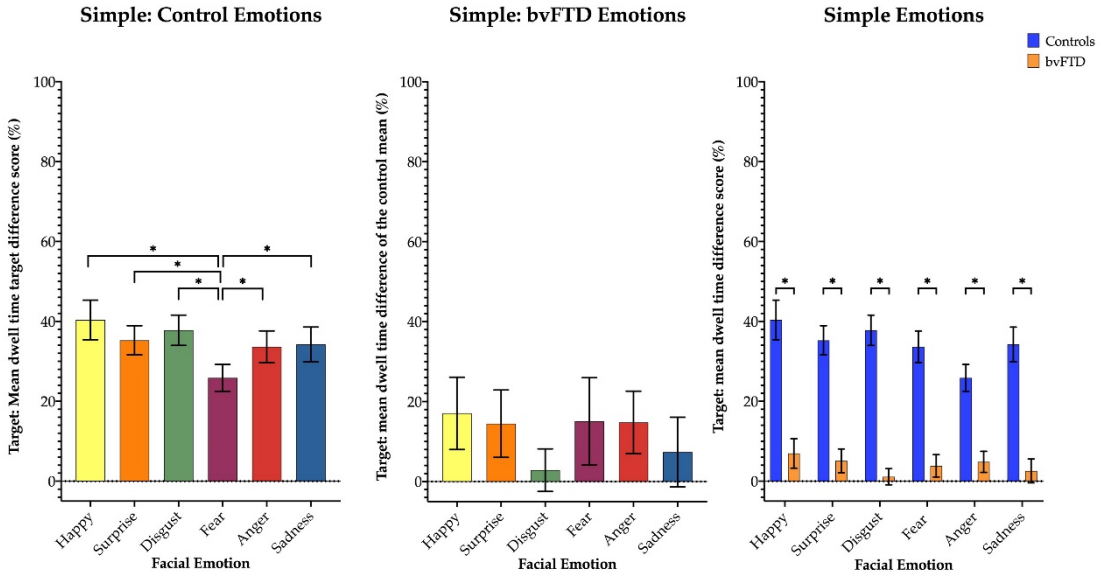

Figure 6-6: Displays the performance on the target interest are across the different emotions on the simple test.

6.4.5 Simple valence

Figure 6-7 summarises the influence of valence on performance in the bvFTD and control groups. Control participants looked considerably more at positive emotions than negative ones ($p = 0.031$). This however was not the case in the bvFTD group ($p = 0.137$) (see Table 6-14). When comparing between the groups, the bvFTD group look significantly less at both positive and negative emotions ($p < 0.001$ for both – see Table 6-15).

Table 6-14: Differences between the positive and negative emotions in each group.

	Mean difference	*p*	CI	
Positive vs negative				
Controls	5%	0.031	0.00	-0.09
bvFTD	3%	0.137	0.01	-0.07

Table 6-15: Between group differences when the emotions are split by valence.

	Control		bvFTD		*p* value	CI	
	Mean	SD	Mean	SD			
Positive	38%	27%	6%	3%	< 0.001	-0.42	-0.22
Negative	33%	27%	3%	18%	< 0.001	-0.38	-0.22

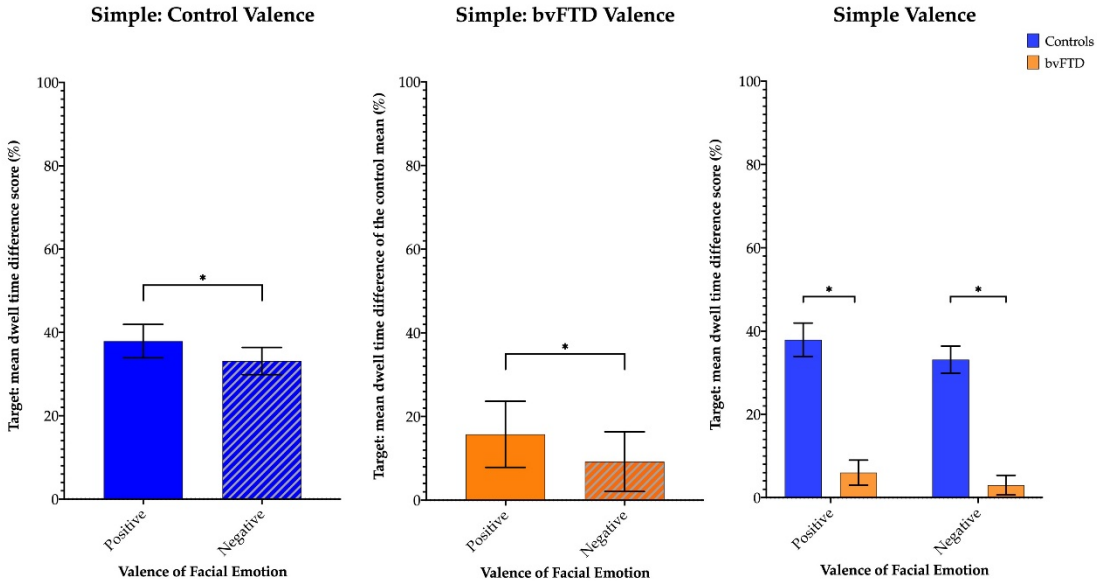

Figure 6-7: Effect of valence of performance on the target interest are first graph on the left is the performance between positive and negative emotions in the control group. the middle graph is displaying performance in the bvFTD group as a percentage of control data and the final graph on the right is displaying he mean dwell time difference score between the groups for both positive and negative emotions.

6.4.6 Theory of mind test

The control group looked significantly more at the drawers than they did at any of the other interest areas (Table 6-16). This same pattern was found in the bvFTD group (Table 6-17); however, no differences were found between the two groups on each of the interest areas (Table 6-18).

Table 6-16: Control performance on the ToM test (measured in milliseconds – ms).

	Control					
	Chair	Drawers		Table		Wardrobe	
Chair		885.7	0.005	-116.1	0.200	-129.2	0.1550
Drawers				-1001.8	0.001	-1014.9	0.001
Table						-13.1	0.817
Wardrobe							

Table 6-17: BvFTD performance on the ToM test (measured in ms).

	bvFTD					
	Chair	Drawers		Table		Wardrobe	
Chair		603.5	0.001	-37.1	0.558	57.5	0.495
Drawers				-640.7	< 0.001	-546.1	0.005
Table						94.6	0.252
Wardrobe							

Table 6-18: Between group differences on the ToM test (measured in ms).

	Control		**bvFTD**		**Significance level: p =**	**CI**	
	Mean	**SD**	**Mean**	**SD**			
Chair	200.0	369.3	150.5	178.6	0.584	-226.6	127.6
Drawers	1085.7	1312.5	754.0	725.0	0.332	-1001.3	338.0
Table	83.9	178.9	113.4	183.5	0.651	-85.5	144.6
Wardrobe	70.8	175.4	207.9	287.5	0.091	-22.1	296.4

6.5 Discussion

This chapter aimed to investigate whether the novel tests were a suitable and valid measure of social cognition in a bvFTD cohort. The results suggest that both the simple and complex test worked, but the theory of mind test did not.

The control groups looked significantly more at the image that matched the probe word in the middle of the screen, when measured using the difference in dwell time before and after the probe word appeared. This was the case for both the simple and complex tests. In the control group, performance on the simple test (45%) was much better than the complex one (18%). The bvFTD group produced a very similar pattern to the control group on these two tasks, but to a much lesser extent (Simple: 7%; Complex: 2%). On the theory of mind

test, the control group looked significantly more at the drawers than they did at the chairs; this was not the expected outcome. Greater looking time should have been directed at the chair where the boy left his book; he did not realise it had been moved by someone else. The bvFTD group followed this same pattern, again looking significantly more at the drawers than the chair, but this was also less than the control group (331.7 ms less). Therefore, whilst the emotion processing tasks look promising, the theory of mind tests does not seem to be effective.

Both groups were matched on both age and gender, however, it is known that social cognition can be affected by both as discussed in Chapter 3: age (Mill et al., 2009; Sullivan et al., 2007; West et al., 2012) and gender (Hoffmann et al., 2010; Kessels et al., 2014; Lee et al., 2002; Montagne et al., 2005). The results suggest that on the complex tests, neither age nor gender affected the amount of time spent looking at the target image after the probe word appeared than before. However, on the simple test, age did correlate with performance, the dwell time for the target decreased with age, and was driven by the control group; this effect was not seen in the bvFTD group. This suggests age may influence performance, and if the participants are not matched, it should be accounted for in the analysis.

6.5.1 The Complex Emotion Processing Test

From the complex results, it is clear that both groups were, on the whole, able to identify the target image that matched the probe word without being instructed to do so. Time spent looking at the target image was significantly greater than the distractor or similar images. The bvFTD group were significantly worse than the control group when comparing between the target image, but no differences were found on the distractor and similar images between the groups. This implied that the bvFTD group could do the

test, although it was to a lesser extent than the control group, suggesting that the test worked. Interestingly, performance on the target image correlated with tests measuring general intelligence and executive function, particularly inhibition, after controlling for disease severity. It is possible that the performance on the test may be due to the control group having a higher level of intelligence than the bvFTD group, and therefore it is possible that general intelligence should have been controlled for in the analysis. Further work should aim to investigate this link and see if the results are influenced by IQ.

The ROI analysis on the complex test indicated the involvement of the dorsolateral prefrontal cortex, bilaterally, on the dwell time difference score for the target image on the complex test. This is consistent with previous findings that the dorsolateral prefrontal cortex plays a central role in the processing of emotions (Golkar et al., 2012; Herrington et al., 2005; Wood & Grafman, 2003). This is also supported by work in bvFTD which demonstrates this link with facial emotion recognition tests (Bertoux, Volle, et al., 2014). The VBM analysis did not support these findings as there were no significant results. It is possible that this is due to the small sample size, and in a larger cohort these areas may have been highlighted. Nevertheless, the ROI analysis found the test does correlate to brain regions associated with processing emotions in others.

6.5.2 The Simple Emotion Processing Test

Consistent with the complex findings, the simple eye-tracking tests also suggest that both the control group, and the bvFTD group were able to complete it correctly by looking more at the target image, than at the distractor or similar images. Again, the control group did significantly better than the bvFTD group, but overall, performance was higher on this test than the complex one. This indicates that the ability to process the six standard

emotions is easier than having to process emotions that are not as well recognised. This is important as the complex test may be better at detecting presymptomatic change as it is harder, and thus could be more sensitive to subtle changes.

The time bin analysis revealed very subtle differences when comparing across the various post time periods. The control group displayed the same performance across the three interest areas in all time bins. When looking at the target interest area only across the time bins, all comparisons were significant except for when comparing between the 4 and 5 second period in which there was no significant difference between them. This suggests that the post period could be shortened to four seconds as there was no increase in difference by keeping the stimuli on the screen for the extra second. A similar pattern emerged for the bvFTD group, however there were a few differences to the control group. The bvFTD group did not look significantly more at the target than the similar image during the 1 second time period, thus suggesting the post period needs to be longer than this. Furthermore, when focusing on the target interest area only, significant differences were observed between two and three seconds but this was not seen at any higher durations than this, thus suggesting that the minimum post time for the bvFTD group would need to be at least three seconds. When comparing between the two groups for the time bin analysis the same pattern of results occurred across all of the time bins, except for over the first second bin in which there was no longer a significant difference between the two groups on the distractor item. This supports the previous within group analysis in that one second post time period would be too short. From these results, it is possible that moving forward the duration of the post period could be shortened to four seconds but it must be more than one second long to show differences between the groups. Furthermore, given that the result plateaus

out towards the longer durations, it is unlikely that a much higher increase in post duration would be beneficial for increasing dwell time for the target image in either group.

The ROI analysis was in line with the complex findings. Again, the bilateral dorsolateral prefrontal cortex was associated with the simple test performance on the target interest area, after controlling for disease severity. This implies that this simple test too, was assessing social cognition. Interestingly the right temporal lobe was associated with time spent looking at the target image as well (a trend for this was also seen on the complex test), and this region is known to be associated with empathy, a skill associated with social cognition (Rankin et al., 2006). Performance on the synonyms tests indicated that comprehension of the emotional words remains relatively intact, as on average the bvFTD group scored 23 out of 25 on the words that were presented to them. This further supports the idea that this is a social cognitive test, and not one influenced by comprehension.

6.5.3 Simple Emotions

In line with the findings found in Chapter 3, the different emotions used on the simple test were processed differently. In this chapter, control participants found it much harder to identify fearful expressions than they did any other emotions. This however, was not the case in the bvFTD individuals, as no significant differences were observed across the different emotions. When comparing performance between the groups, the bvFTD group did perform significantly worse than the control group on all emotions. Consequently, this means that all emotions are impaired for individuals with bvFTD. This claim is further supported when looking at the impact of valence by combining the positive and negative emotions together. No significant differences were found between the processing of positive vs. negative emotions, which is

converse to some of the previous literature (Fernandez-Duque et al., 2010; Kipps, Mioshi, et al., 2009; Lavenu et al., 1999), and in contrast to the performance in the control group.

6.5.4 Disease severity

Much of this work considers the impact that disease severity has on performance on this test. As an individual with bvFTD becomes more severe, the nature of the disease will of course, mean that they become worse at everything they do. To interpret the results therefore, disease severity should be held constant to see the impact the disease has on the performance, rather than the severity of the disease. It is however, interesting to note that both the simple and complex test both correlate with disease severity: the more severe the individuals symptoms are, the worse they do on the test. This again goes some way to validate the tasks, as performance declines with severity rather than remains constant, or even increases.

6.5.5 The Theory of Mind Test

The theory of mind test was unable to identify the false belief. Control participants looked at the place where the book was moved to by the girl, not where the boy would look for it, as he was unaware that it had been moved. This is disappointing as previous work has found promising results using this set up in eye-tracking tests. It is possible that the stimuli created were not realistic enough, or that because the test was instructionless, the participants were unclear what they were being asked to do – previous tests have given explicit instructions (Rubio-Fernández & Glucksberg, 2012). In order to establish whether it is the test stimuli or the lack of instructions causing the negative result, the test should be run again in a control population, but asking participants to look where they think the male character will look for the book.

6.5.6 Strengths and limitations

Despite the negative theory of mind result, both the simple and the complex test show promise; it will be very intriguing to see how they are tolerated in a presymptomatic cohort. The tests are designed to overcome many of the problems associated with standard psychometric testing. They are extremely simple to participate in and administer due to the very limited test instructions, and are relatively quick, taking approximately 10 to 15 minutes in total. The time may also be reduced if fewer trials are needed to produce similar results; future work should aim to investigate this. The tests also provide quantitative data, thus removing the problem of experimenter bias, subjective scoring, and consequently improves interrater reliability. Future work should also aim to retest the same participants on the tasks to see if they are sensitive to change over time, or if there are any practice effects in a control population. Overall the test was well tolerated by the individuals with bvFTD, despite their attentional and apathetic deficits. This is most likely because these tasks are relatively passive, and do not require a lot of active engagement with the experimenter. The bvFTD cohort used in this work however, are a relatively mild group. It is possible that those who display more severe symptoms may not be able to do the tests. That being said, the overarching aim of this work is to develop tests that are more sensitive to presymptomatic change, and therefore the target population would be younger individuals or individuals in the very early stages of the illness.

One of the biggest questions about these tests, is whether or not they are assessing one's social cognitive abilities, or measuring something else. It could be argued that they are only a measure of disease severity or intelligence, due to the correlations with those measures. The task did correlate to the DLPFC, however this region is known to be involved in both social cognition and

executive function. Future work should aim to increase the group sizes to distinguish which cognitive domains are impacting on performance.

Another concern with this work, is that the test performance did not correlate with the standard psychometric tests. It is possible that this is because these eye-tracking tasks are more sensitive at detecting deficits in performance than the standard tests are, which of course, is the reason for developing them. This was seen in Primativo et al. (2017), in which the novel eye-tracking test was able to identify more individuals as having deficits in their executive function abilities, than the standard pen and paper test was. Future work should analyse each individuals performance on both the simple eye-tracking test and the FER test, in a similar analysis to Primativo et al. (2017), to investigate this further.

6.6 Chapter Summary

To conclude, these novel emotion processing eye-tracking tests provide exciting results which may be indicative of valuable and useful outcome measures. They suggest that instructionless eye-tracking tests are a viable tool for assessing cognition in bvFTD, and future work could aim to develop tests that tap into a multitude of cognitive process, and not social cognition alone. Whilst participants performed better on the simple tests than the complex one, it is likely that differences in the presymptomatic cohorts may be observed here. There are a variety of avenues to take this work moving forward. Analysis of the tests in a much larger population would be advantageous to assess replicability and reliability of the results. Despite the tests only being administered in individuals with bvFTD, they were initially designed to be accessible to any individual with a clinical diagnosis of FTD. Future work should therefore assess the viability of these tests in individuals with PPA as well. Finally, these tests should be tested in a presymptomatic cohort to see if they are more accurate at detecting early social cognitive change than the standard psychometric tests. If they are, they may be a useful tool in upcoming clinical trials.

CHAPTER 7: EMOTION PROCESSING EYE-TRACKING TEST IN A PRESYMPTOMATIC FTD COHORT

7.1 Chapter Overview

The work in Chapters 5 and 6 is combined in this chapter to assess the novel eye-tracking tasks in a presymptomatic cohort of FTD individuals. In this pilot, pro-saccades and anti-saccades tasks are used to measure oculomotor function and executive functioning abilities respectively. The simple and complex emotion processing tasks are used to measure social cognition. The aim of the chapter is to evaluate whether or not these tasks should be carried forward into a larger cohort of individuals at risk of FTD, in order to develop tests that may be sensitive to early presymptomatic change, of which could possibly be useful in upcoming clinical trials.

7.2 Introduction

With clinical trials for FTD on the horizon (Greaves & Rohrer, 2019), consideration for outcome measures to assess the efficacy of potential treatments is needed. The Food and Drug Association (FDA) in America, recently proposed a draft guidance for the development of treatments for Alzheimer's Disease (Centre for Drug Evaluation and Research, 2018). Despite many drugs being trialled as a treatment for AD over the past decade, so far, none have been effective, despite showing much promise in the early phase trials (Sabbagh et al., 2019). This has led to much debate over whether it is the treatments that are not effective, or if it is the outcome measures that are causing the trials to fail. In the draft guidance by the FDA they suggest a more explicit staging system: Stage 1 are for individuals who show pathophysiological changes but display no symptoms; Stage 2 includes individuals with pathophysiological changes, plus subtle changes on sensitive psychological tests; Stage 3 includes those above, in addition to functional impairment in everyday life; and Stage 4 is for individuals who have severe functional impairment and develop "overt dementia". In order to prevent the same problems occurring in FTD trials, lessons must be learnt from the work in AD. The staging criteria as outline by the FDA, is relevant to familial FTD as there are individuals who fall into the Stage 1 category if they have a known mutation in their family. Those who are on the cusp of developing symptoms with a known mutation, would fall into the Stage 2 category, however the tests being used to detect these subtle changes must be accurate, reliable and highly sensitive.

As demonstrated in Chapter 3, a current standard social cognitive test was only able to detect early presymptomatic change in the *C9orf72* mutation carriers who were within 5 years to their estimated onset (i.e. those in stage 2) It is not until the individual presents with functional and neuropsychometric

problems (i.e. Stages 3 and 4), that changes can be observed across all three of the genetic mutations using these tests (see section 3.4). This therefore indicates that the tests are not suitable outcome measures for the upcoming trials in the earlier stages of the disease. Furthermore, these tests are subject to issues that arise from standardised cognitive testing, such as poor interrater reliability resulting due to the subjective scoring of assessments. This causes problems with variability in tests results as discussed in sections 1.4.5 and 5.2.

The development of novel tests that overcome these issues are therefore crucial for treatment trials to be successful. It must be clear that the outcome measures are valid and consistent, whilst having clinical validity (Centre for Drug Evaluation and Research, 2018). The tests developed in Chapter 6 show promise. Whilst the ToM test was ineffective (the patients performed similar to controls, and the outcome was not as expected), the emotion processing tests worked. They provide a simple and quantitative analysis of emotion processing in symptomatic individuals with bvFTD. Given that the complex test was harder than the simple test, it is possible that subtle differences may be seen in presymptomatic individuals on the complex task.

The aim of this chapter is therefore to analyse the performance on the simple and complex emotion processing eye-tracking tests, to see if they can identify changes in the processing of emotions in presymptomatic mutation carriers. Their performance will be compared to a control population made up of age matched non-mutation carriers and healthy volunteers. The focus will be in individuals under the age of 50, as this is the expected time in which they will fall into stages 1 or 2, given the average age of onset in the genetic conditions (see section 1.3). Basic oculomotor function will also be assessed using the pro-saccade test. Executive function abilities will also be monitored using the anti-saccade test, as some studies have already identified changes in executive

function in presymptomatic cohorts (Barandiaran et al., 2012; Dopper et al., 2013; Papma et al., 2017).

7.3 Methods

7.3.1 Participants

29 participants were recruited from the GENFI project. After the data was blinded, and genetic status added to the data, 19 individuals were positive for one of the three main genetic mutations (*C9orf72*, *GRN* or *MAPT*). The remaining 10 were found to be negative for any of the three genes, and therefore referred to as non-mutation carriers. As there was an imbalance between the numbers of mutation carriers and non-carriers, 11 age-matched healthy controls were recruited into the study to give a total of 21 control participants.

7.3.2 Procedure

The same equipment and set up was used as in Chapter 5 and Chapter 6, and described in section 4.3.3 and 4.3.4. The experiment took a maximum of 20 minutes to complete. Participants completed the pro-saccade and anti-saccade tasks as described in section 4.4.2, as well as the simple and complex emotion processing tasks as described in sections 4.3 and 4.4.3.

7.3.1 Statistical analysis

Demographic and psychometric data

As the data was blinded for this cohort, in order to maintain anonymity the demographic and psychometric information for each individual was removed.

Task analysis

The pro-saccade, anti-saccade, simple and complex emotion processing tests were analysed in the same way as they were in Chapters 5 and 6 (see sections 2.7, 5.4.5 and 6.3.4). In this chapter however, the groups were mutation positive carriers and mutation negative carriers (controls). The analysis was further split by genetic mutation for the positive mutation carriers (*C9orf72*, *GRN* and *MAPT*) for the simple and complex emotion processing analysis. The only difference in this analysis however, was that the data was normally distributed for the simple and complex eye tracking tests, and so bootstrapping was not performed. Age and gender could not be included in any of the models as the demographic information was not available due to the small sample size, and maintaining anonymity.

7.4 Results

7.4.1 Demographic data

In order to ensure that the genetic status of the individuals remained unknown, very few demographic details were available after the genetic statuses were added to the data. Individuals were placed into age groups: 20s (20.0-29.9), 30s (30.0-39.9), 40s (40.0-40.9) and 50s (50.0-59.9). Using these age bins to calculate the average age, the mutations carriers had a mean age of 33.15 (SD: 5.82) and the control group had a mean age of 34.28 (SD: 7.46). When breaking down the carrier group into the individual mutations, the mean ages were as follows: *C9orf72* = 32.5 (SD: 4.63); *GRN* = 34.0 (8.94) and *MAPT* = 33.3 (5.16).

Table 7-1: The distribution of individuals across the age groups for controls and mutation carriers, as well as splitting mutation carriers by genetic group.

	Age				
	20's	30's	40's	50's	Total
Controls	1	12	6	2	21
Carriers	0	14	4	1	19
C9orf72	0	6	2	0	8
GRN	0	4	0	1	5
MAPT	0	4	2	0	6

7.4.2 Pro-saccades

There were no significant differences observed between the control group and the mutation carriers on any of the pro-saccade measures (see Table 7-2 and *Figure 7-1*).

7.4.3 Anti-saccades

Significant differences were observed between the control and carrier group on the correct number of anti-saccades made in the vertical condition; the carrier group had significantly less correct anti-saccades than the control group (see Table 7-2 and *Figure 7-2*).

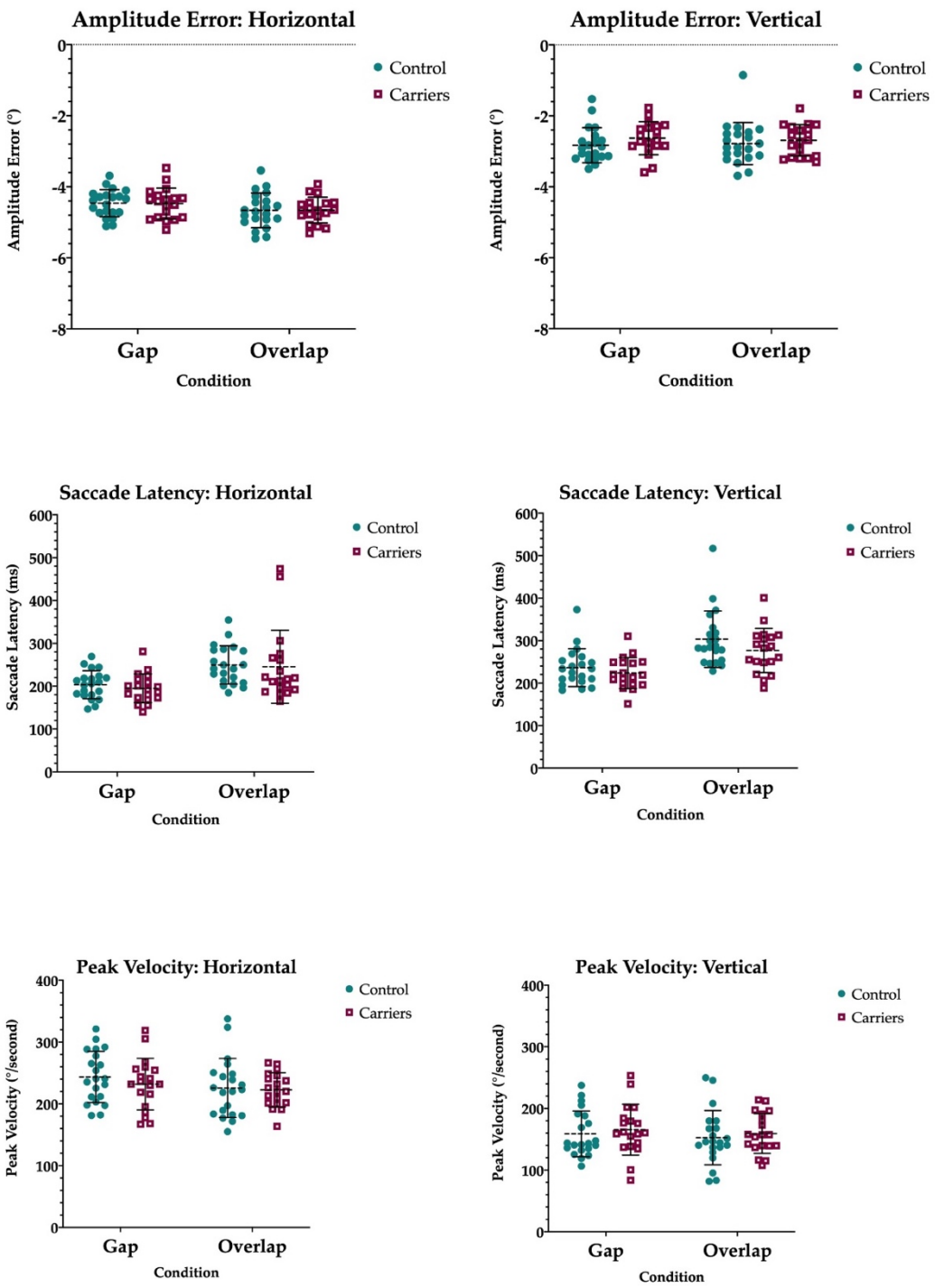

Figure 7-1: Performance on the pro-saccade tests in the control and carrier groups. Whiskers represent standard deviation.

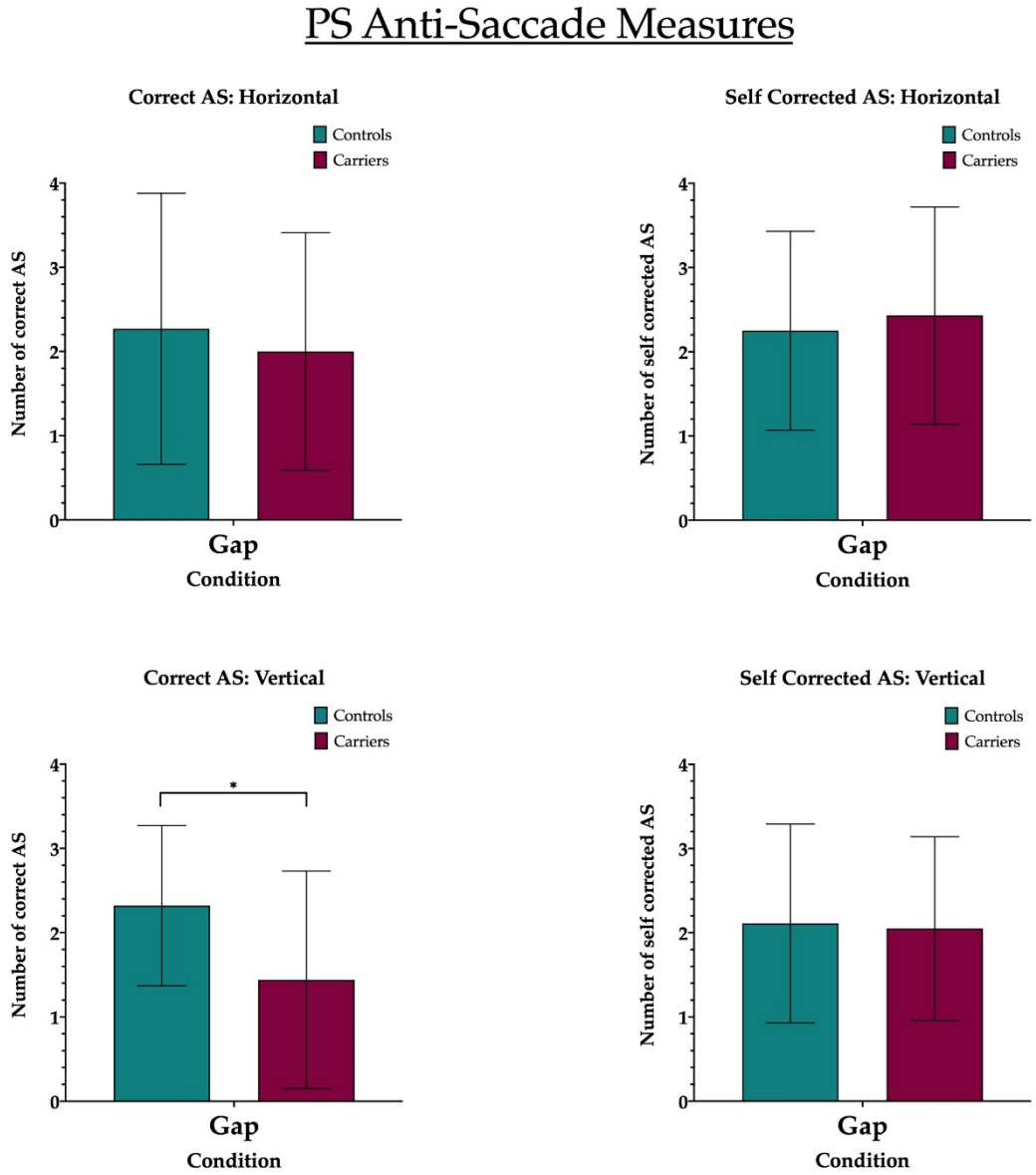

Figure 7-2: Performance on the anti-saccade test in the control and mutation carrier groups. Whiskers represent standard deviation.

Table 7-2: Mean scores and SD between the control and mutation carrier groups on the pro-saccade and anti-saccade tests, with significance level and confidence intervals.

Test	Analysis	Direction	Gap / Overlap	Visual angle	Control		Carriers		p =	Confidence intervals	
Pro-Saccades	Amplitude error	Horizontal	Gap	8	-4.46	0.38	-4.47	0.44	0.996	-0.26	0.26
		Horizontal	Overlap	8	-4.67	0.49	-4.66	0.36	0.992	-0.27	0.27
		Vertical	Gap	5	-2.83	0.49	-2.63	0.47	0.148	-0.08	0.50
		Vertical	Overlap	5	-2.78	0.60	-2.69	0.44	0.571	-0.24	0.42
	Saccade latency	Horizontal	Gap	8	200.19	29.85	195.00	33.55	0.313	-0.93	0.31
		Horizontal	Overlap	8	247.18	44.57	245.47	85.33	0.770	-1.42	1.06
		Vertical	Gap	5	229.42	32.48	223.54	363.60	0.481	-1.00	0.48
		Vertical	Overlap	5	292.70	45.93	276.69	52.01	0.297	-1.38	0.43
	Peak velocity	Horizontal	Gap	8	243.51	41.45	232.00	41.81	0.403	-35.52	14.59
		Horizontal	Overlap	8	195.18	26.09	191.59	31.42	0.806	-23.74	18.57
		Vertical	Gap	5	158.81	37.07	165.55	41.33	0.756	-22.83	16..70
		Vertical	Overlap	5	152.68	44.05	159.31	32.24	0.769	-14.85	19.93
Anti-Saccades	Number of correct anti-saccades	Horizontal	Gap	8	2.27	1.61	2.00	1.41	0.532	-1.15	0.64
		Vertical	Gap	5	**2.32**	**0.95**	**1.44**	**1.29**	**0.016**	**-1.60**	**-0.16**
	Number of self-corrected anti-saccades	Horizontal	Gap	8	2.25	1.18	2.43	1.09	0.666	-0.63	0.98
		Vertical	Gap	5	2.11	1.18	2.05	1.09	0.346	-0.42	1.20

7.4.4 Complex

Figure 7-3 displays the mean dwell time difference scores for the control group and the mutation carriers on the complex emotion processing test. Both the control group and the mutation carriers all looked significantly more at the target interest area, than the distractor or similar items; this was also the case when the mutation carriers were split by mutation (see Table 7-3).

When comparing performance on the complex emotion processing tests between the two groups, no significant differences were found in the amount of time spent looking at any of the interest areas (see Table 7-4).

The mean scores and standard deviations for each of the genetic mutations are displayed in Table 7-5, and visualised in *Figure 7-4*. No significant differences were found between any of the mutation groups compared to the controls on the target (Table 7-6) or similar (Table 7-7) interest areas. For the distractor interest areas (Table 7-8), the *GRN* mutation carriers performed significantly better than controls and *C9orf72* mutation carriers.

Table 7-3: Within group differences for each of the interest areas on the complex EP test.

		Mean difference	*p* =	CI	
Controls	Target vs Positive	-22%	**<0.001**	**-0.25**	**-0.19**
	Target vs Negative	-22%	**<0.001**	**-0.25**	**-0.19**
	Positive vs negative	0%	0.777	-0.03	0.03
Carriers	Target vs Positive	-24%	**<0.001**	**-0.27**	**-0.21**
	Target vs Negative	-24%	**<0.001**	**-0.27**	**-0.21**
	Positive vs negative	0%	0.765	-0.03	0.04
C9orf72	Target vs Positive	**-20.0**	**<0.001**	**-0.25**	**-0.15**
	Target vs Negative	**-18.5**	**<0.001**	**-0.23**	**-0.14**
	Positive vs Negative	0.0	0.528	-0.03	0.06
GRN	Target vs Positive	**-28.5**	**<0.001**	**-0.35**	**-0.22**
	Target vs Negative	**-31.6**	**<0.001**	**-0.38**	**-0.25**
	Positive vs Negative	-3.04	0.335	-0.09	0.03
MAPT	Target vs Positive	**-26.5**	**<0.001**	**-0.32**	**-0.21**
	Target vs Negative	**-24.4**	**<0.001**	**-0.30**	**-0.19**
	Positive vs Negative	2.1	0.464	-0.04	0.07

Table 7-4: Mean scores and standard deviations for the control vs. mutation carrier groups with *p* values and confidence intervals for the three interest areas on the complex emotion EP test.

	Control		Carriers		*p* =	CI	
	Mean	SD	Mean	SD			
Distractor	-4.0%	13%	-5.4%	14%	0.327	-0.01	0.04
Similar	-3.6%	19%	-5.8%	20%	0.203	-0.01	0.06
Target	18.0%	27%	18.4%	29%	0.879	-0.06	0.05

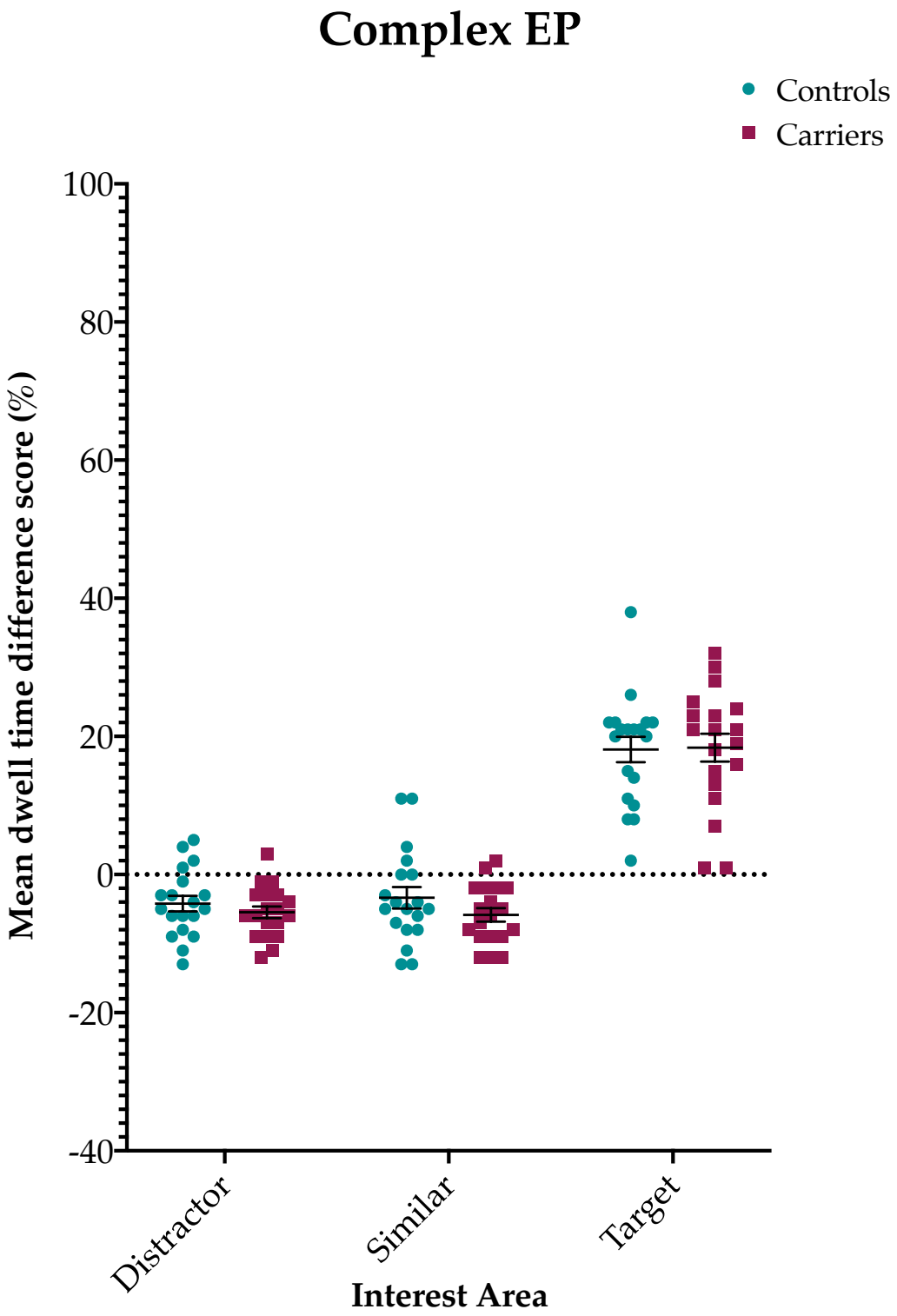

Figure 7-3: Summarises the control and mutation carrier performance on the complex EP test for each of the interest areas. Whiskers display the standard error.

Table 7-5: Mean scores and standard deviations for the control group and each of the carrier groups split by genetic mutation.

	Controls		*C9orf72*		*GRN*		*MAPT*	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Distractor	-4.0%	13%	-3.6%	14%	-8.2%	12%	-5.4%	14%
Similar	-3.6%	19%	-5.0%	21%	-5.2%	20%	-4.5%	19%
Target	18.0%	27%	14.9%	26%	23.3%	31%	19.0%	30%

Table 7-6: P values and confidence intervals for the target interest area between the carrier groups and the controls on the complex EP test.

	Complex: Target IA			
	Control	*C9orf72*	*GRN*	*MAPT*
Control		0.359 -0.10 0.04	0.186 -0.03 0.13	0.790 -0.06 0.08
C9orf72			0.065 -0.01 0.17	0.344 -0.04 0.13
GRN				0.373 -0.13 0.03

Table 7-7: P values and confidence intervals for the similar interest area between the carrier groups and the controls on the complex EP test.

	Complex: Similar IA			
	Control	*C9orf72*	*GRN*	*MAPT*
Control		0.528 -0.06 0.03	0.557 -0.07 0.04	0.123 -0.09 0.01
C9orf72			0.959 -0.06 0.06	0.397 -0.08 0.03
GRN				0.480 -0.09 0.04

Table 7-8: P values and confidence intervals for the distractor interest areas between the carrier groups and the controls on the complex EP test.

	Complex: Distractor IA			
	Control	*C9orf72*	*GRN*	*MAPT*
Control		0.789 -0.03 0.04	**0.039** **-0.08 -0.00**	0.460 -0.05 0.02
C9orf72			**0.044** **-0.09 -0.00**	0.395 -0.04 0.03
GRN				0.255 -0.02 0.08

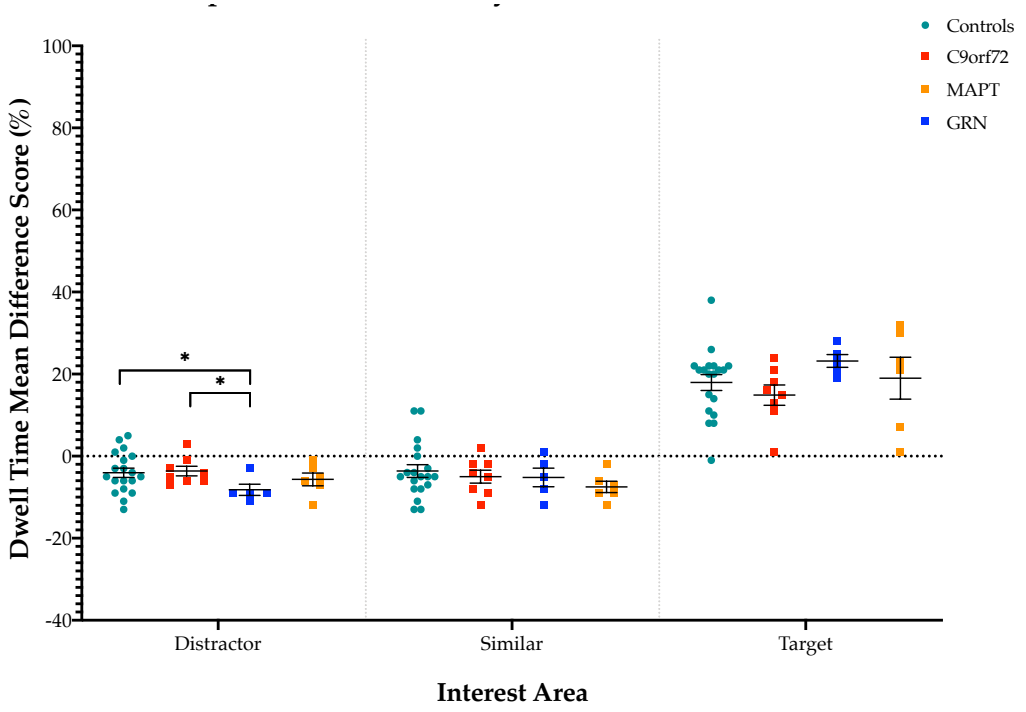

Figure 7-4: Summary of the mean group performances across the genetic mutations and the control group for each of the interest areas. Whiskers represent the standard error.

7.4.5 Simple

Performance in the controls and mutation carriers is summarised in *Figure 7-5*. All groups (including the breakdown across the genetic mutations) looked significantly more at the target interest area than they did at the similar or distractor interest areas; this was also the case for each of the individual genetic mutations as well (see Table 7-9).

No significant differences were observed on the amount of time spent looking at any of the interest areas between the control and mutation carrier group (see Table 7-10).

The mean scores and standard deviations for each of the genetic mutations are displayed in Table 7-11, and visualised in *Figure 7-6*. No significant differences were found between any of the mutation groups compared to the controls on the target (Table 7-12), similar (Table 7-13) or distractor (Table 7-14) interest areas.

Table 7-9: Within group differences on the simple EP test across the interest areas.

		Mean difference	*p* =	CI	
Controls	Target vs Positive	**-53%**	**<0.001**	**-0.57**	**-0.50**
	Target vs Negative	**-54%**	**< 0.001**	**-0.58**	**-0.51**
	Positive vs Negative	-1%	0.466	-0.05	0.02
Carriers	Target vs Positive	**-59%**	**<0.001**	**-0.61**	**-0.56**
	Target vs Negative	**-60%**	**<0.001**	**-0.62**	**-0.57**
	Positive vs Negative	-1%	0.541	-0.03	0.02
C9orf72	Target vs Positive	**-57.2**	**<0.001**	**-0.61**	**-0.53**
	Target vs Negative	**-60.7**	**<0.001**	**-0.65**	**-0.57**
	Positive vs Negative	*-3.5*	*0.089*	*-0.08*	*0.01*
GRN	Target vs Positive	**-64.8**	**<0.001**	**-0.69**	**-0.60**
	Target vs Negative	**-63.9**	**<0.001**	**-0.68**	**-0.59**
	Positive vs Negative	0.90	0.690	-0.36	0.05
MAPT	Target vs Positive	**-55.8**	**<0.001**	**-0.60**	**-0.51**
	Target vs Negative	**-54.8**	**<0.001**	**-0.59**	**-0.50**
	Positive vs Negative	1.0	0.671	-0.04	0.06

Table 7-10: Between group comparisons on each of the interest areas on the simple EP test.

	Controls		Carriers		*p* =	CI	
	Mean	SD	Mean	SD			
Distractor	-13.9%	10.8%	-14.9%	11%	0.630	-0.05	0.03
Similar	-11.6%	15.8%	-14.1%	14%	0.159	-0.06	0.01
Target	39.6%	29.2%	44.8%	27%	0.326	-0.05	0.16

Table 7-11: Mean scores for the control group and the individual genetic groups for the mean dwell time difference across the interest areas.

	Controls		*C9orf72*		*GRN*		*MAPT*	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Distractor	-14.2%	11%	-15.9%	12%	-14.8%	10%	-13.6%	12%
Similar	-12.9%	17%	-12.4%	15%	-15.7%	13%	-14.6%	13%
Target	40.2%	28%	44.8%	27%	49.1%	25%	41.2%	30%

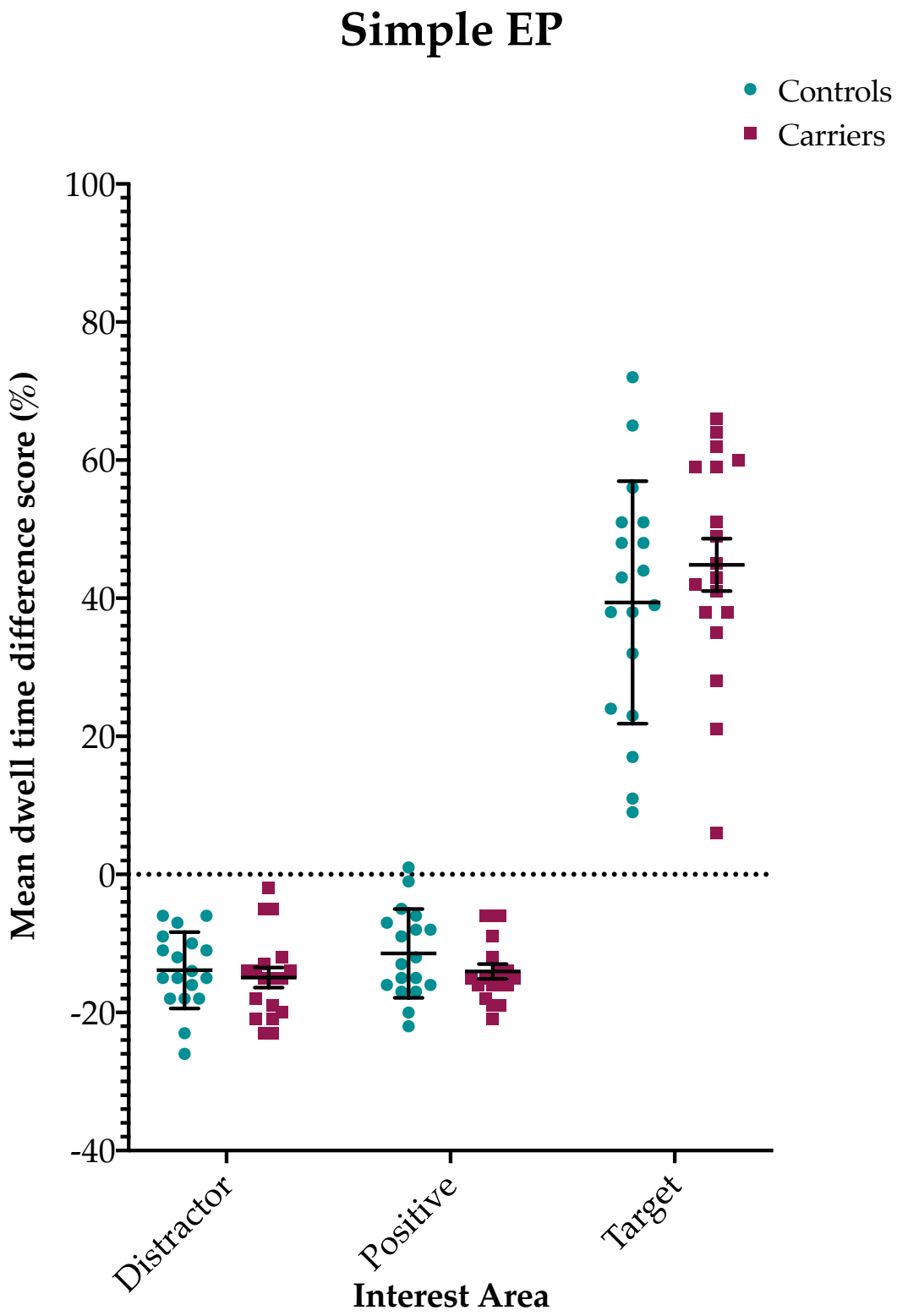

Figure 7-5: Summarises the control and mutation carrier performance on the simple EP test for each of the interest areas. Whiskers display the standard error.

Table 7-12: P values and confidence intervals for the target interest area between the carrier groups and the controls on the simple EP test.

	Simple: Target IA			
	Control	*C9orf72*	*GRN*	*MAPT*
Control		0.463 -0.09 0.19	0.424 -0.06 0.26	0.808 -0.13 0.17
C9orf72			0.651 -0.14 0.23	0.703 -0.21 0.14
GRN				0.431 -0.27 0.12

Table 7-13: P values and confidence intervals for the similar interest area between the carrier groups and the controls on the simple EP test.

	Simple: Similar IA			
	Control	*C9orf72*	*GRN*	*MAPT*
Control		0.707 -0.06 0.04	0.119 -0.10 0.01	0.220 -0.08 0.02
C9orf72			0.289 -0.10 0.03	0.459 -0.08 0.04
GRN				0.733 -0.05 0.08

Table 7-14: P values and confidence intervals for the distractor interest area between the carrier groups and the controls on the simple EP test.

	Simple: Distractor IA			
	Control	*C9orf72*	*GRN*	*MAPT*
Control		0.421 -0.07 0.03	0.746 -0.07 0.05	0.882 -0.05 0.06
C9orf72			0.740 -0.05 0.08	0.442 -0.04 0.09
GRN				0.699 -0.05 0.08

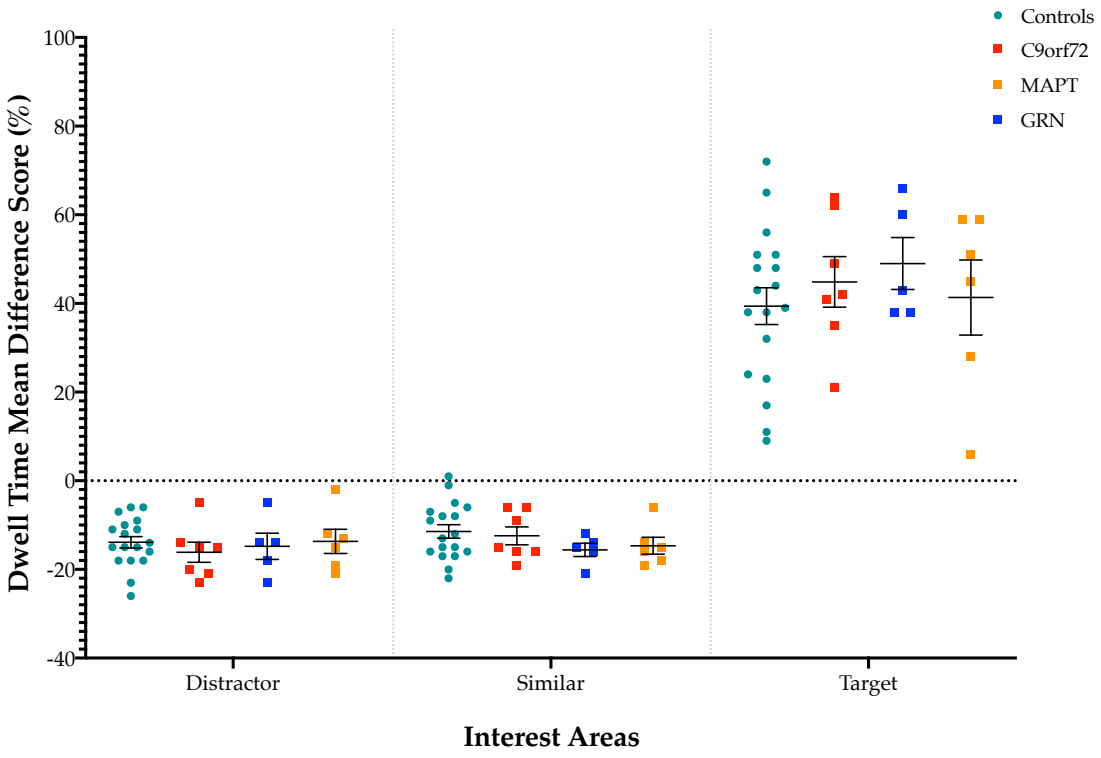

Figure 7-6: Summary of the mean group performances across the genetic mutations and the control group for each of the interest areas on the simple EP test. Whiskers represent the standard error.

Simple Emotions

No differences were observed between the control group and the mutation carriers on each of the individual emotions (see Table 7-15). However different within group patterns did emerge. The control group performed best on trials with happy expressions when compared to all other emotions (see Table 7-16). In contrast, the mutation carriers did score higher on happiness as well, but this was only significantly different to items of fear, with a trend towards significance on items of disgust (see Table 7-17).

Table 7-15: Between group differences on the individual emotions on the simple EP test.

	Control		Carriers		*p* value	CI	
	Mean	SD	Mean	SD			
Happy	49.2%	27.4%	52.3%	31.5%	0.630	-0.10	0.16
Surprise	35.8%	27.6%	41.3%	26.4%	0.400	-0.08	0.19
Disgust	33.6%	29.3%	42.0%	27.5%	0.354	-0.07	0.19
Fear	37.5%	30.5%	39.7%	27.0%	0.564	-0.09	0.16
Anger	40.0%	32.0%	47.3%	24.1%	0.259	-0.05	0.20
Sadness	40.3%	26.5%	45.3%	26.0%	0.400	-0.07	0.18

Table 7-16: Within group differences on the different emotions on the simple EP test for the control group.

	Controls					
	Anger	Disgust	Fear	Happy	Sadness	Surprise
Anger		0.710 - 0.10 0.07	0.159 - 0.15 0.03	**0.043** **0.00 0.18**	0.974 - 0.09 0.09	0.321 - 0.14 0.05
Disgust			0.301 - 0.14 0.04	**0.017** **0.02 0.20**	0.736 - 0.07 0.11	0.529 - 0.12 0.06
Fear				**0.001** **0.07 0.45**	0.171 - 0.03 0.15	0.706 - 0.07 0.11
Happy					**0.041** **-** **0.18 0.00**	**0.003** **- -** **0.23 0.05**
Sadness						0.339 - 0.14 0.05

Table 7-17: Within group differences on the different emotions on the simple EP test for the mutation carriers.

	Carriers					
	Anger	Disgust	Fear	Happy	Sadness	Surprise
Anger		0.347 - 0.16 0.06	0.172 - 0.19 0.03	0.374 - 0.06 0.16	0.711 - 0.13 0.09	0.330 - 0.18 0.06
Disgust			0.668 - 0.13 0.09	*0.067* - *0.01 0.21*	0.571 - 0.08 0.14	0.916 - 0.13 0.11
Fear				**0.024** **0.02 0.24**	0.320 - 0.05 0.17	0.771 - 0.10 0.14
Happy					0.208 - 0.18 0.04	0.072 - 0.23 0.01
Sadness						0.529 - 0.16 0.08

7.5 Discussion

This chapter aimed to assess the two novel emotion processing tests that were developed in Chapter 4 and tested in Chapter 6, in a presymptomatic cohort of individuals at risk of developing FTD. In order to ensure that the participants eye-movements were not affecting performance on the test, individuals completed the pro-saccade test. The anti-saccade test was also administered to assess executive function abilities as these have been found to be affected in presymptomatic individuals previously.

Neither the control group nor the mutation carrier group displayed any problems with their eye movements as measured using the pro-saccade test. There were however, deficits observed on the anti-saccade test, as the mutation carrier group had fewer correct anti-saccades in the vertical condition than the control group. When comparing the performance on the target interest areas for both the complex and simple emotion processing tests, no significant differences emerged between the control group and the

mutation carrier group, or between the control group and the different genetic mutations. Nevertheless, the *C9orf72* mutation carriers did have a lower mean dwell time on the target than the other groups on the complex test. These results are encouraging as the anti-saccade test was able to identify changes in the presymptomatic cohort, and the complex test suggests that the *C9orf72* group may be impaired compared to the other genetic groups. This is the first eye-tracking test to be able to detect presymptomatic differences.

As previously mentioned, there is evidence to suggest that there are executive function deficits in presymptomatic *C9orf72*, *GRN* and *MAPT* carriers (Barandiaran et al., 2012; Dopper et al., 2013; Papma et al., 2017). So far, deficits in social cognition have been established as a unique cognitive characteristic of presymptomatic *MAPT* mutation carriers (Jiskoot et al., 2016; Jiskoot et al., 2018) but not the other two groups. However, the results of Chapter 3, demonstrated deficits in social cognition on the FER test in the late *C9orf72* mutation carriers. In all of these studies however, the average age of the participants ranged from 42-56 years of age, and deficits were typically found in the older mutation carriers (Dopper et al., 2013). Despite having to group individuals into age categories to ensure the genetic statuses were not revealed in this work, the average age was lower than this (the ages provided only act as a guide due to grouping the ages into categories, however only three out of the eighteen carriers were in their 50's, suggesting a slightly younger cohort). This is noteworthy as previous work has been shown to only detect differences across tests of executive function in presymptomatic mutation carriers around 5 years prior to their estimated onset (Rohrer et al., 2015). This is similar in the studies above and is supported by the findings in Chapter 3 using the standard Mini-SEA. Therefore, these novel eye-tracking measures may be more sensitive than the standard tests.

As previously noted in section 6.5, the vertical anti-saccade test is a much harder condition than the horizontal test. It is possible that this is why there is a decreased number of correct anti-saccades in the carrier group as a whole. This test correlated with frontal brain regions in Chapter 5, including the orbitofrontal cortex. These are known areas that correlate with executive function and inhibitory skills (Jurado & Rosselli, 2007), and in addition, these areas are known to be affected early on in presymptomatic FTD carriers across all three of the genetic mutations (Cash et al., 2018). This therefore may explain why a lower number of anti-saccades are being correctly identified.

The lower mean performance in the *C9orf72* mutation carriers on the complex emotion processing test, may be a consequence of early atrophy in regions such as the thalamus and cerebellum (Bocchetta et al., 2016; Cash et al., 2018) and these regions have been associated with problems in social cognition (Van Overwalle, Baetens, Marien, & Vandekerckhove, 2014; Van Overwalle, D'Aes, & Marien, 2015; Wilkos, Brown, Slawinska, & Kucharska, 2015). The dorsolateral prefrontal cortex was also significantly associated with test performance in Chapter 6. This is typically not a region known to be affected early on in *C9orf72*. However, given that the connections of the dorsolateral prefrontal cortex extend to multiple different structures, such as the thalamus, hippocampus, and insula which are all regions known to be affected early in *C9orf72* (Rohrer et al., 2015), and they are all known to be involved in social cognition as well (Gallese, Keysers, & Rizzolatti, 2004; Laurita & Spreng, 2017; Wilkos et al., 2015), this may be why the association is found here. The lack of findings on the simple emotion processing test was to be expected. The work in Chapter 6 highlighted that it was a much easier test than the complex one, hence less likely to be able to identify presymptomatic changes.

Whilst this study provides promising results as to the viability of eye-tracking in identifying early changes in presymptomatic FTD individuals, there are a

number of limitations. Firstly, due to sample size being small and from a local cohort, the demographic information was not provided to ensure that the genetic statuses of the individuals were not revealed. This is an issue as it has not been possible to ascertain the exact mean age of the groups, or to provide some understanding about any symptoms they may be experiencing. Secondly, due to maintaining the anonymity of the presymptomatic data, psychometric and imaging data were also not available at present. Once this information is gained, it will provide some understanding about the neuroanatomical mechanisms influencing test performance, particularly on the anti-saccade and complex test. Thirdly, when looking at the mean ages by using the age categories, it suggests that the *C9orf72* group is slightly older than the other two genetic groups. It is possible that this age is influencing the deficit in the *C9orf72* mutation carriers. Correlational analysis using the actual ages of participants may be able to help identify if older individuals with *GRN* and *MAPT* mutations may perform worse around this age as well.

Despite these limitations, the tests are very promising and has a number of advantages. The tests are relatively short and easy to administer, as mentioned in Chapter 6. Due to the increased experience with the work in Chapter 6, less data was lost throughout this work in Chapter 7, and the software has become much more manageable and time efficient. This increased knowledge has also indicated that other analyses may be possible to carry out on this work given the vast amount of data that is collected at the time of testing. While the main focus of the work so far has been looking at the dwell time on each of the interest areas in the emotion processing tests, a variety of other analyses can be completed, including looking at the order of saccades made, time taken to reach the correct image, or the number of saccades made in a particular area, i.e. the eye or mouth region on the simple test. Different analyses such as these may be able to detect more subtle

differences; future work could explore these. By increasing the sample size, having access to the demographic, imaging and psychometric data, and carrying out the tests on a longitudinal basis, it is possible that they will be able to detect changes in executive function and emotion processing in presymptomatic individuals across all three mutations. This work therefore highlights the beneficial use of eye-tracking as a more reliable measure of assessing psychological performance. Other tests, similar in design to the emotion processing and anti-saccade tests but assessing different aspects of cognition, would be highly valuable as well as we move towards assessing the efficacy of treatments in clinical trials, and so additional tests should be designed.

7.6 Chapter summary

To conclude, the novel complex emotion processing test was able to identify lower performance in the *C9orf72* presymptomatic mutation carriers when compared to the control group. Significant deficits in executive function were also identified in all mutation carriers when measuring the number of correct anti-saccades made in the vertical condition relative to controls. This suggests that eye-tracking tests such as these, may be sensitive to early presymptomatic change, however further validation and development of the tests should be carried out to assess their viability as cognitive markers in any upcoming clinical trials.

CHAPTER 8: DISCUSSION

8.1 Summary

In this thesis, I have aimed to develop novel eye-tracking tests that assess social cognition in both familial and sporadic FTD, with specific focus on bvFTD due to the social difficulties associated with the condition. The main objective was to develop tests that overcome the problems associated with standard pen and paper psychometric tests, and improve the reliability of psychometric measures through eye-tracking.

Chapter 3 highlighted the need for alternative tests assessing social cognition in presymptomatic cohorts. The mini-SEA was able to identify poorer social cognitive skills in symptomatic individuals when compared to controls, but only the late *C9orf72* mutation carriers performed significantly worse than the control group when investigating the presymptomatic individuals. The decrease in performance correlated with known regions associated with emotion processing and theory of mind, and made up a basal ganglia-orbitofrontal-insula network across all three genetic mutations, in both presymptomatic and symptomatic individuals. The test however, was not able to distinguish between any of the other genetic mutations, or identify early changes in the presymptomatic cohort overall. This suggests that alternative measures are required if they are to be used as outcome measures in clinical trials.

The development of the novel tests was outlined in Chapter 4. The initial test design was taken from the Reading the Mind in the Eyes Test which is a test that is commonly used in the symptomatic bvFTD literature. I wanted to design the novel tests so that they were accessible across the FTD spectrum, not just bvFTD, and overcome some of the problems associated with pen and

paper tests, for example, reducing the instructions required. Further inspiration for the use of an instructionless eye-tracking test came from the work by Primativo et al. (2017). This chapter therefore outlined the process of developing the novel tests. It outlines the pilot work at the Science Museum, which tested the viability of instructionless eye-tracking tests, and the analysis of the data.

From Chapter 5 onwards, the aim of the work was to assess how practical the novel tests were. Chapter 5 specifically investigated the oculomotor functioning in individuals with bvFTD. The previous literature provided conflicting information as to the functioning of the eyes in bvFTD, and so the four oculomotor tests in Chapter 5, were used to assess whether performance on the rest of the tasks would be compromised by deficits in oculomotor functioning. Overall, individuals with bvFTD did not have any trouble moving their eyes towards stimuli on the screen. There was a decrease in peak velocity and a greater amplitude error in the bvFTD individuals, however this was only in the most difficult condition, and is not something that was replicated in the other tests. In addition, the smooth pursuit of a target was not affected in the bvFTD group; however, problems were observed on the ability to fixate on a target. It is likely that this is a consequence of attentional and inhibitory problems associated with the condition. Problems with executive function were also identified in this chapter, as highlighted by the anti-saccade test; performance correlated with psychometric measures and anatomical regions associated with executive function.

The next chapter tested the novel social cognitive tests in symptomatic cases of bvFTD relative to controls. It was clear that both groups were able to complete the complex and the simple emotion processing tests, as they looked significantly more at the target interest area. However, the bvFTD group looked significantly less at the target, in both tests, than the control group did.

It was also clear, that the complex test was much harder than the simple test; the percentage of time spent looking at the target was considerably lower than it was for the simple test for both groups. Performance on both test correlated with the dorsolateral prefrontal cortex, a region known to be associated with social cognitive processing. Unfortunately, the theory of mind test did not work, with the control group not performing the test correctly; there was also no differences observed between the groups. This work in Chapter 6 not only suggests that the emotion processing tests have worked, but also that eye-tracking is a viable tool in bvFTD, as the individuals with bvFTD understood and completed the test – just to a lesser extent than the controls. The lack of finding in the ToM test however, highlights the importance of test design.

Chapter 7 is the final chapter, and aimed to assess the sensitivity of the two emotion processing tests in a presymptomatic cohort. Unfortunately, neither test was able to detect any significant differences between the control group and the mutation carriers, even when split by genetic mutation. When looking at the mean scores, there did appear to be a lower performance in the *C9orf72* mutation carriers on the complex test. This does provide some promise for the tests in the future. A larger sample, with access to the demographic, psychometric, and imaging data would be beneficial for taking these tests forward. Interestingly, the anti-saccade test was able to detect problems with executive functions in the presymptomatic mutation carriers. This is encouraging as subtle changes are able to be identified, and suggests that eye-tracking could be the tool that is more sensitive to monitoring presymptomatic change. Alternative eye-tracking test should be designed to investigate this.

8.2 Clinical implications and relevance of this work

FTD is a devastating illness and one that not only affects the individual, but their families, friends and loved ones too. The impact of the social cognitive deficits makes the maintenance of relationships extremely difficult, and can cause the family and friends to feel as if the individual in front of them, is not one they once knew. This work helps to identify the types of social problems that someone with FTD might have, and builds upon the extensive work aiming to identify the mechanism that cause the breakdown of these social abilities which leads to this change in personality. Chapters 3 and 6, highlights that in symptomatic bvFTD, both the ability to understand the emotions in others, and to be able to detect inconvenience's in social situations diminishes, thus explaining some of the blunted behaviour that is often observed. This work however, goes beyond the current work, as the test is specifically designed with the FTD cohort in mind. For research purposes, it is easy to administer, and no formal psychology training is required. Due to the qualitative nature of the test, interrater reliability is improved and consistent results will occur, irrelevant of experimenter bias. Furthermore, it is clear that the development of novel tests such as these are applicable, and measure the desired outcome. As a result, this work could help to reduce patient distress during psychometric testing in both a clinical and experimental setting. It may help with the diagnostic process, as it is possibly more sensitive to early changes than the standard tests. Furthermore, it also has the potential to discriminate between different neurodegenerative and psychiatric conditions, such as AD and schizophrenia, thus arriving at the correct diagnosis quicker, but further work needs to be completed to investigate this. Once a diagnosis has been given, it may also help with the clinical prognosis of the patient, as the novel tests removes individuals from scoring at floor. This is beneficial as once individuals are no longer able to complete the standard psychometric

tests, they often lose contact with the clinic. Test such as these may be able to help maintain contact with the clinician for longer, as they will be able to complete the tests. This may also mean that patients are able to enter clinical trials at a later stage in the illness, as they are still able to monitor disease progression, where they once would not have been able to do.

The Mini-SEA has never been used before to assess the social cognitive skills of presymptomatic FTD individuals. However, the results reveal that it may not be a useful outcome measure in upcoming clinical trials, as it was only able to detect presymptomatic change in *C9orf72* mutation carriers that were within 5 years of their estimated symptom onset. This is extremely useful to know, as the selection of psychometric markers, as discussed in the FDA guidance, is crucial in determining if a potential therapeutic treatment is effective or not. The wrong marker could cause the trial to fail. Unfortunately, despite much promise of the emotion processing eye-tracking tests in Chapter 6, they too were unable to detect any presymptomatic change. However, as a consequence of measuring oculomotor function in Chapter 5, an interesting finding emerged on the anti-saccade test in the presymptomatic cohort. Executive function skills were lower in the presymptomatic group than the control group. This therefore emphasises that eye-tracking is a viable tool in detecting presymptomatic change; it is perhaps that the emotion processing test is not the correct design for this. Consequently, pharmaceutical companies should consider eye-tracking as an outcome measure, but caution should be applied as to the design of the chosen test.

The work in Chapter 5 focusing on oculomotor functioning in sporadic bvFTD, highlighted a noteworthy finding that the previous literature had not covered. The ability to fixate on specific targets was impaired in bvFTD when using the eye-tracking tests; there was an increase in the number of square wave jerks made, and the maximum period of fixation was shorter. There was

also a trend towards a larger number of intrusive saccades occurring. It is likely that this is a consequence of attentional and inhibitory problems that occur as part of the condition, which is supported by the anatomical findings, but it is unclear what impact this may have on the individual's everyday life; future work should aim to investigate this.

8.3 Limitations and future work

There are a number of limitations to consider when evaluating the work in this thesis. Whilst aiming to overcome many of the problems associated with the investigation of social cognition in FTD, a number of gaps remain.

8.3.1 Chapter 3

It is often reported by carers, that social cognitive problems are one of the earliest changes that they notice (Woollacott & Rohrer, 2016). This leads to the question of why changes were only observed in the *C9orf72* late presymptomatic cases and not in the other two late presymptomatic groups. It is possible that the tasks are not sensitive enough to detect these subtle changes, but it also could be due to a number of limitations with the methodology of the work in this chapter.

Firstly, despite the nature of the GENFI project increasing group numbers to much larger than what has previously been studied cross-sectionally, the sample size was still relatively small in some of the groups, particularly the *MAPT* mutation group which had around half the sample size of the other two genetic groups. This makes it difficult to draw conclusions about the results as they are not all equally matched. As the GENFI cohort grows it is likely that it will be possible to study these groups in more detail, and particularly understand their performance longitudinally over time.

Secondly, the groups were split into the early and late presymptomatic groups using their estimated years to symptom onset. This is calculated by subtracting the individual's age away from the mean age at onset in the family. This was noted to be problematic in a recent study exploring the relationship between individual and mean family age at onset of symptoms, where it was shown that while the correlation between these two was statistically significant in all three genetic mutations, it was found to be relatively weak in the *C9orf72* and *GRN* mutation carriers (*C9orf72:* r = 0.36; *GRN*: r = 0.18; *MAPT*: r = 0.63) (Moore et al., 2020). The implications of this finding for the work in chapter 3, could mean that the late presymptomatic group, does not actually contain all of those that are closest to symptom onset. However, this is a challenging problem to overcome as it is extremely difficult to know when individuals are going to start experiencing symptoms, particularly as these changes can be very subtle over a long period of time. One way to overcome this problem would be to monitor those individuals who are classed as "converters". These are individuals who enter the study as presymptomatic individuals, but over the course of their participation become symptomatic. This gives a much clearer picture about the changes in performance over time and greater accuracy surrounding the age at onset of symptoms.

It is possible that demographics may have also played a part in the deficit on the FER task being observed in the late *C9orf72* presymptomatic mutation carrier group, as they were older than the *MAPT* mutation group and had a lower level of education than the *GRN* mutation group. Whilst age and sex were accounted for in the model, education was not. In future analyses it would be helpful to account for this, initially performing a correlation of each of the two tasks with education to see if there is an impact on performance. If

this did display a significant correlation, education should then be included in the model.

Finally, the work in this chapter did not consider the clinical phenotype of the symptomatic carriers. The *MAPT* mutation group were mainly diagnosed with bvFTD and the *C9orf72* symptomatic group were predominantly diagnosed as bvFTD with/or without ALS, but the *GRN* mutation carriers had a relatively even split in diagnosis between bvFTD and PPA. It is therefore possible that there may be a disease effect on performance on these tasks rather than a genetic one. This heterogeneity in clinical presentation may account for some of the differences observed in this chapter. Particularly in the *C9orf72* group, both individuals with bvFTD (see section 1.4) and individuals with ALS are known to have problems with emotion processing (Crespi et al., 2014; Zimmerman, Zachary Simmons, & Barrett, 2007) and theory of mind (Carluer et al., 2015). Whilst it is known that individuals with PPA do show some difficulties with social cognition, often problems associated with task administration and comprehension account for many of the deficits observed, so one would perhaps be less likely to expect an effect in the *GRN* mutation group than the other two groups. While we are unable to know what diagnosis presymptomatic individuals will go on to develop, this may explain why these differences are not being observed in the *GRN* mutation group, although it may not explain the *MAPT* mutation group, given their main diagnosis is usually bvFTD. It is possible that the younger age of the *MAPT* mutation group may be the driving factor behind the lack of findings in the late group and a larger sample may start to show these deficits earlier on. A consideration for further analysis could be to look at the diagnosis of the parental generation and split the late presymptomatic groups by phenotype within the genetic groups in an effort to identify if these tasks are sensitive enough to earlier social cognitive symptoms.

One additional problem that was somewhat overlooked in the analysis, was the use of the z scores. Whilst the aim was to account for the variation in language on the FP task, they are generated based on the control sample for each individual language. For some groups, particularly the German and Portuguese group, the sample size is very small and may not be representative of the language as a whole. This therefore makes the z scores less reliable. An alternative approach would have been to use the raw scores for the FP task and include language as a covariate in the analysis to try and mitigate this problem slightly.

8.3.2 Chapter 5

The aim of chapter 5 was to ensure that eye movements in individuals with bvFTD would not affect performance on the tasks in chapter 6. I concluded that individuals with bvFTD did not display deficits in their oculomotor function which would impact upon performance on the social cognition eye tracking task. However, there are a number of confounds to consider for those tasks that displayed no significant differences between the groups.

The sinusoidal pursuit suggested that the individuals with bvFTD were able to do the tasks as well as controls, however when looking at the figures generated to display the data, the two examples of pursuit between the controls and bvFTD looked slightly different. While the control groups data is relatively smooth, this is not the case with the bvFTD group. An increase in the number of trials and the length of pursuit may show a greater discrepancy between the two groups and would be worth exploring in a future analysis.

Another issue to consider is the interpretation of the results for the pro-saccade tasks. For the saccade latency and peak velocity measures, a square root transformation was performed to overcome the problem of the abnormal distribution of the data. Consequently, this changed the scale of the data

making the confidence intervals much more difficult to interpret and thus, caution should be applied when summarising these results. An alternative way to overcome this problem would have been to use a simpler transformation to be able to interpret the results better or to use bootstrapping to ensure that the scale remained the same.

Despite the anti-saccade task being promising in tracking disease progression or being used clinically in a diagnostic setting, there remains some overlap in scores between the controls and those with bvFTD. There was also a limited number of trials used on this task. Whilst being significantly different to one another, it may have been useful to identify the predictive power of this task. However, with that being said, the anti-saccade task can be employed in a clinical setting very simply by using the hands to depict the stimuli and the experimenter asking individuals to look the other way. It is difficult to say from this data, whether the addition of the eye tracker to measure anti-saccades adds any value than doing it manually. Work aiming to assess this would be beneficial to prevent the development of tasks that are no better than those already usable in clinical practice.

Finally, as the aim of this chapter was to investigate eye movements for the social cognitive tests, the oculomotor tasks were somewhat overlooked as tests in and of themselves, particularly the fixation task. It is clear from the fixation task that there were clear differences observed between the control and the bvFTD group. This is supported in the statistical analysis of the small square wave jerks and the longest period of fixation analysis and the predictive power calculations that suggest that these two measures are reasonably good at determining cases from controls. In order to take this forward, replication in a larger cohort is required and it would also be beneficial to test in different disease groups to identify if this deficit is specific to bvFTD, FTD or neurodegeneration in general.

One measure not considered in this analysis was the blink rate. It is possible that the individuals with bvFTD blinked more than the control group which therefore made the longest period of fixation much shorter as it was calculated between blinks, however, they may not have deviated from the cross when they looked back. An additional analysis to identify this would be to assess the number of blinks made between the two groups and to perform an interest area analysis around the fixation cross to understand if they were still within the same area when they returned from their blink. From the fixation graph, it is clear there is more movement in the eye, as found by the square wave jerk analysis but as there were not significant differences between the number of large square wave jerks and large intrusive saccades, it is more likely that the deficit on the longest period of fixation is due to the blink rate. It is possible that their blink rate may be higher due to an attentional and/or inhibition deficit.

8.3.3 Chapter 6

The biggest question surrounding the novel emotion processing tests used in chapter 6, is whether or not they are measuring social cognition or something else, such as executive function. It is very difficult to design psychology tests that are targeting a single domain as many of our abilities and skills are multifaceted, and thus to claim this was purely a social cognitive task may be inaccurate. Whilst the link to the dorsolateral prefrontal cortex in Chapter 6 would suggest that the tests are tapping into social abilities, this region is also known to be associated with executive function supporting the idea that it may not be a pure social cognitive test. However, with that being said, this task has been developed as much as possible to remove as many other elements as possible such as executive function by keeping the tasks very simple and instructionless. Furthermore, the tasks are taken from the social cognitive literature so they are all grounded in the realm of social cognition

and in line with the tradition and history of assessing social abilities. Despite the attempts to remove this problem however, it would be extremely difficult to eradicate it completely and is important to consider when interpreting the results.

Another question to consider, is why the psychology tests did not correlate with any of the social cognitive measures on the standard psychometric tests. A number of reasons may account for this. This work is underpowered due to the relatively small sample size and in order to find a significant correlation, the correlation would need to be 0.68 or higher to have 80% power. This is a relatively high correlation needed so in order to find any correlations, it is likely that the sample size would need to be increased to overcome this issue. An alternative reason could be that they are measuring different aspects of social cognition. As previously mentioned, social cognition is not a unitary concept and covers a wide variety of different processes (Pinkham, 2014). It is possible that this novel task is measuring something that the other task do not. That may not mean that these novel tasks are not measuring social cognition, but rather a different aspect of social cognition.

Whilst both the simple and complex novel tasks were analysed independently, they were not compared to one another to establish which task was better than the other. This is something that should have had further investigation as it is possible that one may be better than the other. While I concluded in the discussion that I felt that the complex task may be best in identifying earlier changes, it is possible that due to the smaller separation between the groups, this may not be the case. From looking at the graphs, it is possible that the simple task may actually be better at discriminating between cases and controls and thus, would be a better task to identify earlier change in a presymptomatic cohort. In order to investigate this further, correlations between the two tasks should be carried out to determine if they

are measuring similar aspects of social cognition, and then predictive power calculations in the form of a ROC curve analysis should be carried out.

In order to move forward with these novel tasks and develop them into something that would be useful for the field, further analysis of the ability to distinguish cases and controls is vital. Replication in a larger cohort and different diseases will be beneficial to determine if they are able to assess social cognition reliably and if the deficits are specific to bvFTD. Furthermore, a longitudinal analysis of the participants in this work would be useful to see how performance changes over time. There should be little problem with interrater reliablity or repeated testing problems as the correct answers are not given and it is very hard for individuals to know if they have done the task correctly or not. One problem may be a issue surrounding engagement and attention towards the task given its repetitive nature which may influence the results as there is very little interaction with the task. In order to understand how individuals are feeling about the tasks, if they are happy to do them and whether they prefer them over the standard tasks, a questionnaire could be developed to generate feedback to improve task design.

Other areas of social cognition are also known to be affected in bvFTD, such as moral reasoning, gaze processing and social perception. I feel that it would be possible to develop instructionless eye-tracking tests aiming to assess these other social cognitive measures and they may provide meaningful insight into the condition. Furthermore, this work focused mainly on the emotions in faces, however emotions can be understood through other measures, such as body language, prosody and tone as well as in dynamic and more ecologically valid stimuli.

8.3.4 Chapter 7

The lack of availablity of the demographic, cognitive and imaging data in chapter 7 had a considerable impact on the analysis and conclusions that are able to be made. This along with the small sample size makes it difficult to make any concrete assumptions about how the novel tasks perform in a presymptomatic population. A larger sample size is require in order to gain access to the additional information. The tasks are going to be administered in a larger cohort of the GENFI population to allow for this to happen and those that have already been tested will be followed up at a 12 month interval to establish how the test perform longitudinally.

As with the data in chapter 6, the simple tasks appeared to be much easier to do than the complex task, however in both, there was a large overlap between the controls and carriers. Furthermore, whilst the performance on the complex task in the control group was similar to the control groups performance in chapter 6, this was not the case for the simple task. The range in performance was much greater on the simple task in the non-mutation carriers than the healthy controls in chapter 6. It is possible that this may be age related, as the non-carriers in chapter 7 are much younger than those in chapter 6. It would be interesting to combine the two control groups and assess the impact of age, gender and education in a much larger group to have a better undertsanding of how health controls are performing on these tasks.

When deciding which tasks to include for the presymptomatic battery, at the time I felt there was more data to be gained from the pro-saccade tasks than the fixation and pursuit taks. However on reflection, I think that the fixation task may be provide the possibility of identifying early presymptomatic change given the AUC for the small square wave jerks and longest period of

fixation. I therefore propose that this task should be included in any presymptomatic battery moving forward.

8.3.5 General limitations and considerations

In many of the chapters in this thesis, there have been several statistical tests being run simultaneously resulting in multiple comparisons. This makes it possible that a type I error will occur, finding a positive result that is not true. One way to control for this is to use a Bonferroni correction. This is where the alpha level (which was set at 0.05 throughout the thesis unless otherwise specified) is divided by the number of tests performed. This is a very stringent way of controlling for type I errors but is often too harsh and produces more type II errors – not finding a result that is there. By not adding this correction however, caution should be applied when interpreting the results, particularly those that are close to the cut off of $p = 0.05$ or close to 0.00 when using the 95% confidence intervals to assess significance.

One final consideration for the use of eye tracking as a standard psychometric tool is the selection and reliability of the eye tracking equipment used. The Eyelink 1000 plus is a highly accurate, efficient and proficient compared to many other eye trackers on the market. It is however extremely expensive and static. Moving forward, ideally these tasks would be able to be portable and so the design and ability to share these tasks across multiple different eye-tracking software and equipment must be considered although caution should be applied comparing results on different equipment. The loss of data is also a concern. While I was able to identify how and why I was losing data, and tried to decrease the problem as much as possible, there is always the risk of more data being lost than if standardised pen-and-paper tests are used. It is therefore important that every effort is made to understand the software

prior to testing and ensure that a back-up system is in place to save the data if the experiment fails.

8.3.6 Summary

With technology ever advancing, and the interest in the use of technology in dementia increasing, the impact of this work extends far beyond this thesis. Portable eye tracking, real life eye-trackers monitoring what you see in everyday life, as well as wearables are all becoming more accessible. The ability of this technology to aid our understanding of the everyday lives of people living with any form of dementia is paramount, and will provide a wealth of knowledge that has so far been inaccessible to researchers. By understanding the difficulties, and through the education of the carers and loved ones about the social problems that the individual is facing, this may go some way to help reduce the emotional burden that is associated with caring for someone with dementia, and may be able to aid communication for the individual. Moreover, by educating those at risk for developing dementia, being able to monitor their changes and develop strategies to help cope with the knowledge of being a risk through new counselling techniques, it may be possible to reduce the anxiety and worry that is associated with living at risk. Finally, hopefully tests such as those developed in this thesis will be able to help in trials that are involved in the development of a potential cure, for this awful and devastating disease.

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APPENDIX

Appendix 1: Informant Questionnaires

Subtype ID		Subject ID		Visit number		Visit date/month/year			

CAMBRIDGE BEHAVIOURAL INVENTORY - REVISED

Name of informant		Relationship to participant		Years known the participant	

We would like to ask you a number of questions about various changes in the subject's behaviour that you may have noticed. It is important that we obtain your views as it will help us in our assessment.

Please read the description of each problem carefully. Then circle the number under the heading "FREQUENCY" that best describes the occurrence of the behavioural change.

Some of the everyday skill questions may not apply. If for instance the person you care for has never done the shopping enter NA (not applicable).

All questions apply to the subject's behaviour OVER THE PAST MONTH.

0	1	2	3	4
never	a few times per month	a few times per week	daily	constantly

		FREQUENCY					
Memory and Orientation							
1	Has poor day-to-day memory (e.g. about conversations, trips etc.)	0	1	2	3	4	
2	Asks the same question over and over again	0	1	2	3	4	
3	Loses or misplaces things	0	1	2	3	4	
4	Forgets the names of familiar people	0	1	2	3	4	
5	Forgets the names of objects and things	0	1	2	3	4	
6	Shows poor concentration when reading or watching television	0	1	2	3	4	
7	Forgets what day it is	0	1	2	3	4	
8	Becomes confused or muddled in unusual surroundings	0	1	2	3	4	
Everyday skills							
9	Has difficulty using electrical appliances (e.g. TV, radio, cooker, washing machine)	0	1	2	3	4	NA
10	Has difficulties writing (letters, Christmas cards, lists etc.)	0	1	2	3	4	NA
11	Has difficulties using the telephone	0	1	2	3	4	NA
12	Has difficulties making a hot drink (e.g. tea/coffee)	0	1	2	3	4	NA
13	Has problems handling money or paying bills	0	1	2	3	4	NA
Self care							
14	Has difficulties grooming self (e.g. shaving or putting on make-up)	0	1	2	3	4	
15	Has difficulties dressing self	0	1	2	3	4	
16	Has problems feeding self without assistance	0	1	2	3	4	
17	Has problems bathing or showering self	0	1	2	3	4	

Subtype ID		Subject ID		Visit number		Visit date/month/year			

		FREQUENCY				
Abnormal behaviour						
18	Finds humour or laughs at things others do not find funny	0	1	2	3	4
19	Has temper outbursts	0	1	2	3	4
20	Is uncooperative when asked to do something	0	1	2	3	4
21	Shows socially embarrassing behaviour	0	1	2	3	4
22	Makes tactless or suggestive remarks	0	1	2	3	4
23	Acts impulsively without thinking	0	1	2	3	4
Mood						
24	Cries	0	1	2	3	4
25	Appears sad or depressed	0	1	2	3	4
26	Is very restless or agitated	0	1	2	3	4
27	Is very irritable	0	1	2	3	4
Beliefs						
28	Sees things that are not really there (visual hallucinations)	0	1	2	3	4
29	Hears voices that are not really there (auditory hallucinations)	0	1	2	3	4
30	Has odd or bizarre ideas that cannot be true	0	1	2	3	4
Eating habits						
31	Prefers sweet foods more than before	0	1	2	3	4
32	Wants to eat the same foods repeatedly	0	1	2	3	4
33	Her/his appetite is greater, s/he eats more than before	0	1	2	3	4
34	Table manners are declining e.g. stuffing food into mouth	0	1	2	3	4
Sleep						
35	Sleep is disturbed at night	0	1	2	3	4
36	Sleeps more by day than before (cat naps etc.)	0	1	2	3	4
Stereotypic and motor behaviours						
37	Is rigid and fixed in her/his ideas and opinions	0	1	2	3	4
38	Develops routines from which s/he can not easily be discouraged e.g. wanting to eat or go for walks at fixed times	0	1	2	3	4
39	Clock watches or appears pre-occupied with time	0	1	2	3	4
40	Repeatedly uses the same expression or catch phrase	0	1	2	3	4
Motivation						
41	Shows less enthusiasm for his or her usual interests	0	1	2	3	4
42	Shows little interest in doing new things	0	1	2	3	4
43	Fails to maintain motivation to keep in contact with friends or family	0	1	2	3	4
44	Appears indifferent to the worries and concerns of family members	0	1	2	3	4
45	Shows reduced affection	0	1	2	3	4

Subtype ID		Subject ID		Visit number		Visit date/month/year			

FRONTOTEMPORAL DEMENTIA RATING SCALE

For each sentence, circle the frequency of the problem on the right hand side. If the question does not apply for them, e.g. he/she did not cook before, then mark NA.

A	B	C
All the time	Sometimes	Never

Behaviour					
1	Lacks interest in doing things – their own interests/leisure activities/new things	A	B	C	
2	Lacks normal affection, lacks interest in family members worries	A	B	C	
3	Is unco-operative when asked to do something; refuses help	A	B	C	
4	Becomes confused or muddled in unusual surroundings	A	B	C	
5	Is restless	A	B	C	
6	Acts impulsively without thinking, lacks judgment	A	B	C	
7	Forgets what day it is	A	B	C	
Outing and shopping					
8	Has problems taking his/her usual **transportation** safely (car if has a driving licence; bike or public transport if does not have a drive licence)	A	B	C	NA
9	Has difficulties **shopping** on their own e.g. to go into the local shops to get milk and bread if did not use to do the main shopping)	A	B	C	NA
Household chores and telephone					
10	Lacks **interest** or **motivation** to perform household chores that he/she used to perform in the past	A	B	C	NA
11	Has difficulties **completing** household chores adequately that he/she used to perform in the past (to the same level)	A	B	C	NA
12	Has difficulty **finding** and **dialling** a telephone number correctly	A	B	C	NA
Finances					
13	Lacks **interest** in his/her personal affairs such as finances	A	B	C	NA
14	Has problems **organising** his/her finances and to pay bills (cheques, bankbook, bills)	A	B	C	NA
15	Has difficulties **organising** his/her correspondence without help (writing skills)	A	B	C	NA
16	Has problems **handling** adequately **cash** in shops, petrol stations etc (give and check change)	A	B	C	NA
Medications					
17	Has problems taking his/her medications at the **correct time** (forgets or refuses to take them)	A	B	C	NA
18	Has difficulties **taking** his/her medications as prescribed (according to the right dosage)	A	B	C	NA

Subtype ID		Subject ID		Visit number		Visit date/month/year			

Meal preparation and eating					
19	Lacks previous **interest** or **motivation** to prepare a meal (or breakfast, sandwich) for himself/herself	A	B	C	NA
20	Has difficulties **organising** the preparation of meals (or a snack if patient was not the main cook) (choosing ingredients; cookware; sequence of steps)	A	B	C	NA
21	Has problems preparing or cooking a meal (or snack if applicable) **on their own** (needs supervision/help in kitchen)	A	B	C	NA
22	Lacks **initiative** to eat (if not offered food, might spend the day without eating anything at all)	A	B	C	
23	Has difficulties **choosing** appropriate utensils and seasonings when eating	A	B	C	
24	Has problems **eating** meals at a normal pace and with appropriate manners	A	B	C	
25	Wants to eat the **same foods** repeatedly	A	B	C	
26	Prefers **sweet foods** more than before	A	B	C	
Self care and mobility					
27	Has problems **choosing** appropriate clothing (with regard to the occasion, the weather or colour combination)	A	B	C	
28	Is incontinent	A	B	C	
29	Cannot **be left** at home by himself/herself for a whole day (for safety reasons)	A	B	C	
30	Is restricted to the **bed**	A		C	

Subtype ID		Subject ID		Visit number		Visit date/month/year			

MODIFIED INTERPERSONAL REACTIVITY INDEX

Indicate how well each statement describes the subject's CURRENT behaviour. There are no right or wrong answers. We just want to get your impression of how you think the subject typically behaves.

		Does NOT describe well	←		→	Describes VERY well
1	The subject shows tender, concerned feelings for people less fortunate than him/her	1	2	3	4	5
2	The subject sometimes finds it difficult to see things from the "other person's" point of view	1	2	3	4	5
3	Sometimes the subject does NOT feel very sorry for other people when they are having problems	1	2	3	4	5
4	The subject tries to look at everybody's side of a disagreement before he/she makes a decision	1	2	3	4	5
5	If the subject sees somebody being taken advantage of, the subject feels kind of protective towards him/her	1	2	3	4	5
6	The subject is likely to try to understand others better by imagining how things look from their perspective	1	2	3	4	5
7	Other people's misfortunes do NOT usually disturb the subject a great deal	1	2	3	4	5
8	If the subject is sure he/she is right about something, he/she doesn't waste much time listening to other people's arguments	1	2	3	4	5
9	If the subject sees someone being treated unfairly, the subject doesn't feel much pity for him/her	1	2	3	4	5
10	The subject is often quite touched by things he/she sees happen	1	2	3	4	5
11	The subject believes that there are two sides to every question and tries to look at both of them	1	2	3	4	5
12	I would describe the subject as a pretty soft-hearted person	1	2	3	4	5
13	If the subject is upset at someone, the subject usually tries to put him/herself "in the other person's" shoes for a while	1	2	3	4	5
14	Before criticizing me, the subject is likely to imagine how he/she would feel if he/she were in my place	1	2	3	4	5

Subtype ID		Subject ID		Visit number		Visit date/month/year			

REVISED SELF-MONITORING SCALE

Indicate how well each statement describes the subject's CURRENT behaviour. There are no right or wrong answers. We just want to get your impression of how you think the subject typically behaves.

		Certainly, always false	Generally false	Somewhat false, but with exceptions	Somewhat true, but with exceptions	Generally true	Certainly, always true
1	In social situations, the subject has the ability to alter his/her behavior if he/she feels that something else is called for	0	1	2	3	4	5
2	The subject is often able to correctly read people's true emotions through their eyes	0	1	2	3	4	5
3	The subject has the ability to control the way he/she comes across to people, depending on the impression he/she wants to give them	0	1	2	3	4	5
4	In conversations, the subject is sensitive to even the slightest change in the facial expression of the person he/she is conversing with	0	1	2	3	4	5
5	The subject's powers of intuition are quite good when it comes to understanding others	0	1	2	3	4	5
6	The subject can usually tell when others consider a joke in bad taste, even though they may laugh convincingly	0	1	2	3	4	5
7	When the subject feels that the image he/she is projecting isn't working, he/she can readily change to something that does	0	1	2	3	4	5
8	The subject can usually tell when he/she said something inappropriate by reading it in the listener's eyes	0	1	2	3	4	5
9	The subject has trouble changing his/her behavior to suit different people and different situations	0	1	2	3	4	5
10	The subject can adjust his/her behavior to meet the requirements of any situation he/she is in	0	1	2	3	4	5
11	If someone is lying to the subject, he/she usually knows it at once from that person's manner or expression	0	1	2	3	4	5
12	Even when it might be to his/her advantage, the subject has difficulty putting up a good front	0	1	2	3	4	5
13	Once the subject knows what the situation calls for, it's easy for him/her to regulate his/her actions accordingly	0	1	2	3	4	5

Appendix 2: Letter Fluency Psychometric Test

Test instructions:

> *"I am going to give you a letter of the alphabet and I want you to name, as fast as you can, all of the words that start with that letter. You may say any word at all except proper names, such as names of people or places. So you would not say 'Rochester' or 'Robert.' Also, do not use the same words again with a different ending, such as 'eat' and 'eating.' For example, if I say B, you could say, 'boat, bring, bed, both.' Can you think of other words that start with B?"*
>
> Allow 20 seconds for participant to produce two responses. After sample, say:
>
> *"Now I want you to tell me all the words that begin with (F/A/S) you can think of in one minute. Ready? Begin."*

Additional information:

> Start timing and record responses for **60 seconds**. ONE prompt ("Tell me all the words that begin with F you can think of") is permitted if the participant makes no response for 15 seconds or expresses incapacity (e.g. "I can't think of anymore"). It is also permissible to repeat the instruction or letter if the participant specifically requests it.
>
> Slang words are also permitted as well as foreign words (e.g., lasagna) that are listed in the dictionary as Standard English.
>
> It is advisable to tape record responses while you write down as many as possible so you can fill in any gaps when scoring.

Appendix 3: Category Fluency Psychometric Test

Test Instructions:

> *"I am going to give you a category and I want you to name, as fast as you can, all of the things that belong in that category. For example, if I say 'articles of clothing', you could say 'shirt', 'tie', or 'hat'. Can you think of other articles of* clothing?"
>
> Allow up to 20 seconds for the participant to produce two responses. Depending on their response read the associated instruction (below)
>
> **No response:**
> *"You could have said 'shoes' or 'coat' since they are articles of clothing."*
> **One or more incorrect responses, no correct response:**
> *"No, ____is (are) not an article (s) of clothing. You could have said 'shoes' or 'coat' since they are articles of clothing."*
> **One or more correct response, no incorrect responses:**
> *"That's right. You also could have said 'shoes' or 'coat'."*
> **One or more correct responses, one or more incorrect responses:**
> *"_____is (are) correct, but _____ is (are) not an article of clothing. You also could have said 'shoes' or 'coat'."*
> **Two or more correct responses:**
> *"That's right."*
>
> *"Now I want you to name things that belong to another category: Animals. You will have one minute. I want you to tell me all the animals you can think of in one minute. Ready? Begin."*

Additional information

> Start timer as you say "Begin". Write actual responses as legibly as possible on the worksheet. Stop the procedure at 60 seconds.
>
> One prompt ("*Tell me all the animals you can think of.*") is permitted if the participant makes no response for 15 seconds or expresses incapacity (e.g., "I can't think of any more."). It is also permissible to repeat the instruction or category if the participant specifically requests it.

Appendix 4: Camel and Cactus Test (Modified)

Test instructions:

> *"In this test, I am going to show you 5 pictures on each page: one at the top, and 4 pictures below. I would like you to choose which of the 4 pictures below goes best with the picture at the top".*
>
> Start with the first practice item. Point to the top picture and say:
>
> *"Which one does this picture go with?"*
>
> Show all 3 practice items (wine-grapes, cactus-desert, nails-hammer) and point out the correct answer if they get it wrong. After the 3 practice items, continue with the test items.

Example Stimuli:

Appendix 5: Mini-SEA Social Cognition Task

MINI-SEA: FAUX-PAS TEST (FP)

Practice Story

- Place the picture story in front of the participant to look at. Then say:
- "**You are going to read some little stories like the one in front of you and I will ask you some questions about the stories after you have read each of them. This is not a memory test so you can read the story at any time again when I ask you a question."**
- Let the participant read the practice story or read it with the participant.
- After reading, say: **"Did anyone say something they shouldn't have said or something awkward? Or in other words was there a faux-pas in the story?"**
- If the participant says: 'No' to this first question, then say that there was a faux-pas and explain it briefly - *do this only for the practice story.*
- If the participant says: 'Yes', make sure that the faux-pas was understood.
- The practice story is not included in the scoring.
- The correct explanation for the practice story is: **"Yes there was a faux-pas; Joe was talking badly about Mike while Mike was in the stalls in the toilet overhearing Joe's remarks. Joe did not know that Mike was there."**

Faux-pas Test Stories

- **"There are a total of 10 stories I want you to read. For each story I want you to tell me whether there was a faux-pas or not. Some stories will have a faux-pas while others will not. If there is a faux-pas I want you to explain it to me."**
- The test procedure for the remaining 10 stories is the same as for the practice story, i.e. if the participant answers 'No' to the first question, go straight to the control questions.
- If the participant answers 'Yes' to the first question, ask all the following questions.
- Make sure that the control questions are always asked to check for comprehension, regardless of whether the first questions was answered 'Yes' or 'No'.
- Do not overdo the reformulating of questions or the clarifications.

- For example, the subject might erroneously attribute the faux-pas to the wrong person in the story. In that case, you should refrain from asking whether the participant is sure this is the right response, as a misattribution error is a common sign of social cognition deficits.
- There might also be subjects that report a faux-pas in every story or none of the stories.
- If the participant gets confused when reading the story, he or she is allowed to re-read it again.
- The control questions reflect the story comprehension and help the clinical interpretation.
- If the total score is very low then the clinician should take into account whether the comprehension of the story was severely compromised, for example by semantic or attentional problems.

Scoring Instructions – Faux-pas Test

- Stories 3, 4, 7, 8, 9 **contain** a faux-pas – marked with a * on the scoresheets.
- Stories 1, 2, 5, 6, 10 **do not contain** a faux-pas.
- For each faux-pas story, the participant gets 1 point for each correct answer to the faux-pas questions (maximum of 6).
- For each non faux-pas story, the participant gets 2 points for the first question (maximum of 2).

First question

- Stories 3, 4, 7, 8, 9 'Yes': correct (1 point) 'No': incorrect (0 points)
- Stories 1, 2, 5, 6, 10 'No': correct (2 points) 'Yes': incorrect (0 points)
- Participants who answered 'No' to the first questions should not be asked the second and following questions, which are then also scored with 0.

Second question

- Any answer that identifies unambiguously the person who committed the faux-pas is allowed.

Third question

- Any answer explaining the faux-pas correctly is allowed. No comprehension of mental state is asked here, only the factual proceedings of the faux-pas.

Fourth question

- The intentions of the people in the story are probed in this question. Please note that the faux-pas is always unintentional. Therefore, the answer of the participant should indicate that one person in the story did not know or realise something. The answer is scored as correct, even if the mental state of the persons is not made explicit.

Fifth question

- The answer is either yes or no. This is a confirmation that the participant considers the faux-pas as unintentional.

Sixth question

- Question 6 probes the empathy of the participant towards the person experiencing the faux-pas. Do they seem to suffer, are embarrassed, are disappointed etc? The answer should reflect an emotion or a feeling fitting the situation.
- It can be quite common to see a patient responding correctly to this question but then using the same response for all the remaining stories as well. For example, the participant might say to each story that the person is disappointed. In that case one can ask the question in different form (for example: 'Okay, but what else can you say about this?'). If the participant fails to give a different emotion/state of mind, then the clinician should consider marking this answer as incorrect and also mark any subsequent identical answers as incorrect. However, the scoring can be difficult in such cases and in the end the clinician should use his/her clinical judgment in such as case.

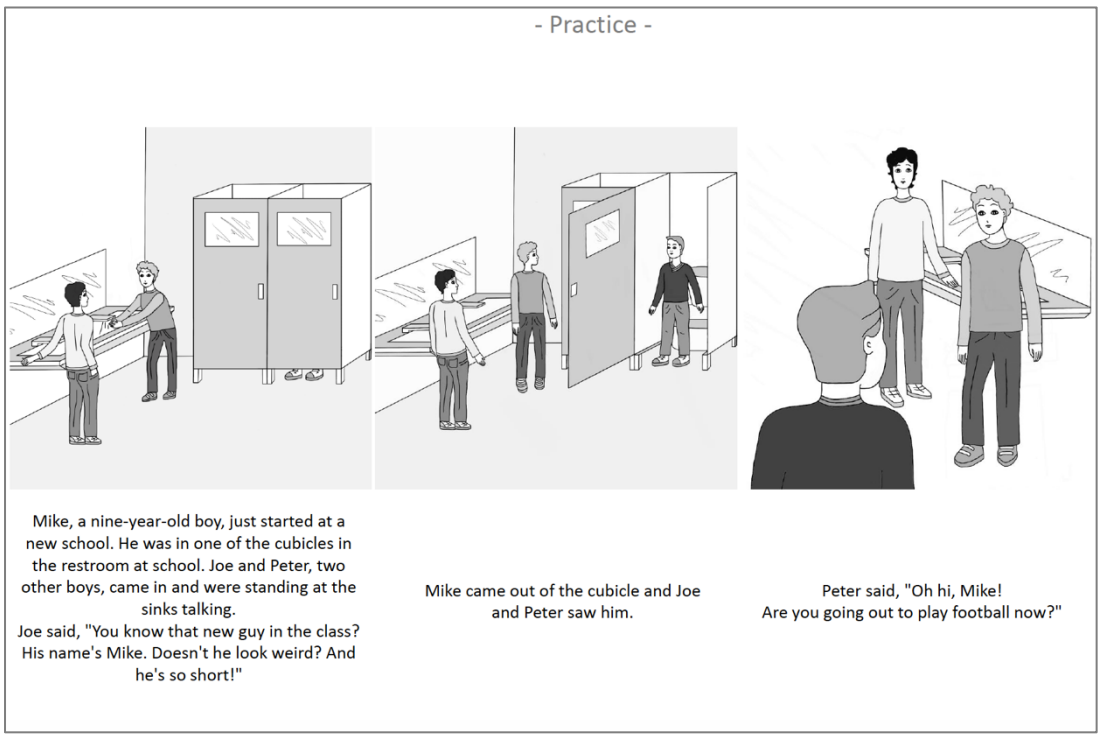
Seventh and eighth questions

- These control questions allow establish whether the patient got confused or forgot the stories. The answers are straightforward and need to be scored separately from the other questions.
- Importantly, the control questions need to be asked, even if the participant responded 'No' to the first question.

Faux-pas Scoring Sheet

	Faux-pas questions						**Control questions**	
	1	**2**	**3**	**4**	**5**	**6**	**1**	**2**
Story 1	/2						/1	/1
Story 2	/2						/1	/1
Story 3 *	/1	/1	/1	/1	/1	/1	/1	/1
Story 4 *	/1	/1	/1	/1	/1	/1	/1	/1
Story 5	/2						/1	/1
Story 6	/2						/1	/1
Story 7 *	/1	/1	/1	/1	/1	/1	/1	/1
Story 8 *	/1	/1	/1	/1	/1	/1	/1	/1
Story 9 *	/1	/1	/1	/1	/1	/1	/1	/1
Story 10	/2						/1	/1

Faux-pas Test – total score for faux-pas stories (/30)	_ _
Faux-pas Test – total score for non-faux-pas stories (/10)	_ _
Faux-pas Test – total score for all stories (/40)	_ _
Faux-pas Test – subscore (=total score for all stories/4)*1.5 (/15)	_ _
Faux-pas Test – total score for control stories (/20)	_ _



Example story from the FP task

Practice story

Mike, a nine-year-old boy, just started at a new school. He was in one of the cubicles in the restroom at school. Joe and Peter, two other boys, came in and were standing at the sinks talking. Joe said, "You know that new guy in the class? His name's Mike. Doesn't he look weird? And he's so short!" Mike came out of the cubicle and Joe and Peter saw him. Peter said, "Oh hi, Mike! Are you going out to play football now?"

Faux-pas questions and score sheet

1.	Did anyone say something they shouldn't have said or something awkward?	**Yes/No**
If answer is 'No' go to control questions. **If answer is 'Yes', ask questions 2-6 below.**		
2.	Who said something they shouldn't have said or something awkward?	
3.	Why shouldn't he/she have said it or why was it awkward?	
4.	Why do you think he/she said it?	
5.	When Joe was talking to Peter, did he know that Mike was in one of the stalls?	
6.	How do you think Mike felt?	

Control questions

1.	In the story, where was Mike while Joe and Peter were talking?	
2.	What did Joe say about Mike?	

MINI-SEA: FACIAL EMOTION RECOGNITION TEST (FER)

- **"I am going to show you some faces with each one having a different one of the following emotions: Happiness, Surprise, Sadness, Fear, Disgust, Anger and Neutral for which no emotion is shown in the face"**
- "**I want you to have a good look at each face and tell me which emotion you think is shown."**
- **"There is no need to rush through the faces, although be aware that each face is shown for 12 seconds only."**

- Present each face until the patient has made a choice or up to a maximum of 12 seconds. After 12 seconds, score it as an error even if the participant gives an answer. The time limit is important as published test results and scoring are dependent on it.
- If the subject struggles to respond to the first few items, give him verbally the choices without helping him, e.g. 'Is this face happy, surprised, sad, fearful, disgusted, angry or neutral?'
- During the test feel free to cue the subjects answer, e.g. 'And for this face, which emotion does it show?' These cues can be repeated for each face, in particular if the patient has a lot of apathy or inertia.

1

Happiness – Surprise – Neutral – Sadness – Fear – Disgust - Anger

Example image of the FER test

FER score sheet

	Happiness	Surprise	Disgust	Fear	Anger	Sadness	Neutral
1	Happiness						
2				Fear			
3			Disgust				
4							Neutral
5					Anger		
6		Surprise					
7						Sadness	
8				Fear			
9					Anger		
10			Disgust				
11						Sadness	
12	Happiness						
13							Neutral
14		Surprise					
15						Sadness	
16		Surprise					
17							Neutral
18	Happiness						
19				Fear			
20					Anger		
21			Disgust				
22		Surprise					
23			Disgust				
24	Happiness						
25						Sadness	
26							Neutral
27				Fear			
28					Anger		
29					Anger		
30				Fear			
31						Sadness	
32		Surprise					
33	Happiness						
34			Disgust				
35							Neutral

Facial Emotion Recognition Test – total score for happiness (/5)	_ _
Facial Emotion Recognition Test – total score for surprise (/5)	_ _
Facial Emotion Recognition Test – total score for disgust (/5)	_ _
Facial Emotion Recognition Test – total score for fear (/5)	_ _
Facial Emotion Recognition Test – total score for anger (/5)	_ _
Facial Emotion Recognition Test – total score for sadness (/5)	_ _
Facial Emotion Recognition Test – total score for neutral (/5)	_ _
Facial Emotion Recognition Test – total score for all emotions (/35)	_ _
Facial Emotion Recognition Test – subscore (=total score /3.5)*1.5 (/15)	_ _

Mini-SEA total score (sum of Faux-pas Test and Facial Emotion Recognition Test subscores (/30)	_ _

Appendix 6: The novel social cognition synonyms test

Participants are required to select the appropriate synonym for the target word (printed in capitals on a sheet presented to them) from the two available options. Participants can gesture a response. The correct answer is highlighted in bold on the response sheet that the experimenter has.

Test instructions:

> *"I have a word in capitals, and two in lower case on the right. I am going to read out the word in capitals. I would like you two read these two other words and circle the one which is most similar in meaning to the word in capitals"*
>
> *"So is 'regretful' more like 'sorry' or 'glad'?"*

Additional information:

> Read out all the items, unless it is apparent that the participant is capable of reading the items independently.
>
> If the participant does not know the answer, encourage a guess rather than a 'DK' response.
>
> There is no time limit on items.
>
> There is no discontinue rule.

Stimuli sheet:

When presented to the participant, no options will be in bold. This is only to emphasis the correct response.

Item	Options	
REGRETFUL	**sorry**	glad
FANTASIZING	doing	**dreaming**
TENTATIVE	sure	**cautious**
PREOCCUPIED	**distracted**	respectful
DEFIANT	**daring**	timid
SKEPTICAL	certain	**doubtful**
THOUGHTFUL	**caring**	rude
UPSET	pleased	**distressed**
CONCERNED	calm	**uneasy**
CONFIDENT	**bold**	shy
INTERESTED	bored	**keen**
CONTEMPLATIVE	impulsive	**thinking**
SUSPICIOUS	**wary**	trusting
WORRIED	**afraid**	relaxed
PLAYFUL	lazy	**joking**
FRIENDLY	mean	**kind**
DECISIVE	weak	**firm**
NERVOUS	**tense**	brave
REFLECTIVE	**remembering**	forgetting
HAPPY	down	**glad**
SAD	**glum**	joyful
ANGER	delighted	**cross**
FEAR	**frightened**	cheerful
DISGUST	liked	**repulsed**
SURPRISE	**amazed**	bored

Appendix 7: List of output variables from Data Viewer software for Chapter 5 and Chapter 6

Saccade Report
RECORDING_SESSION_LABEL
TRIAL_INDEX
TRIAL_START_TIME
CURRENT_SAC_START_TIME
CURRENT_SAC_START_X
CURRENT_SAC_START_Y
CURRENT_SAC_END_TIME
CURRENT_SAC_END_X
CURRENT_SAC_END_Y
CURRENT_SAC_BLINK_DURATION
CURRENT_SAC_BLINK_END
CURRENT_SAC_BLINK_START
CURRENT_SAC_CONTAINS_BLINK
CURRENT_SAC_AMPLITUDE
CURRENT_SAC_AVG_VELOCITY
CURRENT_SAC_PEAK_VELOCITY
CURRENT_SAC_DURATION
CURRENT_SAC_DIRECTION
CURRENT_SAC_START_INTEREST_AREA_LABEL
CURRENT_SAC_START_INTEREST_AREAS
CURRENT_SAC_INDEX
NEXT_FIX_DURATION
NEXT_FIX_START
NEXT_FIX_X
NEXT_FIX_Y
NEXT_FIX_END
NEXT_SAC_AMPLITUDE
NEXT_SAC_AVG_VELOCITY
NEXT_SAC_CONTAINS_BLINK
NEXT_SAC_DIRECTION
NEXT_SAC_DURATION
NEXT_SAC_START_TIME
NEXT_SAC_END_TIME
NEXT_SAC_PEAK_VELOCITY
NEXT_FIX_INTEREST_AREAS
NEXT_FIX_INTEREST_AREA_DWELL_TIME
NEXT_FIX_INTEREST_AREA_ID
PREVIOUS_FIX_DURATION
PREVIOUS_FIX_INTEREST_AREAS
PREVIOUS_FIX_INTEREST_AREA_DWELL_TIME
PREVIOUS_FIX_INTEREST_AREA_ID
Diagnosis
Test
fix_practice_trial
fix_trial_number

Fixation Report
TRIAL_INDEX
CURRENT_FIX_INTEREST_AREAS
CURRENT_FIX_INTEREST_AREA_DWELL_TIME
CURRENT_FIX_INTEREST_AREA_FIX_COUNT
CURRENT_FIX_START
IP_INDEX
IP_LABEL
CURRENT_FIX_BLINK_AROUND
CURRENT_FIX_DURATION
CURRENT_FIX_END
CURRENT_FIX_X
CURRENT_FIX_Y
CURRENT_FIX_INTEREST_AREA_LABEL
CURRENT_FIX_INDEX
Diagnosis
Test
fix_practice_trial
fix_trial_number

Interest Area Report
RECORDING_SESSION_LABEL
IP_LABEL
IA_DWELL_TIME_%
IA_LABEL
Simple_trial_number
Diagnosis

* Variables in capitals are automatically generated by the Data Viewer software. Those in lower case are generated manually by the researcher in Data Viewer after data collection (i.e. diagnosis) or are generated in Experiment Builder as part of the test design (i.e. trial number).

Appendix 8: List of publications

Bocchetta, M., Iglesias, J. E., Russell, L., Greaves, C. V., Marshall, C., Scelsi, M. A., . . . Rohrer, J. (2019). Segmentation of medial temporal subregions reveals early right-sided involvement in semantic variant PPA. *Alzheimer's Research and Therapy*. *11*, 41

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Marshall, C. R., Hardy, C. J. D., Allen, M., Russell, L. L., Clark, C. N., Bond, R. L., . . . Warren, J. D. (2018). Cardiac responses to viewing facial emotion differentiate frontotemporal dementias. *Annals of Clinical and Translational Neurology*. *5* (6), 687-696

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