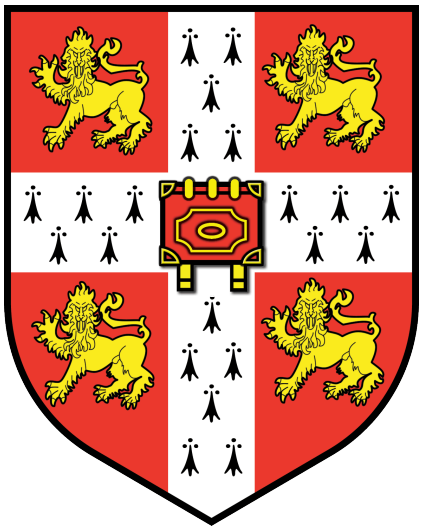
Understanding mechanisms related to psychosis in Motor Neurone Disease



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Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where declared in the text.

This work is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University of similar institution. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution.

The word count of 55,280 does not exceed the prescribed word limit.

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Darwin College and evenings resting my brain at Dar Bar.

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Abstract

Psychosis is a challenging feature of the syndromes of motor neurone disease (MND), frontotemporal dementia (FTD) and their overlap (FTD-MND). Clinically evident psychosis is not common, except in those with C9*orf*72+ expansions. However, subthreshold psychosis or pre-psychosis processes are common and provide the opportunity to study the mechanisms of psychosis in MND and FTD-MND.

My aim was to identify the prevalence and the cognitive and neural correlates of psychosis, and related processes, in MND. I used a tiered cohort study approach. Tier 1 introduced screening as standard in a regional MND clinic (*N*=111) using the Edinburgh Cognitive and Behavioural ALS Screen and Cambridge Behavioural Inventory-Revised (CBI-R). In Tier 2, 60 patients and 30 controls underwent neuropsychological assessment, including (i) evidence-based decision-making, to quantify *jumping to conclusions* (JTC), (ii) *attentional* control and associative learning, (iii) *perceptual inference,* and (iv) psychiatric screening with Neuropsychiatric Inventory (NPI), Brief Psychiatric Rating Scale (BRPS), and the Comprehensive Assessment of At-Risk Mental States (CAARMS). Tier 3 included magnetic resonance imaging of 30 patients and 20 controls.

Carer reports in Tier 1 indicated that 10% of patients exhibited features suggestive of psychosis and 40% exhibited behavioural change. In Tier 2, many patients manifested abnormal behaviours (CBI-R 41%; NPI showed 19%; BPRS 24%), with 12-16% showing psychosis-specific symptoms (CBI-R and NPI psychosis index scores). In the *jumping to conclusions* task, patients made decisions based on less evidence than controls and were insensitive to negative feedback. Carer ratings of patient behaviour correlated with performance on the *jumping to conclusions* task when decisions were rewarded or costs fixed. *Attentional* shifting and *perceptual inference* were normal in MND. A principal

component analysis (PCA) of questionnaires revealed two component scores, reflecting distinct patients' and carers' perspectives.

The imaging analyses focused on the correlates of *jumping to conclusions* and insensitivity to negative feedback*,* as a potential risk profile for psychosis, with exploratory analyses of the correlates of the CBI-R psychosis index, and carers' ratings of behaviour from the PCA*.* Using a Freesurfer regions-of-interest approach, grey matter volume correlated inversely with CBI-R psychosis index in the caudate, amygdala, cingulate and hippocampus. Using tract-based spatial statistics, increased mean diffusivity (MD) of diffusion weighted imaging correlated with the CBI-R psychosis responses in inferior longitudinal and uncinate fasciculi. Cost sensitivity in the JTC task correlated with cingulate and cerebellar grey matter volumes. White matter correlates of cost sensitivity included reduced FA with increasing cost sensitivity in white matter connecting the inferior frontal lobe in controls and patients.

Although overt psychosis is uncommon in MND, many patients displayed abnormal behaviour or cognitive symptoms, including suboptimal reasoning biases and inferential impulsivity. Degeneration of cerebellar, cingulate and striatal grey matter, and adjacent major white matter tracts, may underlie these cognitive impairments and together represent a vulnerability to develop psychosis. Compromised reasoning and inference have implications for clinical management, including decisions around treatment options and management of well-being in MND.

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Abbreviations

ALS-FRS-R Amyotrophic Lateral Sclerosis – Functional Rating Scale - Revised

bvFTD behavioural variant Frontotemporal Dementia

C9*orf*72 chromosome 9 open reading frame 72

CBI-R Cambridge Behavioural Inventory – Revised

DSM Diagnostic and Statistical Manual of Mental Disorders

DTD Draws To Decision

DTI Diffusion Tensor Imaging

FTD Frontotemporal Dementia

FTD-FRS Frontotemporal Dementia – Functional Rating Scale

JTC Jumping to Conclusions

MND Motor Neurone Disease

MRI Magnetic Resonance Imaging

NPI Neuropsychiatric Inventory

PCA Principal Component Analysis

TBSS Tract Based Spatial Statistics

Chapter 1 Introduction

This chapter outlines the clinical features of motor neurone disease and motor neurone disease with frontotemporal dementia, the shared pathological underpinnings and leading genetic mutation that emphasise the continuum on which motor neurone disease and frontotemporal dementia represent the extremes. One very challenging clinical symptom that occurs along the continuum is psychosis. This chapter then reviews the evidence of psychosis features in MND, describes the psychosis continuum in the context of primary psychosis conditions and outlines the neurobiological mechanisms of psychosis. I review three candidate cognitive mechanisms by which psychosis emerges and the associated brain regions and pathways that are affected with MND, FTD and psychosis disorders, to complete the introductory background.

The thesis focuses on psychosis features and the cognitive and neural mechanisms of psychosis, and subthreshold 'pre-psychosis' states in MND. Although infrequent at the MND end of the FTD-MND continuum, when present, these challenging symptoms worsen the existing challenges faced by many people living with MND and cause significant carer stress. Understanding the wider at-risk population will be necessary to support the psychiatric wellbeing of patients.

1.1 Motor neurone disease

Motor neurone disease is a fatal progressive neurodegenerative condition in adulthood. It is synonymous with amyotrophic lateral sclerosis (ALS), but I will be using the label motor neurone disease (MND). MND encompasses a spectrum of phenotypes affecting motor

neurons. The specific clinical pattern of signs and symptoms vary depending on the (upper or lower) motor system which is predominantly affected. Most patients have a combination of upper and lower motor neurone loss, but some phenotypes of MND are restricted to the extremes of either upper or lower motor neurones (Al-Chalabi & Hardiman, 2013; Turner, 2019). The initial clinical presentation is commonly classified by site of symptom onset. 70% of patients present with a limb onset, characterised by focal muscle weakness and wasting, muscle twitches and fasciculations, falls/trips, and loss of dexterity (Kiernan et al., 2011). 25% of patients present with bulbar onset, characterised by slurred or quiet speech, dysphagia for liquids and/or solids, excessive saliva, choking and tongue fasciculations (Kiernan et al., 2011). Initial trunk or respiratory onset occurs in 5% of patients (Kiernan et al., 2011). Truncal and respiratory involvement is common following limb and bulbar onset.

MND affect adults as young as 20 years and as old as 90 years, however the typical median age of onset is in the seventh decade of life (Logroscino et al., 2010). Survival is highly variable: patients can survive a few months to more than 20 years. The typical median survival from symptom onset is in the range of 8 months – 5 years, with a small percentage surviving beyond 10 years (Al-Chalabi & Hardiman, 2013; Kiernan et al., 2011; Talbot, 2009). The mean delay in diagnosis from first symptom onset is typically reported at 12 months (Al-Chalabi & Hardiman, 2013), although can be longer. The majority of patients develop MND sporadically. 5-10% of patients have a family history of MND, of which more than half can be linked to a known genetic abnormality (Kiernan et al., 2011).

Diagnosis is made by history taking and clinical examination, often accompanied by electromyography investigation (Ferguson & Elman, 2007). Formal diagnostic criteria have been developed, validated and revised to facilitate standard diagnosis for research, especially clinical trials (Brooks, 1994; Brooks et al., 2000; De Carvalho & Swash, 2009). However, these systemic approaches appear to have low sensitivity in a clinical practice (Al-Chalabi et al., 2016; Talbot, 2009), omitting clinically important features for management

such as rate of progression, genetic basis or functional impact. While there is currently no definitive diagnostic test, clinical findings together with nerve conduction and electromyography investigations improve diagnostic sensitivity and exclude differential, treatable diagnoses. Treatment of MND consists predominantly of symptom management and may include life-prolonging interventions, such as non-invasive ventilation and PEG feed insertion (percutaneous endoscopic gastronomy). The current standard drug shown to slow progression and prolong survival by only a few months in some patients is the anti-excitotoxic drug Riluzole (Miller et al., 1996), Food and Drug Administration (FDA) approved in 1995 and UK-NICE recommended in 2001 (https://www.nice.org.uk/guidance/TA20). 22 years later, in Japan and the USA only, Edavarone, an anti-oxidant drug was FDA approved. This is a relentless neurodegenerative condition which is currently incurable and imposes poor quality of life on patients and their family and carers. The daily complex physical needs are further compounded by changes in cognition and behaviour in a surprising number of patients, which largely contribute to poorer prognosis and quality of life (Bede et al., 2013) and increased carer stress (Lillo, Mioshi, & Hodges, 2012; Merrilees et al., 2010).

1.1.1 Motor neurone disease with frontotemporal dementia

Cognitive and behavioural changes in MND are now well-recognised in a substantial proportion of sporadic MND patients. They range from clinically recognisable frontotemporal dementia (FTD) (in up to 20% of patients) to mild alterations (in up to 50% of patients) (Hudson, 1981; Phukan et al., 2012; Ringholz et al., 2005). Behaviour and personality changes are closely similar to those reported in behavioural variant FTD and are typically the first clinical features to present in FTD-MND patients (Lillo et al., 2010a). Behaviour changes include apathy, behavioural disinhibition, loss of empathy, perseverative, stereotypical, compulsive behaviours, altered food preferences unrelated to swallowing

difficulties, mood alterations (depression and anxiety). Longitudinal studies have indicated that deteriorations in cognition and behaviour are not inevitable. For many patients with MND, normal cognition at baseline may remain so over time, whereas significant worsening of cognition and behavioural is common if these are impaired at baseline (Benbrika et al., 2019; Elamin et al., 2013; Woolley et al., 2018).

Presentations may also include overt psychosis (Cui et al., 2014; Lillo et al., 2010a), commonly delusions and hallucinations. As such, presentations with psychosis may be misdiagnosed as a primary psychosis condition such as schizophrenia or bipolar disorder. Conversely, the expression of psychosis symptoms in many FTD-MND patients can be much milder, symptoms which on their own would not be sufficient for a categorical diagnosis of a primary psychosis condition, a description that more commonly suits the expression of psychosis features in MND patients. Similar cognitive deficits in MND closely resemble the cognitive profile of FTD, characterised most commonly by executive impairments extending to changes in social cognition and language. Notably, emotional reflex hypersensitivity (pseudo-bulbar affect) and cognition involving predominantly executive processes are considered to be more prominent in bulbar onset MND (Abrahams et al., 1997; Thakore & Pioro, 2017).

The common presence of FTD-like symptoms in MND is now reflected in consensus criteria for the involvement of frontotemporal dysfunction in MND (Strong, 2017; Strong et al., 2009) with the 2017 revision specifically acknowledging the recognition of neuropsychiatric involvement in MND, central to this thesis. Where neuropsychological services are engaged, their rigorous investigation reveals a high number of patients with at least mild alterations of behaviour and cognition.

The clinical implications of aberrant behaviour and cognitive impairment, particularly executive impairment, include problems with judgement, decision-making abilities,

compliance with treatment and general deterioration in undertaking routine daily tasks. The implications matter for patients to empower them to have agency or control about their health care conditions, which requires sound mind. They also matter for carers' quality of life, who report increased burden and stress as a result of behaviour and cognitive alterations in patients, more than physical changes (Lillo et al., 2012; Merrilees et al., 2010).

The varying degrees of frontotemporal involvement, supported by neuropsychological evaluation and neuroimaging together with post-mortem pathologic assessment, place MND at one extreme of a heterogenous neurodegenerative continuum with FTD at the opposite extreme (Figure 1).

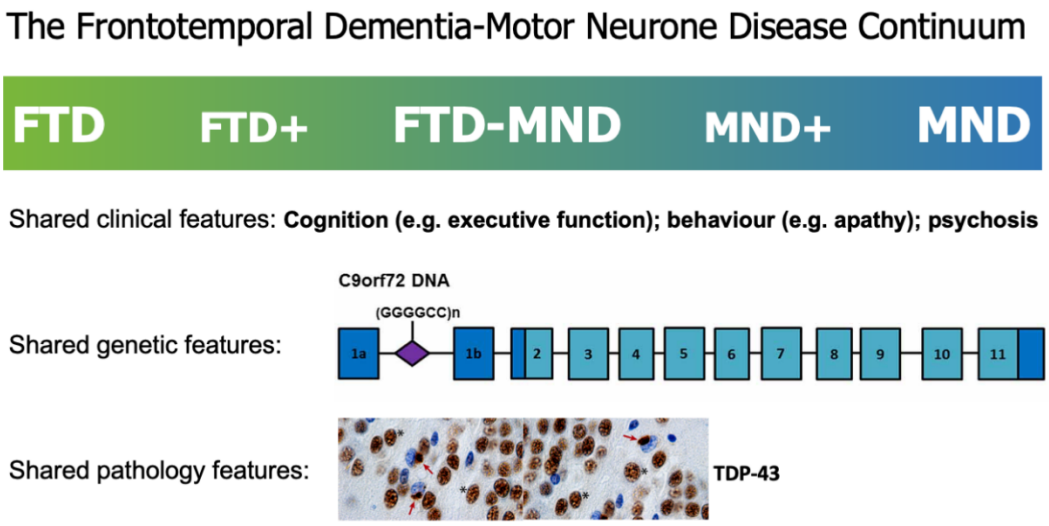

Figure 1: The Frontotemporal Dementia-Motor Neurone Disease Continuum.

Along the continuum, the involvement of FTD or MND features may change with disease progression. For example, as MND can present with frontotemporal behaviours and cognitive involvement, many FTD patients progress to develop motor neurone features

(Convery et al., 2019; Neary et al., 2000). These overlapping features and complex clinical manifestations make diagnosis along this continuum and among the clinical phenotypes of MND challenging, especially in the early stages of disease. Anatomical brain imaging techniques, such as volume parcellation and diffusion tensor imaging, have shown that the predominant motor network impairment extends to structural abnormalities and dysconnectivity of non-motor system networks (Abrahams et al., 2005; Agosta et al., 2007; McCluskey et al., 2014; Menke et al., 2018; Menke et al., 2014b), including atrophy of the frontal and temporal lobes. Moreover, the extensive extra-motor involvement in MND is shown to underlie many of the behavioural (Consonni et al., 2019; Mioshi et al., 2013) and cognitive (Agosta et al., 2016; Consonni et al., 2018; Tsermentseli et al., 2012a) features in MND and also observed in MND patients without cognitive impairment (Agosta et al., 2016; Chang et al., 2005).

In addition to common clinical features and brain imaging patterns that span the FTD-MND continuum, common pathological and genetic substrates strongly link MND to FTD and largely contribute to the phenotypic characterisations along the continuum. Pathologically, frontotemporal atrophy is associated with neuronal loss and cortical gliosis on post-mortem pathology. FTD-MND is predominantly associated with underlying intraneuronal TAR DNA binding protein (TDP-43) inclusions, which are present in nearly all patients with MND and around half of patients with FTD (Neumann et al., 2006). Genetically, the link between FTD and MND was strengthened by the discovery of the C9*orf*72 gene expansion (DeJesus-Hernandez et al., 2011; Renton et al., 2011), causing MND in 30-60% of familial cases and 10% of sporadic cases (Byrne et al., 2012; Renton et al., 2011; Talbot, 2011), and causing FTD in approximately 30% of familial cases and in sporadic FTD reports range from 2-21% of cases (Majounie et al., 2012).

1.2 Psychosis

In this section I discuss psychosis as a clinical symptom and label, and introduce the hypothesis that psychosis is not a discrete or binary phenomenon but is present as a continuum from expression in healthy individuals to primary disorders such as chronic schizophrenia. This will clarify how I will refer to psychosis symptoms later in the thesis and the motivation behind drawing links between psychosis in various primary psychosis groups and psychosis in MND.

1.2.1 Defining psychosis

Psychosis is a common and functionally disruptive symptom of many primary psychiatric and neurodegenerative conditions. It is the defining feature of schizophrenia, a variable feature of affective disorders, and is present across the FTD-MND continuum. In the psychiatric literature, the concept of psychosis is evolving and is variably defined.

Traditionally, psychosis has been defined as a loss of contact with reality and impairment of mental function (Kaplan & Sadock, 1995). Such impaired reality testing is manifested by hallucinations and delusions (sensory alterations/fixed false beliefs in the absence of external stimulus or incontrovertibly contradicting evidence) (Arcinieagas, 2015). Broader definitions include the presence of hallucinations and delusions with or without insight, disordered thought or speech, or behavioural abnormalities such as disorganisation, gross excitement/overactivity or psychomotor retardation/catatonia (Cardinal & Bullmore, 2011). Cognitive impairment often co-occurs and may present early and become severe with illness chronicity (Sheffield et al., 2018). The term psychosis may be used to describe the behaviour of a person or a condition in which reality testing is impaired (Kaplan & Sadock, 1995), for example schizophrenia is a classic psychosis condition.

Psychosis symptoms are assessed from a number of perspectives: patient, clinician and carer. Psychosis experience may be reported by the patient, which requires intact insight and memory but can provide rich experience not accessible by others. Symptoms such as hallucinations and delusions are increasingly subjective and if not described by the patient must be inferred from their behaviour by a clinician or someone who knows them well, such as a spouse or carer. Quantification through a clinician's judgment relies on whether or not a patient exhibits, remembers or reports symptoms at the time of assessment. Carer reports of psychosis symptoms are a necessary corroborative source of information, provided they can recognise and accurately report on patient behaviour but this is not to be confused with psychosis experience reported by the patient.

Classificatory systems within psychiatry, such as the *International Classification of Mental and Behavioural Disorders* (*ICD-10*) and the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), emphasises primary psychosis disease. However, with the fifth revision of the *DSM* (*DSM-V*), the formulation of psychosis in the context of primary psychosis conditions expanded to adopt a dimensional approach that emphasises these disorders occur along a continuum.

The *DSM-V* identifies psychosis (or psychosis features/symptoms) as one of several dimensions of neuropsychiatric disturbance in primary psychosis conditions (Arcinieagas, 2015) with other dimensions encompassing abnormal psychomotor behaviours, emotional and negative symptoms, and cognitive impairment. Relevant to the current thesis, the *DSM-V* strongly recognises the presence of psychosis secondary to neurological conditions, such as frontotemporal lobar degeneration (Neurocognitive Disorders section, page 591), and that there are many different manifestations of psychosis symptoms in these conditions. As such, the *DSM-V* suggests qualifying the primary cognitive disorder diagnosis with the specifier "with behavioural disturbance …(psychotic symptoms)" rather than offering a

concurrent schizophrenia spectrum disorder diagnosis (for example DSM-V page 606 of the Neurocognitive Disorders section).

For the purpose of this thesis, the emphasis will be on reported subclinical features that are characteristic of psychosis, such as unusual, bizarre beliefs and hallucinations, rather than on a categorical clinical diagnosis of a psychosis condition. I also include symptoms that are suggestive of psychosis – these will be referred to as "psychosis symptoms". Other clinical features suggestive of possible psychosis, include suspiciousness, overvalued or fixed ideas, disordered cognition, mood swings, aggression, inappropriate behaviour, disinhibition and obsessive-compulsive phenomena (Yung & McGorry, 1996a, 1996b). Such features include a mixture of mood-related symptoms (some of which are reactive to other symptoms), and behavioural changes (also in response to experiential phenomena). In the primary psychiatric literature, differential diagnoses of these overlapping symptoms are varied. They include frontotemporal dementia, which will be the most common in the context of the current study. Frontotemporal behaviours, such as stereotypical motor behaviours and abnormal behaviours, are included in the "psychosis symptoms" descriptor or as "symptoms suggestive of psychosis". Clinical evaluation of psychosis in the context of neurodegenerative conditions can pose a significant challenge due to behavioural problems, memory, language or speech impairments and which may distort the presentation of obvious symptoms. However, in some neurodegenerative conditions, such as Alzheimer's disease, there is evidence to suggest a relationship between abnormal behaviours (carer-rated) and delusions and visual hallucinations (e.g. Quaranta et al., 2015). Broader symptoms such as apathy and mood will be referred to as "broader neuropsychiatric symptoms/features". These symptoms are clearly defined common features of psychosis in both primary psychosis disorders, including along the psychosis continuum, and across the FTD-MND continuum.

1.2.2 The psychosis continuum with health

Here I present the concept that psychosis exists on a continuum with normal experience within the healthy population through to chronic psychosis conditions (Van Os et al., 2009). This is relevant for my thesis as the psychosis continuum is embedded within the continuum of patients with FTD-MND, however it is not known whether psychosis in MND resembles that of an established psychosis condition or a phenotype that lies earlier along the psychosis continuum. Acknowledging that psychosis phenomena can arise from a wide range of mental disorders (American Psychiatric Association, 2013) and as a result of focal brain damage and neurochemical imbalance, causing varied durations and presentations of psychosis, I draw on insights from diverse psychosis phenotypes. Different psychosis phenotypes can have important differences in their presentation of psychosis. For example, psychosis as it presents in a first episode with unknown aetiology may differ from established schizophrenia. These psychosis phenotypes inform the way I investigated psychosis and related cognitive mechanisms in MND.

Even in the healthy population, endorsement of items on community-based surveys related to psychosis symptoms is not uncommon (Eaton et al., 1991; Heilskov et al., 2019; Scott et al., 2006). However, while many healthy people experience mild psychosis phenomena of disorganisation or a lack of motivation, they do not often experience persistent false perceptions. Prior to the DSM-V's re-labelling of schizophrenia to reflect a continuum disorder and its general shift from rigid categorical nomenclature of psychosis conditions, a long-standing concept that psychosis phenotype is expressed at levels well below its clinical manifestation existed. These subclinical, manifestations have been referred to as "psychosis proneness", "psychotic experience", or "schizotypy" (Meehl, 1962; Siever et al., 1993; Van Os et al., 2009; Yung et al., 2003), the persistence and severity of which indicate where along the continuum someone lies.

Under the framework of a psychosis continuum, many patient groups who do not have a clinical psychosis disorder, can be investigated on the same symptoms that are observed in patients with primary psychosis conditions, such as schizophrenia. The period leading up to the first psychosis episode that signals the onset of a primary psychosis disorder, is characterised by a prodromal phenotype of subthreshold psychosis symptoms, for example, subliminal, vague perceptual experiences (subthreshold hallucinations), and over-valued ideas (subthreshold delusions) (Yung et al., 1996). The experience of subclinical symptoms suggestive of psychosis, together with other factors such as whether or not a first-degree relative has a primary psychosis diagnosis (DeVylder & Lukens, 2013; Faridi et al., 2009), is associated with enhanced risk for converting to first episode psychosis and potentially a more chronic psychosis diagnosis, compared to the general population (Fusar-poli et al., 2015; Vijayakumar et al., 2016). Within the at-risk phenotypes, some have resolution of psychosis symptoms and some experience persistent non-psychotic conditions (i.e. low-level subthreshold symptoms) (Vijayakumar et al., 2016). Interest in the prodromal stage and at-risk psychosis groups has grown such that there are detailed bodies of research investigating cognitive profiles (Fusar-Poli, et al., 2012; Keefe et al., 2006) and brain structure (Fusar-Poli et al., 2011), function (Smieskova et al., 2010), connectivity (Crossley et al., 2009; Paolo Fusar-Poli et al., 2010; Karlsgodt, 2020) and neurochemistry (Davis et al., 1991; Stahl, 2018; Stone et al., 2009) to delineate why some transition to overt psychosis and others do not and the mechanisms underlying the development of psychosis symptoms.

That individuals experience clinical and subclinical psychosis symptoms, of varying severity and frequency, and which may persist or resolve is relevant to my thesis because this varied experience of psychosis is embedded across the FTD-MND continuum. Some patients experience florid psychosis others subclinical levels or behaviours suggestive of psychosis. Together with related disordered cognition, these behaviours may occur in the absence of a concomitant psychiatric diagnosis (section 1.3).

Studying such groups along the psychosis continuum of chronicity are powerful in that each psychosis phenotype has the potential to provide valuable insight into the neurobiological and cognitive mechanisms underlying the emergence of early psychosis and milder psychosis symptoms. There is currently no hallmark genetic, brain or cognitive marker of psychosis in primary psychosis conditions. Psychosis symptoms can emerge from a wide range of cellular, macroscopic brain lesions, functional dysconnectivity and neurochemically, which means the definition of psychosis is varied and complex. Direct comparisons between a single primary psychosis phenotype and neurodegenerative conditions have many caveats, because of the differences in neurodevelopmental factors, different pathological processes, and the presence of dementia, among others. However, similar symptoms of psychosis, such as hallucinations, delusions, disorganised thought and abnormal behaviour are core features that distinguish psychosis from other psychiatric disorders or as a result of focal lesions, or drug-induced psychosis. Therefore, valuable insights into the emergence of subclinical psychosis symptoms as they present in MND might be drawn from primary psychiatric literature, by aligning neurobiological and cognitive frameworks of psychosis symptoms.

1.3 Psychosis symptoms in MND

Psychosis is a challenging clinical symptom of the syndromes of MND, FTD and their overlap, which in the current thesis is the focus at the MND end of the continuum. The association of a primary psychosis condition and MND has been infrequently reported in the literature but may not be a rare occurrence. The association of psychosis symptoms and MND was suggested from the period when Jean-Martin Charcot was first differentiating ‘ordinary’ muscular atrophy from MND in 1870. He suggested that psychic disturbance was not essential to the diagnosis but sometimes associated with it (cited in Ziegler, 1930:930).

Through the 1900's numerous MND case studies described common associations of paranoia, hallucinations and irrational, peculiar behaviour (Friedlander & Kesert, 1948; Howland, 1990; Wechsler & Davison, 1932; Ziegler, 1930).

In the absence of sufficient post-mortem examination, it was commonly concluded that most cases of MND were without psychosis manifestations but when in the presence of psychosis, were likely to be a coincidental association with a functional psychotic disorder (Howland, 1990; Lawyer & Martin, 1953). Among these accounts, it was recognised yet simultaneously debated whether the psychosis manifestations were part of the degenerative process underlying the motor disturbance or the result of brain changes which by chance happened to be associated with the upper and lower motor neurone disease. Case reports cited in Wechsler & Davison (1932) argued that the clinical picture would have to resemble an organic dementia and not a manic depression or other emotional or psychogenic psychosis in order to confidently conclude the pathological process causing MND was also capable of causing symptoms suggestive of psychosis. Close inspection of the abnormal behaviours described by many of the case reports, such as "childish", "silly behaviour", "perseverate", "careless about his person", "at times went without clothes", "lost interest", in hindsight describe a characteristic behavioural variant FTD patient, which without such a label at the time would not have been diagnosed as a dementia.

When psychosis symptoms present clinically in MND, they manifest similarly to psychosis expression in concomitant FTD-MND patients, especially those with C9*orf*72: there are less frequent observations of florid psychosis symptoms (delusions and/or hallucinations), and when overtly present this can lead to an initial diagnosis of a primary psychosis condition such as schizophrenia, delusional psychosis, somatoform psychosis or paranoid schizophrenia. However, accurate prevalence rates in MND alone are not common due to previous research mostly reporting on psychosis behaviour in FTD and FTD-MND. More commonly observed are milder, subthreshold behavioural and delusional psychosis

symptoms resembling complex repetitive behaviours, suspiciousness, paranoid and irrational ideation, somatisations (“crawling” sensation on or beneath the skin), fixed or overvalued ideas about comorbid illness (Devenney et al., 2014; Snowden et al., 2012). Importantly, these symptoms are subtler than those observed in typical primary psychosis patients, and the mere presence of which is not sufficient to make a psychosis diagnosis.

Temporally, psychosis presentations in MND can occur in close proximity to the emergence of typical MND symptom onset. They often *anticipate* or occur during the period of motor symptom onset (Mioshi et al., 2014; Turner et al., 2016) and when they precede typical MND onset by a longer period (years earlier) they may be part of a longstanding primary psychosis condition (Zucchi et al., 2019). Such varied onset of psychosis symptoms has made a causal relationship difficult to infer. Nonetheless, the relationship between either single psychosis events or longstanding diagnoses and MND has been well-supported. For example, using a large hospital record linkage database, Turner et al. (2016) found hospitalizations with a first diagnosis of a psychiatric condition was significantly associated with a diagnosis of MND within the following year. Possible explanations include a prodromal experience prior to clinical presentation of overlapping FTD, or pathological overlap with FTD by the C9*orf*72 gene expansion. Within the FTD-MND continuum, Lillo et al. (2010) evaluated clinical features of FTD that later evolved to motor neurone disorder and found the presence of delusions was the best predictor of such progression. However, these studies predate the 2011 discovery of the C9*orf*72 gene expansion or interrogate archival patient records in which patients would not have been tested for the gene expansion. Shortly after the discovery of C9*orf*72, there was an influx of research investigating cognition and behaviour in MND, sub classifying MND even more accurately. Snowden and colleagues (2012) linked an increased association of psychosis symptoms with C9*orf*72, in the context of FTD-MND.

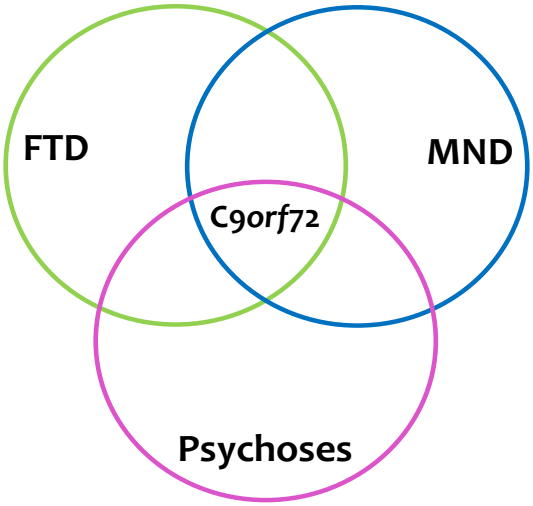

Figure 2: Schematic of the FTD-MND continuum, overlap with primary psychiatric conditions and the common genetic marker.

The association between psychosis and MND is further strengthened by clinical and epidemiological observations that suggest MND and primary psychosis conditions, including schizophrenia, may share heritability (Figure 2). High rates of schizophrenia have been reported in first- and second-degree relatives of people living with MND, including in kindreds associated with the C9*orf*72 gene expansion (Byrne et al., 2013; Longinetti et al., 2017; O'Brien et al., 2017). Prior to the discovery of C9*orf*72 expansions in 2011, patients with schizophrenia had disturbances in motor neurone function at the central (Goode & Manning, 1988) and peripheral level (Crayton et al., 1977 and Crayton & Meltzer, 1979 cited in Zucchi et al., 2019:3), findings which provide valuable insight into the prodromal nature of psychosis symptoms in MND and potential psychosis risk factors.

To describe psychosis symptoms in MND patients, historical studies traditionally used personality inventories commonly describing distinct personality profiles, which included "*unusual behaviour*" among the descriptions (Howland, 1990), scores derived from patients' self-rated psychoticism, and psychiatrists' ratings of patients on a number of symptoms (Griffith et al., 1980). These psychosis-typical interviews or structured questionnaires have been validated in and are generally more suited to a young adult population. However, the utility of conventional inventories in a busy multidisciplinary clinic setting may be valid for identification of overt psychosis symptoms but insufficient for detailed examination of underlying processes that may put patients at-risk for psychosis.

There is no established recommendation for management of psychosis symptoms in patients with MND and FTD-MND. Few studies experimenting with the effects of antipsychotic medication in symptomatic C9*orf*72 carriers with FTD have concluded effects were more adverse than beneficial to patients (Pijnenburg et al., 2003; Tsai & Boxer, 2014), and the rationale for the application of antipsychotic medication was targeted toward behaviours such as agitation rather than psychosis specifically (Manoochehri & Huey, 2012; Young et al., 2018).

In summary, while few MND patients exhibit overt psychosis, many more experience milder psychosis-like behaviour and alterations in thinking and cognition. These behaviours are considered to be below the threshold for a categorical diagnosis of psychosis but are sufficiently present to warrant attention. Even though psychosis symptoms do not predominate the clinic picture of MND, when present they are highly disabling in the day-to-day lives of people living with MND, and their carers. Therefore, it is important to understand the wider at-risk population if neuroprotective interventions are to be usefully applied, and to support the management of psychiatric well-being in MND.

The next section shifts from the phenomenology of psychosis and its clinical presentation in MND to the genetic, brain and cognitive mechanisms by which psychosis emerges in psychosis conditions. I also include their relevance to MND.

In MND there is a strong link between psychosis symptoms and the C9*orf*72 gene expansion, which has been recognised in some primary psychosis conditions (McLaughlin et al., 2017). There are, however, a number of functional neural pathways commonly affected in psychosis conditions, some of which have been linked to specific psychosis symptoms and which are implicated in neurotransmitter dysregulation. Cognitive deficits are also a robust feature of established schizophrenia (Barnett et al., 2010; Bortolato et al., 2015;

Heinrichs & Zakzanis, 1998) and are a central manifestation of the pathophysiology (Van Os et al., 2010). Given cognitive impairments have been documented to be present at the time of the first episode of psychosis illness (Daglas et al., 2015) and even predate the onset of first psychosis illness (Fusar-Poli, et al., 2012; Keefe et al., 2006; Pukrop et al., 2007; Yung et al., 1996), previous research has identified underlying changes in cognitive processes as potential mechanisms to the emergence of psychosis symptoms (Dudley et al., 2016; Garety et al., 2001; Griffin & Fletcher, 2017; Hemsley & Garety, 1986).

1.4 Mechanisms of psychosis development

Three levels of mechanisms by which psychosis symptoms develop will be summarised in this section: genetic, brain and cognitive mechanisms, of which brain and cognitive will be revisited in the empirical chapters of this thesis. One of the aims of this thesis is to draw links between neural structures and cognitive processes that inform psychosis symptoms, which in the context of MND are currently quite weak. These sections will detail how psychosis can emerge and vary according to genetic abnormalities, structural and functional brain changes, and neurochemical alterations.

1.4.1. Neurobiology of psychosis

I set out to understand the neurobiology of psychosis in MND, of which little is known but insight can be gained from other primary psychosis conditions, such as schizophrenia. I am going to consider psychosis at the level of cellular and genetic associations, then at the functional anatomy level, finally at the level of neurotransmitters and pharmacology.

1.4.1.1 Cellular and genetic associations

The pathogenesis of psychosis conditions, such as schizophrenia, is substantially genetic (Pardiñas et al., 2018) with estimated twin and familial heritability in the range of 65-85% (Hilker et al., 2018; Sullivan et al., 2003). Genetic risk for psychosis conditions arises from different forms of genetic variation, including single nucleotide polymorphisms (SNPs) and copy number variants (CNVs). Both act as risk factors, with evidence for partial overlap of genetic influences among psychosis disorders and with non-psychosis disorders (O'Donovan et al., 2008). For example, evidence from genome wide association studies (GWAS) revealed association with susceptibility to schizophrenia at *ZNF804A* (zinc finger protein 804A) on chromosome 2, which also shows an association with bipolar disorder (O'Donovan et al., 2008). GWAS has also revealed an association with variants in the major histocompatibility complex (MHC) on chromosome 6 (Ripke et al., 2013). Despite the recently identified 270 risk-associated loci (Ripke et al., 2020), these associations are generally not disease specific and are no confirmed causal mutations, with mendelian inheritance.

Relating to MND, an initial link to psychosis had been suggested through vulnerability to oxidative stress. MND is (albeit rarely) caused by mutations in the genes encoding the cytoplasmic copper/zinc superoxide dismutase (SOD1) (Rosen et al., 1993), while mitochondrial superoxide dismutase may be associate with schizophrenia (Akyol et al., 2005; Michel et al., 2004). However, a seminal clinical finding by Snowden et al. (2012) linked an increased association of psychosis symptoms with the C9*orf*72 gene expansion, in the context of FTD-MND. Considered the most distinguishing feature of C9*orf*72 carriers from non-carriers, Snowden et al.'s finding prompted a heightened awareness of psychosis symptoms and features suggestive of psychosis in clinical practice.

Psychosis symptoms are more commonly observed at the FTD end of the continuum with a clear over-representation of psychosis in C9*orf*72-related behavioural variant FTD compared to those without the C9*orf*72 expansion: large series have identified 28-56% of patients with C9*orf*72 had hallucinations and delusions compared with 4-18% of patients without the expansion (Rohrer et al., 2015). In patients with FTD-MND, relating to C9*orf*72, psychosis symptoms have been reported in 28% of cases (Snowden et al., 2012). The strong association of psychosis symptoms and C9*orf*72 has triggered a surge in the close delineation of psychosis across the FTD-MND continuum, both related and unrelated to C9*orf*72.

Despite the strong association of C9*orf*72 with FTD-MND, and especially in cases showing psychosis symptoms, extra-motor symptoms, including psychosis, are not unique to this gene expansion, supported by a number of findings (Crockford et al., 2018; Westeneng et al., 2016). Nonetheless, the research investigating psychosis in non-carriers is under-recognised. Analyses on retrospective MND archival cohorts (Turner et al., 2016) together with prospective (Abrahams et al., 2014; Crockford et al., 2018; McHutchison et al., 2019) and population studies (Longinetti et al., 2017), have supported that psychosis symptoms occur in less than 10% of sporadic MND patients and of those, C9*orf*72 is the leading cause. Critical to this thesis, there is a clear gap in the literature and under-recognition of the investigation of psychosis symptoms and risk for psychosis in sporadic MND.

Considering the prevalence of psychosis symptoms in symptomatic C9*orf*72 carriers and the gene expansion seemingly being the most common cause of psychosis symptoms in the context of the FTD-MND continuum, few studies have explored whether the repeat expansion is present in patients with a primary psychosis condition in the absence of clinical signs of FTD-MND. Case studies (Galimberti et al., 2014; Meisler et al., 2013) and large cohorts across USA, Europe and Japan, in patients with a primary psychosis diagnosis of schizophrenia or bipolar disorder have identified less than 1% with C9*orf*72 (Silverman et al.,

2019; Watson et al., 2016). In Watson et al.'s study (2016), all reported cases were in the absence of a dementia, however authors predicted that the schizophrenia and bipolar disorder patients would highly likely develop a dementia, specifically FTD-MND, given the high penetrance of the expansion. Although rare, and given it's similar prevalence estimates found in healthy controls (up to 0.15%) (Beck et al., 2013), these studies are a recognition of the presence of C9*orf*72 in primary psychosis conditions.

1.4.1.2 Functional anatomy

Schizophrenia has been referred to as a "disconnection syndrome" (Friston & Frith, 1995a) whereby the symptoms of delusions, hallucinations and thought disorder are decisively understood in terms of abnormal connections between different cortical, subcortical and striatal regions with the prefrontal lobe most centrally implicated. Schizophrenia cannot be explained by impairment of a single brain region (Friston, 1998). Rather, the complexity of the psychosis symptoms is reliant on the interconnections between many regions, which facilitate the integration of perception (extrinsically generated) and action (self-generated) (Friston, 1998; Salzman & Fusi, 2010; Ullsperger et al., 2014). Disruption to cortical-subcortical connections, especially involving the prefrontal cortex, including the frontal-limbic, frontal-striatal and thalamus connections are commonly reported. Evidence of dissociable altered connectivity for delusions and hallucinations has demonstrated the experience of hallucinations in association with altered connectivity to the hippocampus and thalamus (Amad et al., 2014; Silbersweig et al., 1995), whereby the representation and integration of expectations (self-generated) into perceptual experience (extrinsically generated) is disturbed (Behrendt, 2010). Conversely, delusions in schizophrenia have been associated with altered connectivity of the prefrontal cortex and the striatum and thalamic networks (Larivière et al., 2017; Spalletta et al., 2013), whereby executive

processes disrupt associative learning and performance monitoring and subsequently facilitate belief formation.

Psychosis symptoms have also been observed in focal lesions in the frontal and temporal lobes, for example in traumatic brain inured patients (Ardila, 2019), post-stroke (Devine et al., 2014; Rabins & Robinson, 1991) and in temporal lobe epilepsy (Clancy et al., 2014; Elliott et al., 2009), and are a common feature of neurodegenerative disease affecting the prefrontal and medial temporal regions, including behavioural variant FTD and MND (Patel & Sampson, 2015; Zucchi et al., 2019) and Alzheimer's disease (Balthazar et al., 2014; Murray et al., 2014). Psychosis symptoms are also reported in cortical-striatal networks through focal lesions to the caudate (Cheng & Liu, 2015) and basal ganglia structures (McMurtray et al., 2014), and neurodegenerative conditions primarily affecting the basal ganglia, such as Parkinson's disease (Williams-Gray et al., 2006) and Huntington disease (Rosenblatt, 2007). The neurobiological evidence here implicates networks specific to certain sensory modalities and the integration of prefrontal cortex associations to the striatum.

The similarities in psychosis symptoms that occur as a consequence of limbic, striatal and prefrontal damage emphasises their anatomical relationship and functional dependence. Evidence from physiological, anatomical and lesion studies in non-human primates (Kemp & Powell, 1970; Lehéricy et al., 2004; Middleton & Strick, 2002) show these regions to be highly interconnected. Frontal lobe loop circuits involving limbic and striatal structures are not sharply segregated (Averbeck et al., 2014) and the symptoms of psychosis and related cognitive mechanisms likely involve a diffuse dysfunction across multiple loops. However, these loops may map on to distinct cognitive processes, such as attentional control, positive-negative processing, adaptive behaviour, and psychosis symptoms (delusions and hallucinations).

Homologous yet structurally and functionally distinct frontal-subcortical loops involving the prefrontal cortex and limbic and striatal structures have long been suggested (Alexander et al., 1986). Each pathway projects from different parts of the frontal lobe and involves dissociable parts of the striatum, globus pallidus and thalamus and influentially feedback to the original frontal region. Of five classic circuits[1], three involve the prefrontal cortex and are behaviourally and cognitively relevant to psychosis symptoms (hallucinations and delusions) and aberrant cognitive processes. The three prefrontal circuits originate in the dorsolateral prefrontal cortex, orbitofrontal cortex and anterior cingulate (Alexander et al., 1986) and project to the striatum and thalamus (Figure 3). The pathways converge to similar regions of the striatum (caudate and nucleus accumbens), thus rather than work in isolation, form interactive networks (Draganski et al., 2008; Haber & Knutson, 2010). Additional, frontal-limbic pathways involving the anterior cingulate and medial temporal lobe contribute to the network that integrates cognitive processes of certain sensory modalities and emotion-based decisions (Benes, 2010; Bogerts, 1997; Orellana & Slachevsky, 2013). Lastly, prefrontal circuitry connections with the cerebellum via subcortical limbic structures and the thalamus are believed to sub-serve executive control and adaptive behaviour (Figure 3) (Heyder et al., 2004; Orellana & Slachevsky, 2013; Strick et al., 2009). Reliant on the integrity and interaction of these pathways, are cognitive processes commonly disrupted in the early stages of psychosis emergence, such as aspects of decision-making, learning from positive-negative feedback and high-order attentional control (necessary to monitor performance and adapt behaviour appropriately) (Fettes et al., 2017; Floresco et al., 2009; Haber & Behrens, 2014; Heyder et al., 2004; Jensen et al., 2008; Rolls, 2019), and balanced integration of

[1] The other two circuits include a motor circuit originating in the supplementary motor area and an oculomotor circuit originating in the frontal eye fields (Alexander et al., 1986)

information (extrinsically and intrinsically) to maintain balanced percepts and appropriately adapt to the environment (Robbins, 1990).

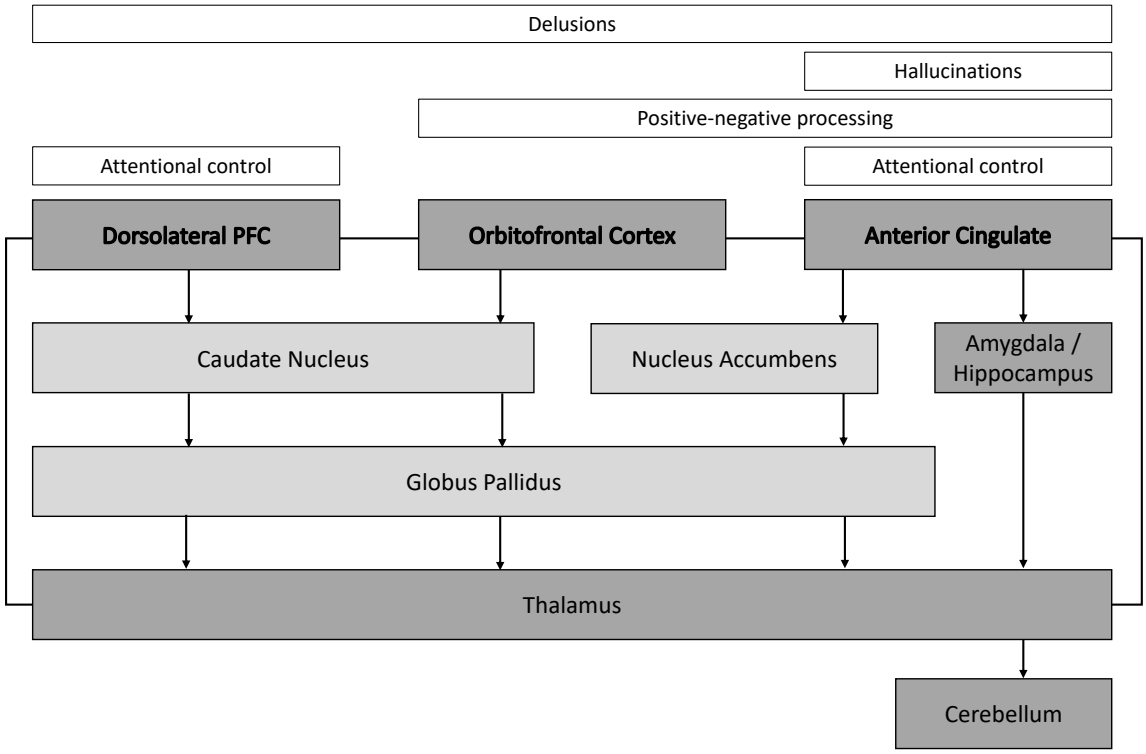

Figure 3: Parallel cortical-subcortical circuitry underlying attentional control, positive-negative processing, extrinsic/intrinsic information processing.

Neuroimaging provides evidence that the aforementioned neural networks are involved in psychosis and aberrant cognition, emphasising the concept of a disconnection syndrome. White matter alterations measured by diffusion metrics in individuals with schizophrenia identify damage to cortical-subcortical limbic networks in association with clinical symptoms and neuropsychology deficits. Positive and negative symptoms and severity are predominantly correlated with reduced diffusion properties in tracts connecting the frontal and temporal lobes (Lener et al., 2015; Skelly et al., 2008), for example correlations between delusions (suspiciousness, ideas of reference) and reduced diffusion properties in the

uncinate fasciculus, connecting the frontotemporal regions, have been reported (Nakamura et al., 2005). Diffusion metrics of the uncincate and cingulum bundle extensively involving the prefrontal cortex pathways have been associated with attentional control (Parnanzone et al., 2017; Quan et al., 2013) and of the striatal-ventral tegmental pathways associated with positive (reward) learning (Rivas-Grajales et al., 2019). Functional magnetic resonance studies (fMRI) identify altered connectivity in the caudate associated with conversion to psychosis in high risk groups (Allen et al., 2019), reduced activation in the ventral striatum during decision-making on a probabilistic decision-task (Rausch et al., 2014) and reduced activation in the prefrontal cortex in association with poor attentional control (Waltz et al., 2013) in patients with schizophrenia. Dissociable hypo-hyper cortical-subcortical connectivity has been identified for delusions and hallucinations using fMRI (Ferri et al., 2018), whereby delusions were negatively associated with thalamic-cerebellar connectivity and hallucinations were positively associated with thalamic-medial-temporal connectivity. Positron emission tomography (PET) studies using ^{18}F-fluorodeoxyglucose have reported glucose hypermetabolism strongly in the frontal lobe, striatum and thalamus in schizophrenia patients with positive and negative symptoms (Hazlett et al., 2004; Shinto et al., 2014; Siegel et al., 1993).

Pathological studies are less consistent as there have been no consistent cellular abnormality in the brains of schizophrenic patients (Halliday, 2001). Some pathological studies confirm *in vivo* neuroimaging volume loss to post-mortem volume loss or cellular changes in frontotemporal and thalamic regions (Fornito et al., 2009; Iritani, 2014; Roberts & Bruton, 1990), and some confirm the involvement of neurotransmitter receptors in subcortical structures, such as the basal ganglia and thalamus (Kleinman et al., 1988; Watis et al., 2008). Similarly, pathological studies in MND and FTD-MND have shown the involvement of striatal networks involving both efferent system components and glutamatergic inputs from cortical areas (Riku et al., 2016, 2017), additionally implicating

these discrete yet overlapping pathways in behavioural abnormality and cognitive involvement in MND and in psychosis.

1.4.1.3 Neurotransmitters and neuropharmacology

Brain structural abnormalities are neither sufficient nor necessary for psychosis phenomena. For example, neurochemically, a healthy individual with healthy brain structure can experience temporary overt psychosis symptoms after consuming LSD. However, in primary psychosis conditions, such as schizophrenia, several neurotransmitters have been implicated in psychosis and in modulating the frontal-subcortical and frontal-striatal circuits discussed above, including dopamine, glutamate and serotonin (Stahl, 2018). Each involves interconnected pathways; thus, it is likely more than one contributes significantly to the delusion, hallucination and cognitive symptoms of schizophrenia and other psychoses. I briefly review each of these neurotransmitters in schizophrenia and consider their relevance in MND.

Dysregulation in the dopamine systems is the most influential neuropharmacological hypothesis about schizophrenia (Davis et al., 1991; Howes & Kapur, 2009; Snyder, 1976). It postulates that hypoactivity in the prefrontal cortex contributes to the negative and cognitive impairments, whereas hyperactivity in the subcortical striatal and limbic structures contributes to the positive symptoms (Howes & Kapur, 2009). Evidence from dopaminergic drugs has demonstrated induced or exacerbated psychosis symptoms in some patients (Kuzuhara, 2001), as a result of overstimulation of cortical-limbic dopamine receptors (Williams-Gray et al., 2006). In MND, reduction of dopamine neurones in the substantia nigra has been identified immunohistochemically (Kato et al., 1993), implicating the nigral dopaminergic system (Takahashi et al., 1993). Using single photon emission computed

tomography (SPECT), there is evidence of reduced ^{123}I-IPT[2] binding (a cocaine analogue that selectively binds to the dopamine transporter) in the striatum (Borasio et al., 1998), suggesting subclinical disruption to nigrostriatal dopaminergic neurons in MND. Additionally, ^{18}F-Fallypride (a dopamine receptor tracer) PET/CT identified decreased dopamine receptors in the nucleus accumbens and frontal and temporal lobes in MND (Fu et al., 2017).

Glutamate is the major excitatory neurotransmitter but is not restricted to well circumscribed anatomical pathways as dopamine, rather, signalling occurs ubiquitously throughout the brain (McCutcheon et al., 2020), thus potentially accounting for a wide range of impairments. The primary glutamate focus in schizophrenia has been on the N-methyl-D-aspartate (NMDA) receptor in the prefrontal cortex following the psychosis-like effects of NMDA antagonists (Goff & Coyle, 2001; Howes et al., 2015), closely resembling the positive and negative symptoms of schizophrenia. In MND, glutamate-induced excitotoxicity has a detrimental influence on motor neurons and has long been at the core of theories behind the pathophysiological mechanisms of MND. Abnormal glutamate levels have been identified in plasma (Plaitakis & Caroscio, 1987), in cerebrospinal fluid (Roisen et al., 1982), and decreased glutamate transport in the spinal cord, motor and sensorimotor cortex (Rothstein et al., 1992). The current FDA-approved drug for MND is Riluzole, which works on the excitatory properties of glutamate. From the early Riluzole drug trials (Bensimon et al., 1994; Miller et al., 1996), psychosis was rarely reported in study participants (see Riluzole drug information sheet from www.accessdata.fda.gov reporting fewer than 1/1000 patients). However, despite its principal actions on glutamate, the effect of Riluzole on psychosis symptoms in MND has not been formally established.

[2] N-(3-iodopropen-2-y1)-2β-carbomethoxy-3β-(4-chlorophenyl)tropane

The serotonin theory in schizophrenia posits that cortical serotonin hyperfunction can result in psychosis by chain reaction which activates glutamate which then activates the reward dopamine pathway, leading to psychosis symptoms (Stahl, 2018). Serotonin has an excitatory influence on motor neurones (Bedard et al., 1987) and the highest density of the serotonin receptors (5-HT-$_{1A}$) are expressed throughout the limbic regions (Varnäs et al., 2004). Abnormalities of regional cerebral serotonin receptor binding using PET imaging ([^{11}C]-WAY100635 ligand) has been identified in MND patients (Turner et al., 2005).

Dysfunction of these neurotransmitter systems is recognised along the FTD-MND continuum, in MND (Blasco et al., 2014; Borasio et al., 1998; Fu et al., 2017; Shaw & Ince, 1997; Turner et al., 2005; Vogels et al., 2000), FTD (Bowen et al., 2008; Huey et al., 2006) and FTD-MND, and may contribute to variable psychosis symptoms. However, symptoms of psychosis caused by neurological and psychosis conditions are not identical, suggesting that different degrees of input from these linked neurotransmitter systems may differentially cause psychosis, even in the absence of structural brain abnormalities.

1.4.1.4 Treatment of psychosis symptoms

Treatment of psychosis symptoms in schizophrenia has largely focused on dopamine intervention, which is widely implicated in the brain's reward and attentional control circuitry in both human and animal studies (Cools et al., 2019; Haber & Knutson, 2010; Klanker et al., 2013; Robbins & Everitt, 1996; Schultz, 2007), and in sensory integration processing (Cassidy et al., 2018). Established evidence from Parkinson's disease demonstrates dopaminergic drugs that mediate dopamine release induce or exacerbate psychosis symptoms in some patients (Kuzuhara, 2001). In contrast, positive and negative symptoms respond well to dopamine receptor blocking treatment in dopaminergic schizophrenia (Howes et al., 2015). However, up to a third of individuals with schizophrenia do not

respond to non-clozapine[3] antipsychotics (McCutcheon et al., 2020), supporting evidence of additional neurotransmitter involvement. Dopamine levels in both cortical (orbitofrontal) and subcortical (striatal) regions in response to drugs that induce dopamine release, such as Sulpiride, directly affect performance on attention flexibility tasks (Klanker et al., 2013; Mehta et al., 1999, 2004), which also appears to be reliant on the interaction with serotonin (Klanker et al., 2013). Glutamatergic drugs in combination with other antipsychotic dopaminergic treatments have both been shown to effectively treat residual positive and negative psychosis symptoms in schizophrenia (Tsai & Lin, 2010), yet be unsuccessful in clinical trials (Goff, 2014; Weiser et al., 2012) or in preclinical work exploring downstream glutamate release (Howes et al., 2015). In addition to its glutamatergic properties, Riluzole also possesses anticonvulsant and neuroprotective properties, and has subsequently been investigated as a treatment candidate for other non-psychotic psychiatric conditions, such as depression, anxiety and obsessive compulsive disorder (Zarate & Manji, 2008). However, its utility on psychosis symptoms is yet to be proven. Hallucinogens, such as lysergic acid diethylamide (LSD), act as serotonin agonists and several antipsychotic compounds, especially the atypical neuroleptics, act as serotonin blockers and mediate the levels of dopamine (Heckers, 2000), however as a monotherapy, serotonin antagonists are not effective (Miyamoto et al., 2005)

Current psychiatric and cognitive pharmacological care in MND includes benzodiazepines, amitriptyline and anti-depressants for emotional lability, depression and anxiety, and anti-depressants for cognitive change (Kiernan et al., 2011). Speculation that neuroprotective effects of some antipsychotics used in schizophrenia and other primary psychosis conditions may prolong survival in MND (Stommel et al., 2007) have shown inconsistencies on such an outcome (Al-Chalabi et al., 2013; El Oussini et al., 2016; Fornai et al., 2008; Pozzi et al.,

[3] The only first-line licensed drug for treatment-resistant schizophrenia

2018; Saute et al., 2010). Reduced dopamine receptor binding in the frontal cortex and striatal structures in MND may contribute to the pre-psychosis cognitive abnormalities but does not suffice to explain the positive symptoms of psychosis. Yet, psychosis behaviour in MND have been considered target symptoms for treatment with novel antipsychotics, and have especially been suggested to treat psychosis symptoms in C9*orf*72 FTD patients (Young et al., 2018). However, there has been insufficient research to investigate the effects of antipsychotics on psychosis symptoms in MND.

Among many theoretical frameworks and cognitive models of positive symptoms of psychosis, I will be drawing on three key cognitive mechanisms proposed as representing a predisposition to the emergence of psychosis symptoms: suboptimal reasoning ability (Garety & Freeman, 1999), poor attentional control and associative learning (Frommann et al., 2011), and an imbalance in visual perceptual inference (Fletcher & Frith, 2009). The following section will move from the biological correlates of psychosis and consider the cognitive mechanisms and the local collaborative tools used to measure them in various psychosis groups, which will be applied in the current thesis.

1.4.2 Cognitive mechanisms of psychosis

Consistent cognitive impairment is well documented in chronic psychosis (Bilder et al., 2000; Dickinson et al., 2004; Freedman & Brown, 2011). Given these impairments have also been documented to be present at the time of the first episode of psychosis illness (Daglas et al., 2015) and even predate the onset of first psychosis illness (Fusar-Poli, et al., 2012; Keefe et al., 2006; Pukrop et al., 2007; Yung et al., 1996), much of the psychosis literature has explored cognition in treatment-naïve, at-risk psychosis groups to elucidate cognitive risk factors of prolonged psychosis. Early cognitive disruption in at-risk individuals has been identified in executive function, attention, information processing and memory at levels

intermediate between patients with schizophrenia and healthy controls (Bang et al., 2015; Hwang et al., 2019; Mam-lam-Fook et al., 2017). Moreover, in investigations of the emergence of specific positive symptoms of psychosis, such as visual hallucinations and delusions, many aberrant cognitive processes have been identified as underlying cognitive mechanisms to the emergence of such symptoms (Dudley et al., 2016; Garety et al., 2001; Griffin & Fletcher, 2017; Hemsley & Garety, 1986).

Evidence to support anomalous conscious experience and change in perceptions of reality in psychosis groups along the psychosis continuum stem from research into specific psychological constructs and cognitive processes.

I focus on the following three cognitive processes:

1. “jumping to conclusions” during probabilistic decision-making (Garety et al., 2013; Garety et al., 1991)
2. attentional control (switching and associative learning) (Frommann et al., 2011; Murray et al., 2008)
3. perceptual inference (the balance of top-down bottom-up information processing) (Teufel et al., 2015).

Cognitive neuroscience techniques have played a key role in understanding the putative cognitive processes which may underlie psychosis symptoms, and their dimensions, experienced by psychosis patients. I argue that these novel tools may provide valuable insight into the emergence of features suggestive of psychosis in MND patients.

1.4.2.1 Jumping to conclusions

A psychological finding in patients with schizophrenia, especially those with delusions, is a tendency to gather less information before making a decision. Known as the "jumping to conclusions" (JTC) bias (Garety & Freeman, 2013), cognitive theories of psychosis propose that the JTC bias is a trait representing liability to delusions. Belief formation and persistence of delusions begins with the easy acceptance of implausible ideas and discounting alternative explanations (Garety et al., 2013; Garety & Freeman, 2013). The JTC bias further represents compromised integration of evidence with a person's belief and their subjective probability that belief is true. This compromised ability to integrate evidence is inherent in probabilistic reasoning, which is commonly associated with a Bayesian approach to the study of belief formation (Moutoussis et al., 2011). Once a belief is formed and the subjective probability of its truth, new evidence updates the probability and influences the belief. However, when beliefs are not updated appropriately on the basis of new evidence, abnormalities in beliefs occur (Hemsley & Garety, 1986), and subsequent poor reasoning. Reviews and meta-analyses have confirmed the specificity, strength and reliability of the association of JTC bias and psychosis symptoms (Dudley et al., 2016; Fine et al., 2007; Garety & Freeman, 2013; Ross et al., 2015) in chronic psychosis groups (Evans et al., 2015; Falcone et al., 2015; Warman et al., 2007) as well as early psychosis groups (Rausch et al., 2016; Ward et al., 2018). The latter early psychosis groups most accurately reflects the subthreshold psychosis symptoms observed in some MND patients, thus it is plausible to assume that our MND cohort may demonstrate qualitatively similar abnormalities in JTC and probabilistic reasoning.

Tasks typically used to measure the JTC bias involve sampling information and then making a decision, such as the classic "beads in the jar" task (Huq et al., 1988). Variants of this task require participants to decide how much information to sample before making a final decision, comparable behaviour to an ideal Bayesian reasoning agent (Huq et al., 1988).

The extreme JTC measurement has been operationally defined as making a decision after viewing just one or two items of information (Garety et al., 2005; Warman et al., 2007), and another commonly used outcome measure is the number of items viewed before making a decision – the number of draws to decision.

Using an updated version of the classic probabilistic reasoning "beads task" (Huq et al., 1988), Ermakova et al. (2019) demonstrated a JTC decision-making style in connection with sampling significantly less information and increased positive symptom scores in their early psychosis group compared to healthy controls. Their results were thoroughly consistent with a wider body of research suggesting that a reduced amount of evidence gathered when formulating a decision may be most strongly associated with presence of delusions (Dudley et al., 2016; Fine et al., 2007; Langdon et al., 2014). There is preliminary evidence that the JTC bias is demonstrated in subthreshold psychosis groups such as those who score highly for delusion ideation on psychiatric inventories (Warman et al., 2007) and established evidence in those considered at-risk (Broome et al., 2007; Ormrod et al., 2012) as well as in patients with chronic schizophrenia (Garety & Freeman, 1999). The presence of the JTC bias across all stages of the psychosis continuum, including primary psychosis disorder, indicates that the JTC bias may be related to a general predisposition towards delusions and indeed play a causal role in the formation of delusions in some patients.

1.4.2.2 Attentional control

Abnormalities in complex attentional control are argued to lead to the inability to distinguish between relevant and irrelevant stimuli (Frith, 1979; Hemsley, 1993; Kapur, 2003) suggesting a liability to perceptual disturbances. One of the most common neuropsychological findings in the psychosis literature are impairments in attentional set-shifting, or cognitive flexibility (Elliott et al., 1995). Proposed mechanisms for poor

attentional control include impaired set-learning related to limitations in attentional resources, and impaired reversal of learned associations (Waltz & Gold, 2007). Impairments in associative and reversal learning (by reinforcement or feedback), indicates an inability to change one's behaviour in response to a change in stimulus. Appropriately changing behaviour requires the ability to learn a new action-outcome association (and ignore a stimulus that was previously relevant) and then be able to sustain that behaviour (either until completion or the relevant stimulus is changed again). This requires constant attentional-switching and working memory to monitor the outcome of behaviour via feedback in order to update and maintain the appropriate behavioural response. Deficiencies at any point in the aforementioned cognitive processes reflect inflexibility and reduced responsiveness to feedback, cognitive symptoms which are all present in primary psychosis conditions (Waltz & Gold, 2007).

Applications of the Cambridge Cognition CANTAB version of a classic attentional control task (the Wisconsin Card Sorting Test (Grant & Berg, 1948)) have observed poor cognitive flexibility in established schizophrenia (Kim et al., 2014; McKirdy et al., 2009; Pantelis et al., 2009) and first episode psychosis (Leeson et al., 2009; Murray et al., 2008; Pantelis et al., 2009). Importantly, this deficit has been noted in some early psychosis patients to present near the time of initial presentation to psychiatric services (Joyce et al., 2002; Murray et al., 2008) and is considered a strong predictor of a primary psychosis diagnosis as disease progresses (Pantelis et al., 2004; Peña et al., 2011). The increasing attentional control dysfunction with chronicity of illness in psychosis compared to the earlier stages suggests different illness-related mechanisms affecting attention may be occurring during the emergence of psychosis symptoms. In the context of MND, early executive dysfunction, including cognitive inflexibility, has been demonstrated (Phukan et al., 2012). Therefore, with disease progression in MND affecting extra-motor frontotemporal regions that underlie

executive abilities and attentional control, a specific cognitive vulnerability to such a process involved in psychosis may be maintained.

1.4.2.3 Perceptual inference

Perceptual disturbances, such as hallucinations or false beliefs, arise when neural and cognitive processes of representation, disambiguation and integration breakdown. In established psychoses hallucinations and false beliefs may arise from weak priors and increased sensory noise (Fletcher & Frith, 2009), whereas in early and at-risk psychosis groups there is greater reliance on priors (Teufel et al., 2015). Such increased reliance on prior expectations is suggested to be associated with perceptual biases (Horga & Abi-Dargham, 2019), which may infer the incorrect cause of an external sensory stimulus. When integrating prior knowledge into perceptual inference, this is often seen as advantageous, however under the strain of a pathological state may represent a point of vulnerability and a more extreme bias.

In general, external stimuli (physical and social environmental factors) dictate how one adjusts predictions to bring or keep our perceptions under control. However, since there is no direct access to relevant states of the world, only to sensory stimulus caused by the environment, incoming stimulus can be inherently ambiguous. In order to generate an unambiguous representation of the world, this challenge can be overcome by way of combining ambiguous sensory information with prior knowledge of the environment (Fletcher & Frith, 2009), leading to a more balanced perception. Perception has thus been viewed as a combination of bottom-up sensory input and top-down influences from prior knowledge (Corlett et al., 2009; Corlett et al., 2019; Fletcher & Frith, 2009b; Grossberg, 2000). Investigating this model of cognitive function is one way to explore the emergence of psychosis symptoms, specifically perceptual disturbances. Under this model, it has been

hypothesised that an imbalance between bottom-up sensory evidence and top-down prior knowledge is at the core of the altered state of mind caused by psychosis (Fletcher & Frith, 2009). Accordingly, in the psychosis literature, when formulating perceptions, there is a trend to over-rely on prior knowledge, which may generate distorted perceptions that have no direct sensory cause, such as hallucinations (Corlett et al., 2019). This over-reliance on prior knowledge has been observed in clinical groups along the psychosis continuum, including overt psychosis (Corlett et al., 2019; Fletcher & Frith, 2009b) to early psychosis groups who have not yet received a clinical diagnosis (Teufel et al., 2015), and even in other neurodegenerative samples who experience psychosis symptoms (Zarkali et al., 2019). The presence of this imbalance in information processing before onset of overt psychosis symptoms suggests that the altered balance could represent a fundamental information processing mechanism that may represent a cognitively vulnerable state and contribute to the emergence of psychosis symptoms rather than a consequence of the psychosis state.

This model of cognitive function has been applied to quantify the effect of prior knowledge. Using subclinical samples whereby psychosis experience was below threshold for a categorical diagnosis and at an early stage or in healthy individuals exhibiting psychosis-proneness[4], Teufel et al. (2015) applied this model to explore the association of altered information processing mechanisms with early psychosis symptoms and at-risk stages. Where performance is typically impaired in individuals with a primary psychosis condition compared to healthy controls generally, the authors observed a performance benefit, highlighting a specific information processing atypicality rather than a deficit (Teufel et al., 2015). The findings from the Teufel et al. (2015) study suggests that individuals at risk for psychosis were susceptible to excessive influence of prior knowledge and expectations on

[4] Psychosis-proneness refers to healthy individuals who exhibit perceptual and belief-related schizotypal personality features (Spauwen & Os, 2006), who may be prone to develop psychosis symptoms.

the perceptual sensitivity of ambiguous visual stimuli and that the strength of this effect was related to hallucination-like perceptual disturbances.

Fortunately, these cognitive and perceptual alterations are not found in *all* MND patients. Nevertheless, psychosis symptoms are present in a proportion of MND patients and thus warrant clinical attention and the careful delineation of cognitive and neural correlates to inform risk-states for the development of psychosis. Having discussed the neurobiology and cognitive mechanisms of psychosis, in the next section I will discuss the grey and white matter structural correlates of MND and primary psychosis disorders, summarising the extensive brain imaging literature and drawing together the overlapping regions of interest in this thesis.

1.5 Grey and white matter involvement in MND

The neural correlates of psychosis in MND remain unknown. The following sections will briefly outline grey and white matter brain imaging findings in MND pertaining to disease severity and behavioural and cognitive phenotypes.

The multimodal imaging approach adopted in the current thesis is becoming standard research practice. It has allowed the combined investigation of the relative contributions of *topological* mechanisms of abnormalities in specific regions (via regional volumetric parcellation) and changes in pathways connecting regions (via white matter diffusion metrics) that underlying cognitive and behavioural changes in MND.

Currently, conventional MRI can support a pre-existing suspicion of MND by way of hallmark corticospinal tract hyperintensity detection and the presence of a T2-hypointense rim in the primary motor cortex (precentral gyrus) (Filippi et al., 2010). The MND brain on routine

clinical MRI investigation, otherwise often appears normal. However, detailed neuroimaging studies, using regional volume parcellation (e.g. FreeSurfer cortical stream on T1 and T2-weighted images (chapter 5)) and white matter diffusion metrics (e.g. tract-based spatial statistics on diffusion-weighted images (chapter 6)), have shown that grey matter and white matter degeneration in MND spread beyond the precentral cortices and corticospinal tracts to include the corpus callosum (Bede et al., 2015; Trojsi et al., 2013), frontotemporal cortices (Abrahams et al., 2005; Mioshi et al., 2013), thalamus (Lillo et al., 2012), midbrain (Menke et al., 2014b) and cerebellum (Prell & Grosskreutz, 2013).

Structural changes that correlate with disease severity, both cognitive/behaviour severity (Alruwaili et al., 2018; Branco et al., 2018; Mioshi et al., 2013) and motor severity (Menke et al., 2018; Trojsi et al., 2015) have been identified. In brief, cognitive severity correlates with grey matter atrophy in key frontotemporal regions, especially the frontal structures (Agosta et al., 2016; Consonni et al., 2018b), and white matter integrity in frontotemporal tracts and the corpus callosum (Agosta et al., 2016; Pettit et al., 2013). The most severe cortical involvement has been observed in patients with clinical features of both MND and FTD (Agosta et al., 2016; Machts et al., 2015; Mioshi et al., 2013). For example, behaviourally, the involvement of apathy has been shown to relate to reduced volume in prefrontal structures, including the orbitofrontal and dorsolateral prefrontal cortices and the frontal pole (Consonni et al., 2019; Tsujimoto et al., 2011), controlling for any affective (depression or anxiety) reaction to the exacerbation of motor symptoms. Defective empathy in MND has been related to reduced anterior cingulate and inferior frontal gyrus volume (Cerami et al., 2014), and pathological laughing and crying related to decreased orbitofrontal, inferior frontal and frontal pole volume (Christidi et al., 2018). Cognitively, poor performance on tasks of attention and executive function have been associated with volume reductions in the dorsolateral prefrontal cortex and inferior frontal cortex (Evans et al., 2015). Specific associations of regional volume reduction with domain-specific cognitive impairment are

inconsistent, usually due to the inclusion/stratification of cognitively heterogenous MND samples (Bede & Hardiman, 2014; Meoded et al., 2013; Mioshi et al., 2013; Schuster et al., 2014). Conversely, demonstrated cerebral grey matter changes in MND patients without cognitive and perceptual impairment (Christidi et al., 2018; Tsermentseli et al., 2012) suggest grey matter abnormalities may precede cognitive changes, a finding consistent with demonstrated structural changes in pre-symptomatic FTD C9*orf*72 carriers 5-10 years before expected symptom presentation (Rohrer et al., 2015).

Similar to regional grey matter atrophy in MND, DTI studies have reported extensive white matter involvement outside of the corticospinal tract in relation to clinical features of MND, including the site of onset and disease severity as measured by the ALS-FRS-R. Stratification by site of onset has revealed progressive white matter changes in both bulbar and limb onset patients (Cardenas-Blanco et al., 2014; Menke et al., 2017), with white matter abnormalities more severe in bulbar patients (Menke et al., 2017). A higher burden of upper motor neurone involvement is associated with DTI diffusion properties in corticospinal tracts, corpus callosum and superior longitudinal fasciculus (Iwata et al., 2011; Menke et al., 2014b; Müller et al., 2012).

White matter changes have also been identified in people with MND without overt cognitive impairment (Abe et al., 2004; Abrahams et al., 2005; Christidi et al., 2018; Ciccarelli et al., 2009; Masuda et al., 2016; Sage et al., 2009; Thivard et al., 2007) and those with variable involvement of cognition and/or neuropsychiatric behaviour (Agosta et al., 2016; Lillo, Mioshi, et al., 2012; Meoded et al., 2013; Pettit et al., 2013; Sarro et al., 2011; Tsujimoto et al., 2011), where patients have been stratified into the same group if they have either cognitive or behavioural involvement. Significant correlations of diffusion tensor imaging (DTI) properties with cognition have mainly been identified for executive tasks. For example, Masuda et al. (2016) demonstrated significant decrease in white matter connectivity between the caudate in the medial prefrontal cortex and the lateral orbitofrontal cortex in MND

patients with executive dysfunction, in patients with FTD-MND and also in MND with normal cognitive function. And further, specific executive functions of attention switching and reversal learning have been significantly correlated with DTI properties of commissural tracts (corpus callosum) and long range association tracts (superior longitudinal and inferior frontal-occipital fasciculi), cingulum, uncinate fasciculus and the anterior corona radiata passing through the frontal, temporal and occipital regions, bilaterally (Kasper et al., 2014; Sarro et al., 2011).

Although no study to date has investigated the neural correlates of psychosis in patients with a diagnosis of sporadic MND, two studies have done so in patients diagnosed with FTD-MND and FTD, stratified by gene status. First, Devenney et al. (2017) explored the grey matter correlates of psychosis symptoms in FTD-MND patients stratified by C9*orf*72 gene status. Majority of patients in this study had a diagnosis of behavioural variant FTD and a small proportion had concomitant MND. Devenney et al. (2017) demonstrated a higher psychosis score was associated with volume reductions in a widespread network of cortical and subcortical regions in C9*orf*72 FTD-MND carriers, compared to non-carriers, including discrete regions of the frontal (medial frontal, anterior cingulate, orbitofrontal), temporal (middle, superior and fusiform gyrus) and occipital (lateral) cortices, the thalamus, insula, striatum (caudate, putamen) and cerebellum.

The second study by Sellami et al. (2018) stratified FTD patients by C9*orf*72, *MAPT* and *GRN* gene status, and found psychosis symptoms correlated with volume reductions in similarly widespread cortical and subcortical structures of C9*orf*72 patients, and specifically delusions related to left frontal cortical atrophy. The extensive range of brain regions identified in these studies makes it difficult to definitively interpret the neuroanatomical underpinnings of psychosis symptoms in these cohorts. The usefulness of these non-specific grey matter findings as psychosis markers in MND is unclear.

These studies have taken a whole brain exploratory analysis approach, primarily seeking significant clusters in the brain, whereas I take a hypothesis-driven region of interest approach motivated in part by select overlapping regions in MND and psychosis conditions (discussed in the following section 1.6). One major caveat in these investigations is the lack of representation of MND patients, which is where the current thesis will largely contribute, to complete the coverage of diagnoses across the FTD-MND continuum by focusing the investigation on sporadic MND.

Major issues in imaging studies arise in terms of cohort size, differences in criteria used to classify cognitive and behaviour impairment, divergence in MRI acquisition protocols, with few studies employing a multimodal approach of grey and white matter changes in the same cohort, and differences in processing methods. When behaviour and cognition are considered, previous studies have selected MND samples with patients of different patterns of cognitive impairment (Mioshi et al., 2013; Sarro et al., 2011; Schuster et al., 2014), compared patients with or without dementia (Christidi et al., 2018; Rajagopalan & Pioro, 2015), or included a cognitively heterogeneous MND group to identify underlying neuroanatomical correlates of specific/variable cognitive processes (Agosta et al., 2016). Volumetric MRI analyses are not sufficiently sensitive in isolation, especially at an individual level (Menke et al., 2017), and at present the role of conventional structural MRI in clinical practice is mainly for the exclusion of MND mimics as part of routine diagnostic workup. Similarly, DTI in isolation has been found to lack sufficient discrimination of MND patients from healthy controls (Foerster et al., 2013). Instrumental markers of cognitive and behavioural impairment in MND are highly valuable for gaining insight into rare but not uncommon symptoms, such as psychosis and subsequently for symptom management. Multimodal structural MR imaging techniques, such as DTI and volume parcellation combined, have previously supported the investigation of and provided valuable insight into the neuroanatomical correlates of some of the most prominent behaviours in MND, namely

apathy (Consonni et al., 2019; Tsujimoto et al., 2011). They therefore have great value in their combined application to some of the more unique, milder and less common behaviours, such as psychosis phenomena.

The current thesis applies a multimodal imaging approach to investigate grey and white matter changes that underlie aberrant pre-psychosis cognitive processes and psychosis symptoms in a cognitively heterogeneous continuous sample of MND patients. The next section will briefly summarise the grey and white matter correlates in primary psychosis conditions before outlining the regions of interest in the current thesis and their overlapping involvement in MND and primary psychosis conditions.

1.6 Grey and white matter involvement in primary psychosis conditions

Functional and structural neuroimaging studies in primary psychosis conditions have concurred that abnormal brain function in psychosis is attributable to impairments in the coordination and connectivity in an extended network of brain structures including the frontal, temporal, and parietal lobes, the basal ganglia, hippocampus, thalamus and cerebellum (Konrad & Winterer, 2008; Samartzis et al., 2014). Wernicke's proposal over a century ago that schizophrenia might arise from a disruption to the brain's association fibres (cited in Fornito et al., 2017:3), has comprehensively been supported by neuroimaging. Specifically, DTI studies have quantified and demonstrated widespread, global damage on a number of microscopic white matter properties along association, projection and commissural white matter pathways linking cortical-cortical and cortical-subcortical regions (Fitzsimmons et al., 2013; Kubicki et al., 2007), for example along the uncinate fasciculus, cingulum, internal capsule, superior and inferior longitudinal fasciculi, and corpus callosum (Ellison-Wright & Bullmore, 2009; Fitzsimmons et al., 2013; Liu et al., 2013; Parnanzone et al., 2017; Wheeler & Voineskos, 2014). Abnormal regional grey matter is localised to specific cortical and

subcortical structures, with preferential involvement of frontal and temporal structures, and has been demonstrated at various stages of chronicity (Borgwardt et al., 2011; Fusar-Poli et al., 2011; Meisenzahl et al., 2008; Torres et al., 2016), to be related to aberrant cognition (Bonilha et al., 2008; Jirsaraie et al., 2018; Koutsouleris et al., 2010) and less consistently directly related to positive symptoms (Barta et al., 1990; Horn et al., 2010; Levitan et al., 1999; Shapleske et al., 2002; Zhang et al., 2015).

Neuroimaging studies in psychosis include comparisons across groups that are at various stages along the psychosis continuum, from at-risk individuals in a prodromal stage to chronic schizophrenia. General results of grey and white matter neuroimaging studies suggest that abnormalities evident in first episode psychosis and those considered at-risk are qualitatively similar but quantitatively different to those evident in established psychosis (Meisenzahl et al., 2008; Pantelis et al., 2003; Torres et al., 2016). In addition, longitudinal neuroimaging studies have valuably shown grey and white matter structural changes within the same patients over time, from early stages through to established schizophrenia (Carletti et al., 2012; Pantelis et al., 2003; Takahashi et al., 2009). Longitudinal studies pre and post psychosis symptom onset have indicated a striking vulnerability of frontotemporal structures in transition to overt psychosis (Benetti et al., 2013; Pantelis et al., 2003; Smieskova et al., 2010). Providing valuable insight to the current thesis, these results inform the pathophysiology of psychosis symptoms. First, with clinical evidence of discrete phases of psychosis illness, associated volume loss progresses in prefrontal, temporal, limbic and striatal structures (Allen et al., 2019; Benetti et al., 2013; Pantelis et al., 2003; Velakoulis et al., 2006), and changes in the prefrontal-limbic white matter connections (Carletti et al., 2012; Ellison-Wright & Bullmore, 2009; Fitzsimmons et al., 2013; Kubicki et al., 2007; Samartzis et al., 2014). Second, specific structures have uniquely been identified in at-risk cohorts and psychosis-prone individuals who experience attenuated symptoms but who do not progress to primary psychosis diagnoses. These include the inferior and superior

longitudinal fasciculi (Bloemen et al., 2010; Carletti et al., 2012; Clemm Von Hohenberg et al., 2014; Cooper et al., 2018; Karlsgodt, 2019; Luck et al., 2011). Third, there are structural vulnerabilities evident during the transition to overt psychosis, notably volume reductions of the medial and superior temporal lobes and of the prefrontal cortex (Allen et al., 2019; Pantelis et al., 2003), and reduced diffusion properties in frontal white matter (anterior limb of the internal capsule, corona radiata, anterior body of the corpus callosum and superior frontal-occipital fasciculus) (Carletti et al., 2012).

In chronic schizophrenia, executive dysfunction is among the most prominent cognitive processes showing strongest correlation with volume reductions in the prefrontal cortex (Antonova et al., 2004; Bonilha et al., 2008; Eisenberg & Berman, 2010; Jirsaraie et al., 2018; Seidman et al., 1994) and cerebellum (Kim et al., 2018; Segarra et al., 2008). Volume reduction in frontal (prefrontal) and temporal (superior and medial) structures has most consistently been negatively related to hallucinations and delusions (Barta et al., 1990; Modinos et al., 2013; Song et al., 2015; Takahashi et al., 2009). Similarly, DTI studies in chronic schizophrenia have provided consistent findings relating to white matter correlates of psychosis symptoms. For example, lower diffusion properties in white matter frontal-temporal, frontal-striatal and frontal-parietal pathways, such as the uncinate fasciculus, sagittal striatum and superior longitudinal fasciculus, have been associate with positive and negative symptom severity (Lener et al., 2015; Parnanzone et al., 2017; Skelly et al., 2008).

Previous findings have supported the hypothesis that specific neuroanatomical abnormalities in psychosis patients may reflect a combination of pre-existing psychosis vulnerability and structural changes associated with the first expression of psychosis symptoms (Fusar-Poli et al., 2011; Pantelis et al., 2003; Smieskova et al., 2010). Insights from such studies that include psychosis patients with similar subclinical variation in psychosis symptoms as MND patients may be valuable in ascertaining key brain structures involved in the emergence of subtle psychosis symptoms in MND.

It is important to highlight that measures of diffusion change with age (Pfefferbaum & Sullivan, 2003). The age at which individuals first experience psychosis symptoms or are diagnosed with first episode or established psychosis varies greatly, often occurring in young adolescents to young adulthood. Careful consideration was taken not to include studies with adolescents when reviewing imaging studies in primary psychosis conditions of relevance to an older MND cohort. Patients with early psychosis and psychosis-proneness compared to patients with categorical psychosis conditions, such as schizophrenia, have variably different brain region involvement that also vary in severity. The following three-part section describes areas of the brain that are implicated in various primary psychosis groups, including early and chronic psychosis stages, which also underlie aberrant behaviour and cognition in MND and FTD-MND.

1.7 Regions and connectivity related to behaviour and aberrant cognitive mechanisms underlying psychosis in MND

Investigation of the association between psychosis and brain structure could be approached in two ways. First, drawing on empirical evidence relating to associations strictly with delusions and hallucination of a primary psychosis phenotype, with the thalamus prominent in the literature (Andreasen et al., 1994; Behrendt & Young, 2004; Byne et al., 2009). Second, selecting regions based on investigations of C9*orf*72-related psychosis. C9*orf*72 not only affects the thalamus early (Floeter et al., 2016; Rohrer et al., 2015) but is one of many regions related to psychosis symptoms in C9*orf*72 FTD-MND (Devenney et al., 2017). I have taken an alternative approach, proposing three hypothesised cognitive processes that put one at risk of psychosis or behaviours suggestive of psychosis. The cognitive processes are of jumping to conclusions, attentional control, and perceptual inference involve functional anatomy, each with their own structural associations.

The neural systems outlined in section 1.4.1.2, together with the three potential cognitive mechanisms outlined in 1.4.2 that put one at risk of developing psychosis guided my selection of regions of interest to interrogate in the current thesis and are detailed in Figure 4.

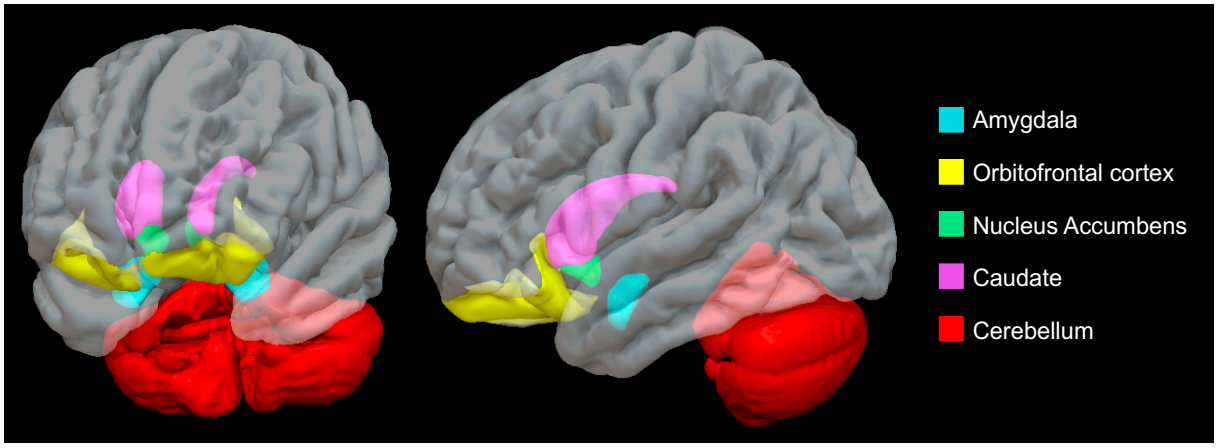

Figure 4: Regions of interest which summarise my hypotheses relating to the functional anatomy of psychosis which will be tested in the experimental chapters 4, 5 and 6. Regions imputed from the Desikan-Killany Cortical Atlas.

By assessing the underlying cognitive processes related to psychosis in relation to specific region and network systems, insight can be gained into the pathophysiological and functional relevance and expand clinical understanding when a degenerative process alters these regions and connections. The regions and networks outlined in this section have been related to psychosis symptoms and sub-serve the cognitive processes of interest to my thesis: decision-making and positive-negative learning, perceptual inference and information processing, and attentional control (Fettes et al., 2017; Floresco et al., 2009; Haber & Behrens, 2014; Heyder et al., 2004; Jensen et al., 2008; Rolls, 2019). These neural systems facilitate the alignment of the neurobiological framework under which psychosis symptoms

can be described and studied in primary psychosis disorders with that used to describe and study psychosis symptoms associated with neurodegenerative conditions.

The principal correlates of the three proposed cognitive processes of interest relating to psychosis emergence, form the regions of interest in the current thesis. They are: the amygdala (limbic system), orbitofrontal cortex, nucleus accumbens and the caudate (frontal-striatal regions), and the cerebellum.

1.7.1 Limbic system: amygdala

The amygdala is a key structure in frontal-subcortical circuitry involved in sensory-information processing and integration (Bogerts, 1997), and emotion-based learning and decisions (Benes, 2010; Li et al., 2011). Its afferent and efferent connections to prefrontal cortex structures, which have differential roles in mediating executive function (dorsolateral prefrontal cortex) and emotion and behavioural inhibition (orbitofrontal cortex), closely involve it in the functional integration of cognitive and emotional processes such as reward, and of certain sensory modalities.

Reduced amygdala volume has been identified in MND patients with (Branco et al., 2018) and without (Machts et al., 2015; Pinkhardt et al., 2006a) cognitive impairment, select involvement of specific amygdala nuclei have been identified (Chipika et al., 2020), diffusion metrics in the white matter indicate compromised white matter integrity (Barbagallo et al., 2014) and pathological studies indicate neuronal loss and ubiquitinated intraneuronal inclusions (Kawashima et al., 2001; Neary et al., 1990; Yokota et al., 2007). Despite this evidence, and clear evidence of behavioural change in MND, studies directly investigating the amygdala and its association with behaviour are surprisingly sparse, yet it is reasonable to speculate on the involvement of the amygdala in association with altered behaviour in MND patients. In psychosis groups, volume changes in the amygdala have been demonstrated to occur after onset of psychosis illness (Bois et al., 2015; Klauser et al.,

2015), indicating the pathophysiological change may be secondarily related to the disease process. Evidence from at-risk groups indicate minimal to no involvement of the amygdala (Bois et al., 2015; Klauser et al., 2015; Velakoulis et al., 2006), whereas by chronic schizophrenia amygdala reductions are pronounced (Ellison-Wright et al., 2008; Wright et al., 2000). Structural and functional deficits in the amygdala impede the amygdala's indispensable role for coupling external sensory information with internal information concerning emotion and affect (Bechara et al., 1995). Subsequently, in many schizophrenia patients, there is a failure in higher integrative and associative brain functions, leading to distortions in external reality interpretations (Bogerts, 1997).

1.7.2 Frontal-striatal pathways: orbitofrontal cortex, nucleus accumbens, caudate nucleus

Each frontal-striatal circuit originating in the prefrontal cortex, links specific prefrontal structures to striatal structures known to be involved in executive processes of decision-making and attentional control, positive-negative learning and subsequent adaptive behaviour (Alexander et al., 1986; Floresco et al., 2009; Haber & Behrens, 2014; Haber & Knutson, 2010). The orbitofrontal cortex, nucleus accumbens and caudate are key regions in frontal-striatal pathways that subserve the aforementioned cognitive processes and are implicated in psychosis symptoms.

The *orbitofrontal cortex* (OFC) is located on the ventral region of the frontal cortex and is strongly connected to cognitive association prefrontal cortices, sensory areas and limbic structures, such as the amygdala. The OFC also provides the main cortical projections to the nucleus accumbens and caudate of the striatum. The relevant processes to this thesis in which the orbitofrontal cortex is strongly implicated are decision-making, involving assigning value and evaluating changing stimulus or internal motivations but also in updating action-

outcome in the context of feedback (Fettes et al., 2017; Robbins & Everitt, 1996). Given the reliance of behavioural abnormalities on the orbitofrontal cortex in behaviour variant FTD (for example: Hornberger et al., 2011; Perry et al., 2006), the role of the orbitofrontal cortex has increasingly been studied in the context of MND, in which there are demonstrable volume reductions, mainly relating to apathy (Consonni et al., 2019; Tsujimoto et al., 2011) but also to pathological laughing and crying (Christidi et al., 2018). In psychosis groups, previous findings in orbitofrontal volume have been inconsistent with some reporting reduced volume (Convit et al., 2001; Gur et al., 2000; Nakamura et al., 2008; Takayanagi et al., 2010), some reporting large volume in first episode psychosis (Lacerda et al., 2007; Szeszko et al., 1999) and others reporting no difference from healthy controls (Chemerinski et al., 2002; Rupp et al., 2005; Sapara et al., 2007). However, relevant to the current thesis, few studies in chronic schizophrenia have demonstrated an association of reduced orbitofrontal volume to perceptual aberrations and thought disorder (Brosey & Woodward, 2017; Nakamura et al., 2008). Importantly, the role of the orbitofrontal cortex in the pathophysiology of psychosis symptoms is suggested from a study identifying volume reduction in at-risk psychosis groups who later developed psychosis compared to those who did not (Borgwardt et al., 2008).

The *nucleus accumbens* and *caudate nucleus* form the ventral striatum. Both structures play an important role in executive functions and reward-based decision-making (Haber & Knutson, 2010; Robbins et al., 1989; Spicer et al., 2007). Given its prefrontal and amygdala connections, the nucleus accumbens is critical for processing motivationally-relevant stimuli, such as reward, and integrating reward and positive feedback properties into behaviour (Le Heron et al., 2019). Similarly, the caudate plays a role in reward-based decision-making (Simpson et al., 2010) and is additionally vital for executive cognitive functions, including attentional set-shifting (Heckers, 2000) associative learning (Anderson et al., 2017), and goal-directed behaviour (de Wit et al., 2012), including updating behaviours based on changing stimulus.

MRI studies have demonstrated patients with FTD-MND have volume changes in nucleus accumbens and caudate compared to MND patients (Machts et al., 2015). However, MND patients with normal cognition have shown a significant decrease in structural connectivity between the caudate head networks (Masuda et al., 2016) and compromised white matter integrity in the caudate (Barbagallo et al., 2014). In psychosis groups, structural changes in the striatum, implicating the caudate and nucleus accumbens, are mixed. Acknowledged effects of neuroleptics likely contribute to findings that show increased caudate volume (Brandt & Bonelli, 2008; Levitt et al., 2010) yet more consistent results in drug-naïve psychosis groups support reduced caudate volume, especially in early psychosis groups, such as first episode psychosis (Levitt et al., 2002; Scanlon et al., 2014; Westmoreland Corson et al., 1999) and reduced nucleus accumbens volume (Bois et al., 2015; Koshiyama et al., 2018). Specifically, early volume reduction of the caudate in first episode patients compared to at-risk patients, identifies the early involvement of this structure in line with psychosis symptom onset (Bois et al., 2015; Ellison-Wright et al., 2008) and in first episode patients, reduced caudate volume is associated with severity of psychosis symptoms (Crespo-Facorro et al., 2007). Similarly, pronounced dysregulation in frontal-striatal circuitry involving the caudate has been strongly associated with positive and negative symptom severity in unaffected first-degree relatives (Fornito et al., 2013). In established schizophrenia, disrupted connectivity with prefrontal cortex structures is compromised by prominent white matter volume reductions in the caudate (Takase et al., 2004). Consistent with frontal-striatal circuity involvement in cognition, reduced volume in the caudate and nucleus accumbens have been associated with impairments in decision-making, reasoning and attentional control in first episode patients (Fan et al., 2019; Levitt et al., 2002).

1.7.3 Cerebellum

The cerebellum contributes to cognitive processing via its connections with cortical association areas, such as the hippocampus, amygdala and frontal lobes (Schmahmann, 1996). White matter alterations (Bede et al., 2015), pathological TDP-43 negative inclusions and increased p-62 inclusions (Cooper-Knock et al., 2014; Mackenzie et al., 2014) have previously been identified in the cerebellum in FTD-MND patients with C9*orf*72.

In pre-symptomatic C9*orf*72 carriers (i.e. unaffected relatives of FTD-MND patients), significant differences have been identified in cerebellar volume up to 10 years prior to expected symptom onset (Rohrer et al., 2015). In sporadic MND, cerebellar white matter changes and grey matter reductions have been described (Bede et al., 2015; Christidi et al., 2018; Thivard et al., 2007). Across the FTD-MND spectrum, Tan et al. (2014) have demonstrated specific sub-region involvement in MND (inferior cerebellum and vermis), behavioural variant FTD (superior cerebellum and crus) and FTD-MND (both patterns of atrophy) with cognitive and neuropsychiatric behaviour most strongly related to reduced grey matter of the superior cerebellum and crus. Given the strong indication of cerebellar degeneration in MND C9*orf*72 carriers and the frequency of psychosis symptoms relating to C9*orf*72 this region requires more detailed interrogation in the context of psychosis symptoms in MND. Additionally, the cerebellum is an important association area and with its connections to limbic structures. Divergent patterns of alterations over time in cortico-cerebellar circuitry have been recognised and play a prominent role in some studies of primary psychosis conditions (e.g. Mittal et al., 2014). The cerebellum is shown to be altered by way of reduced grey matter volume and blood flow in at-risk (Fusar-Poli et al., 2012) and first episode (Kim et al., 2018; Squarcina et al., 2015) psychosis groups. Reduced grey matter volume has specifically been related to poor attentional flexibility in first episode patients (Kim et al., 2018), indicating early involvement of cerebellar structure and function as a cognitive modulator proximal to the emergence of psychosis onset.

1.7.4 Summary

Despite the recognition that psychosis symptoms (overt and subtle) occur in around 10% of MND patients and in up to a third of C9*orf*72 expansion carriers (Snowden et al., 2012), more so with concomitant FTD, comprehensive investigations of the neuroanatomical correlates of psychosis in MND are lacking. There are grounds for a hypothesis-driven regions-of-interest approach, based on studies of other psychosis disorders, to identify mechanisms that underlie psychosis in MND and FTD-MND: abnormalities in frontal-striatal, limbic and cerebellar grey matter volume and dysregulation in white matter connectivity.

These regions of interest play a vital role in supporting network communication for higher order cognitive and information processing. Therefore, neurodegenerative disruptions to these key areas, for example relating to MND by way of pathological protein aggregation (TDP-43), neuronal loss or axonal degeneration, can disproportionately and adversely affect balanced function and give way to some of the perceptual, cognitive and information processing aberrations observed in MND. Additionally, psychosis illness has been linked not merely to dysfunction within an isolated region or loop but to disruption across multiple networks. The integrity of these structures may represent a putative risk phenotype for the development of psychosis symptoms, and a correlate of sub-threshold pre-psychosis phenomenology.

1.8 Thesis Aim, Objectives, Hypotheses

1.8.1 Thesis aim

The overarching aim is to develop a framework to better stratify MND patients based on their risk for psychosis. This is important to predict progression of disease and therefore tailor individual patient management, psychological support and potentially treatment.
Early recognition of features suggestive of psychosis in MND is crucial due to the impact such unusual and often challenging behaviours have on carer stress, functional decline, survival, compliance with interventions and vital decision-making. To achieve this aim I have identified four objectives.

1.8.2 Objectives

The objectives of the current thesis are:

1. To recruit a population representative sample of patients through MND services and to study the prevalence and severity of psychosis and pre-psychosis cognitive phenomena.
2. To test the hypothesis that one or more of the cognitive processes outlined in 1.4.2 is a contributor to psychosis in MND.
3. Where I identify the abnormalities of cognitive processes underlying emergence of psychosis, to examine underlying neural correlates using MRI.
4. To set these changes in psychosis mechanisms and brain structure in the context of other cognitive deficits of MND.

The thesis exploits state of the art neuroimaging techniques and unique cognitive tools that have previously detected and informed early psychosis in those considered at-risk in primary psychosis cohorts, and for the first time applies them to a neurodegenerative sample with similarly presenting subthreshold psychosis symptoms.

1.8.3 Thesis structure

In chapter 2, I set out the general methods: how I recruited the MND and control samples and the tools I used to study them.

In chapter 3, I describe my MND patient population and the sample recruited through the Cambridge MND Care Centre. Given the relatively low prevalence of overt psychosis symptoms in MND I explore the prevalence of attenuated or subthreshold psychosis symptoms in this group using measures that capture such symptoms from individual assessments and carer reports. I also describe the prevalence and severity of other neuropsychiatric behaviour and cognitive deficits. I hypothesise that overt psychosis symptoms will be present in up to a third of the MND participants, but subclinical psychosis symptoms will be more frequent.

In chapter 4, I test the complimentary hypothesis that MND participants will have deficits in 1. Decision-making (jumping to conclusions), 2. Attentional control, and 3. Perceptual inference and that these will be related to behaviours and symptoms suggestive of psychosis.

In chapter 5, I focus on the grey matter correlates of decision-making because, as I will have shown in chapter 4, aspects of decision-making are abnormal, so therefore I present the

grey matter changes associated with disease, psychosis symptoms and aspects of decision-making.

In chapter 6, I take a corollary approach with a focus on white matter change using the DTI method of tract-based spatial statistics.

In chapter 7, I summarise the evidence to date, I interpret it in light of existing literature and discuss limitations and future directions.

Chapter 2 General Methods

In the following chapter, I describe the methods I employed including a brief outline of patient demographics (a detailed description will formulate chapter 3). This chapter will also outline a detailed description of the neuropsychological and cognitive assessment tools, and provide an overview of the MRI acquisition and analytical methods employed to examine the data. The results will be discussed throughout chapters 3-6, including basic statistical techniques (chapter 3), *t*-tests, correlations, multivariate principal component analysis, logistic regression (chapter 3), volumetric parcellation and regression (chapter 5) diffusion tensor imaging and regression (chapter 6). Detailed imaging-specific analysis methods are provided in the relevant chapters.

2.1 Ethics approval and sponsorship

This project was carried out under the Causes of Cognitive and Behavioural Change in Neurodegeneration and Related Disorders study, which was ethically approved by the NRES Committee London, Queens Square, reference: 14/LO/2045. The study was jointly sponsored by the University of Cambridge and Cambridge University Hospitals Foundation NHS Trust.

2.2 Locations

The research was coordinated from the Herchel Smith Building at the University of Cambridge Biomedical Campus where the regional specialist neurology Centre for

Frontotemporal Dementia and Related Disorders is held. Majority of MND patient recruitment occurred through the regional specialist neurology MND Care Centre at the Arthur Rank Hospice. Both centres are under the Cambridge University Hospital NHS Foundation Trust. A third general neurology MND clinic at Peterborough Hospital was included as a recruitment site (under the North West Anglia NHS Foundation Trust), for which an ethics amendment was approved. MRI scans were performed at the Wolfson Brain Imaging Centre (WBIC) at the University of Cambridge Biomedical Campus. Neuropsychological and behavioural assessments were conducted at the Herchel Smith Building or in participants' own homes. Bloods or saliva were collected at all locations.

2.2 Participant Recruitment

All patient participants were recruited between September 2017 and September 2019 from the specialist neurology Centre for Frontotemporal Dementia and Related Disorders at the Herchel Smith Building, the MND Care Centre at the Arthur Rank Hospice and the neurology MND clinic at Peterborough Hospital. All healthy control participants were recruited from the Join Dementia Research national volunteer panel (www.joindementiaresearch.nihr.ac.uk) or were spouses of the volunteer participants with MND. Diagnosis was based on standard diagnostic criteria for motor neurone disease (El Escorial criteria (Brooks et al., 2000)), and motor neurone disease with frontotemporal dementia (ALS-FTD revised diagnostic criteria (Strong et al., 2017)). In majority of cases, patients in the MND Care Centre at the Arthur Rank Hospice had received their diagnosis before attending clinic, however in cases where this was unclear and patients were seeking a second opinion, diagnosis was made in the opinion of the lead clinic consultant neurologist following clinical interview, physical examination, cognitive and functional tests, relevant confirmatory tests such as electrophysiology and where necessary brain imaging. Disease staging was assessed with

the ALS-Functional Rating Scale-Revised (Cedarbaum et al., 1999) and FTD-Functional Rating Scale (Mioshi et al., 2010). Disease duration was calculated from symptom onset to cognitive screen date in months. *N*=186 patients attended the clinics, of which *N*=111 were cognitively screened and 60 were recruited to participate in the in-depth cognitive and MRI investigations. Details of disease and demographic characteristics in addition to the *N*=30 healthy control participants are thoroughly presented in chapter 3 (page 112).

Written, informed consent was sought from each participant for all components of the research. Where appropriate, a personal consultee process was employed to assess the potential participation of patients who were either unable to sign the consent form due to physical difficulty, or who lacked mental capacity, in accordance with UK law. First, in cases where this applied, patients' willingness to consider research participation at a level compatible with their cognitive and physical abilities was evaluated. Second, a nominated individual was consulted, which included a spouse, an appropriate next of kin, or chosen personal consultee or holder of Lasting Power of Attorney as outlined in the Mental Capacity Act (2005).

2.3 Experimental Strategy

The study was conducted across a four-tiered system (Figure 5). Tier 0 included all patients who attended clinic (in-person and phone consultation) between September 2017 and September 2019. Data on these patients included diagnosis (sub-divided by site of onset (limb, bulbar), PLS, or FTD-MND), date of death, age and sex. Patient participants who were willing and able were recruited into Tier 1 for cognitive screening using the Edinburgh Cognitive and Behavioural ALS Screen (Abrahams et al., 2014) and the Cambridge Behavioural Inventory-Revised (Wear et al., 2008), family history, and a genetic blood or saliva sample. Guided by carer reports from Tier 1 of behavioural involvement considered to

be a change from diagnosis, and those willing and able, patients were recruited into Tier 2. Tier 2 involved in-depth paper-pen neuropsychological assessments and experimental computer tasks (detailed in section 2.6 below, all performed by myself to ensure reliability and consistency in test administration, scoring, and data processing). Comparison healthy control participants were recruited into Tier 2 simultaneously. For those who were willing and able, patient and control participants were recruited into Tier 3 where a structural and functional fifty-minute magnetic resonance brain scan was performed (detailed in section 2.7 below).

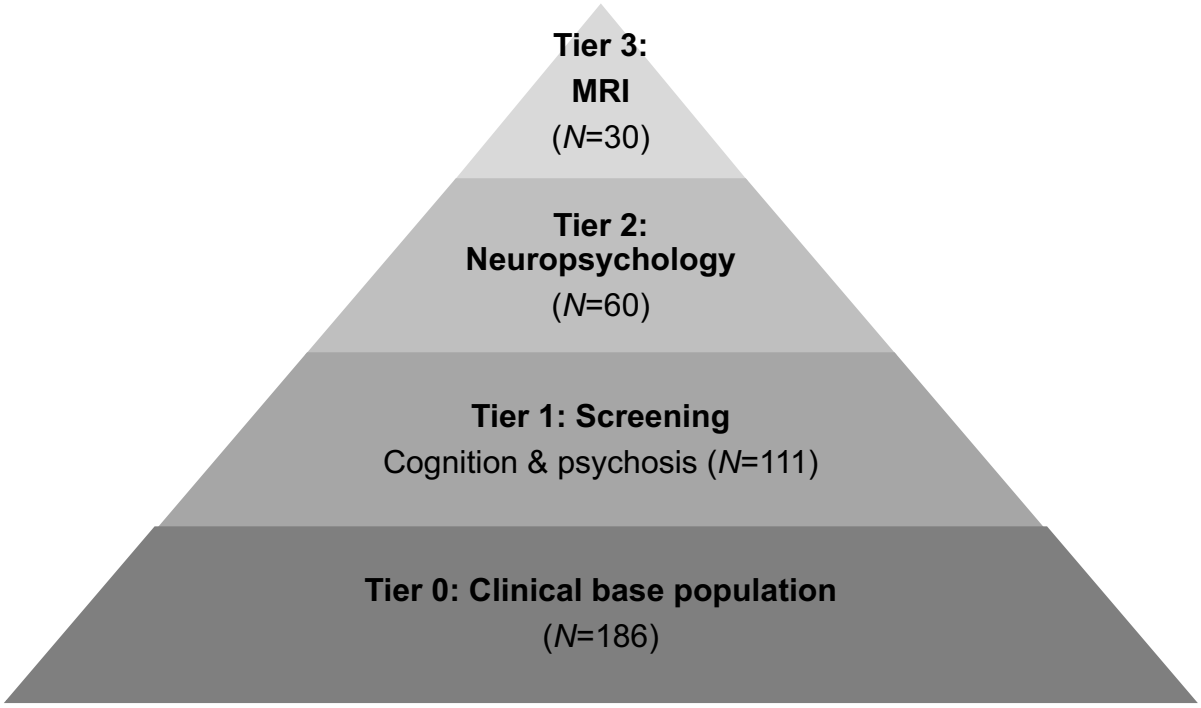

Figure 5: Overview of the study Tiers.

2.4 Inclusion and Exclusion criteria

Inclusion and exclusion criteria for MND patient and comparison healthy controls differed depending on the Tier and are detailed in Table 1.

Table 1: Inclusion and exclusion criteria across the four study Tiers.

TIER	INCLUSION	EXCLUSION
0	Over the age of 18 years.	Nil
1	Tier 0 patients willing and able to participate in cognitive, psychosis and genetic screening. Relevant diagnosis of MND-limb, MND-bulbar, or FTD-MND.	End stage disease. Absence of a reliable study partner.
2	Tier 1 patients willing and able to perform in-depth neuropsychology. Neurological intact controls over the age of 18 years old.	An alternative diagnosis to MND. End stage disease. Vision and hearing impairment sufficient enough to impede a significant proportion of the protocol but participation would still be possible. Concomitant neurological or psychosis condition unrelated to MND. Use of psychotropic medications. Medical condition affecting motor function, cognition or causing dementia; previous history of high consumption of alcohol or illicit drug use
3	Tier 2 patients willing and able to physically lay flat in MR scanner without risk of choking or breathing difficulties. Tier 2 neurological intact controls.	Contraindication to 3T MRI. As above.

2.5 Power and group size calculations

Power calculations adopted a dimensional approach widely used in other branches of psychiatric neuroscience. The variance expressed across the full cohort in terms of severity of clinical *and* subclinical psychosis was included so as not to be dependent on the recruitment only of psychosis individuals. Tier one analyses defined the prevalence of overt and subclinical psychosis symptoms in the current sample, as well as extended behavioural (mood and apathy) and cognitive screening data. Based on a pilot (see Appendix A) capturing behavioural data with the CBI-R on MND patients attending the Cambridge MND Care Centre prior to recruitment commencing, it was expected that approximately one third would express psychosis symptoms and 10-15% to carry the C9*orf*72 gene expansion (the local screening positive rate). General linear models, ANCOVA and *t*-tests, compared Tier 2 psychosis, broader neuropsychiatric and cognitive variable data by group. GPower Software estimates indicated 0.86 power to detect between-group differences by *t*-test with medium effect size d=0.5, α=0.05, and 0.80 power to detect effects by general linear models (ANCOVA) with effect size f=0.4, α=0.05. Tier 3 focused on between-group differences, using general linear models (ANCOVA) and correlation with identification of structural volumes and connecting pathways of the cerebellum, parts of the limbic system and key frontal-striatal regions, with similar power to standard regional volume and tract-based spatial statistics analyses of grey and white matter structures respectively. Given the data distribution in the pilot CBI-R data, the N=60 patients and N=30 controls provides excellent power to detect group differences, comparable to similar studies in MND (Menke et al., 2018; Menke et al., 2014a) and frontotemporal dementia (Lansdall et al., 2017; Sellami et al., 2018).

2.6 Cognitive and neuropsychological assessments

Patient and control participants underwent an identical clinical and research assessment battery (Table 2). Two cognitive screening measures were used during Tier 1 to measure global cognitive function and aid recruitment, which reflected the routine assessment in the respective Cambridge specialist neurology clinics. Tier 2 in-depth assessments included semi-structured psychiatric interviews with patient and the carer, structured patient and carer assessment of functional severity, mood scales and apathy scales. Tier 2 neurocognitive computer tasks of decision-making, visual perception, and attentional control were included based on their association with subclinical psychosis involvement and emergence in early psychosis and at-risk for psychosis populations (Ermakova et al., 2018; Robbins et al., 1994; Teufel et al., 2015).

Table 2: Summary of Tier 2 neurocognitive and psychiatric assessments.

	Scale	Outcome Measure
Patient Self-report Questionnaires	Dimensional Apathy Scale (DAS)	Apathy (subsets: executive, emotional, behaviour/cognitive initiation)
	Beck's Depression Inventory (BDI)	Depression
	Hospital Anxiety & Depression Scale (HADS)	Anxiety/Depression
Patient Interview	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALS-FRS-R)	Physical function (fine and gross motor)
	Comprehensive Assessment of At-Risk Mental States (CAARMS)	At-risk mental states for psychosis
	Brief Psychiatric Rating Scale (BPRS)	Psychiatric function
Carer Questionnaires	Cambridge Behavioural Inventory-Revised (CBI-R)	Behaviour change (without activities of daily living (ADL))
	Frontotemporal Dementia Functional Rating Scale (FTD-FRS)	Behaviour and ADL function
	Cambridge Questionnaire for Apathy and Impulsivity (Cam-QuAIT)	Apathy
Carer Interview	Neuropsychiatric Inventory (NPI)	Neuropsychiatric behaviour
Computer-based tasks	Fish Decision Task	Decision-making, positive-negative feedback learning
	CANTAB's Intra/Extra Dimensional Set Shift	Attentional control
	Perceptual Processing Task	Visual perception

2.6.1 Global cognitive screening

In the MND Care Centre global cognition was measured using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (Abrahams et al., 2014). In the Centre for Frontotemporal Dementia and Related Disorders administered the Addenbrooke's Cognitive Examination-III (ACE-III) (Hsieh et al., 2013) was used with the ACE-R addendum to ensure accessibility of comparisons across previous FTLD and MND cohorts collected on the ACE-R within the Centre.

The ECAS has three total scores: an overall global cognitive score, an ALS-specific and ALS-non-specific total. The ALS-specific score is comprised of the language, executive and verbal fluency components with a cut-off for intact functioning in these areas set at <77/100. The ALS-non-specific score is comprised of the memory and visuospatial components, indicating an Alzheimer-like dementia process, with a cut-off set at <24/36. The overall global cognitive total score has a cut-off of <105/136. Attached to the ECAS cognitive assessment administered directly to the participants, there is a carer report to query someone who knows the patient participant well on the presence of behaviour variant FTD behaviours and psychosis symptoms observed in the patient. These are to be considered if a change from patients' previous behaviour is observed. The list of 10 behaviours spans across five domains (Behavioural Disinhibition, Apathy, Loss of Sympathy/Empathy, Perseverative/Stereotyped Behaviour, Hyperorality/Altered Eating Behaviour) followed by three questions on the presence of psychosis symptoms.

The ACE-III has a global cognitive score in addition to five domain scores (Attention, Memory, Fluency, Language and Visuospatial). Healthy comparison controls were defined with this measure by an ACE-III score greater than 82/100, together with a score greater than 105/136 on the ECAS and absence of regular memory complaints, signs/symptoms of dementia or significant medical illness (Table 1).

2.6.2 Functional Rating Scales

Two functional rating scales were included (the FTD-FRS and the ALS-FRS-R) as they measure different deficits encountered within the FTD-MND disease continuum. These measures significantly differ on a number of counts: the 12-item ALS-FRS-R (Cedarbaum et al., 1999) assesses fine motor and gross motor skills and does not assess behaviour such as motivation. While not equivalent to activities of daily living performance, the ALS-FRS-R measures the impact of motor deficits on basic daily activities, such as walking, handling utensils, dressing, swallowing, personal hygiene and breathing. In contrast, the 30-item FTD-FRS (Mioshi et al., 2010) identifies and operationalises six stages of functional severity (very mild to profound) and weighs more on behavioural disturbances and the organisation of daily activities, such as shopping, household chores/telephone use, finances, medication administration, meal preparation, eating, self-care and mobility.

The ALS-FRS-R grades performance on 12 everyday activities using a 5-point scale (0-4 points). The maximum score is 48, indicating optimal function, whereas a lower score indicates greater motor impairment. The FTD-FRS raw scores were used to calculate a logit score, which can be converted to a percentage, that reflects the severity of behavioural and functional impairment. FTD-FRS logit score cut-offs grade impairment as “very mild” (>4.12, >97%), “mild” (4.11 to 1.92, 80-96%), “moderate” (1.91 to -0.40, 41-79%), “severe” (-0.39 to -2.58, 13-40%), “very severe” (-2.57 to -4.99, 3-12%) and “profound” (<-4.99, <2%).

2.6.3 Mood and Apathy Scale

Suffering from a relentless life-limiting illness such as MND might be expected to be associated with significant depression and psychological dysfunction following diagnosis and as disease progresses. Included are two measures previously applied in combination to

examine mood in MND (Taylor et al., 2010; Tedman et al., 1997; Wicks et al., 2007). The widely-used self-report 21-item Beck Depression Inventory Version 2 (BDI-II) (Beck et al., 1961), which measures depressive symptoms over a two-week period, and the self-report 14-item Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) consisting of two sub-scales, anxiety and depression, which measures mood symptoms during a preceding one-week period. As the HADS was designed for hospital patients with concomitant physical ailments, it is thus not reliant upon the inclusion of physical symptoms.

Apathy is both a syndrome and symptom prevalent in neurodegenerative and psychosis conditions, however it is not to be confused with depression. Studies have reported a variable relationship between the two, with some describing them as distinct factors (Levy et al., 1998), and others reporting an association (van Reekum et al., 2005). However, these two dimensions have distinct neural circuitry (Levy et al., 1998; Starkstein et al., 2005) thus it was essential to ensure the included apathy scales could discriminate between the two. Two apathy scales were included: the recently developed Cambridge Questionnaire for Apathy and Impulsivity (Cam-QuAIT) within our department and the Dimensional Apathy Scale (DAS) (Radakovic & Abrahams, 2014). The DAS is a multi-dimensional self-report scale composed of 24 items assessing three subtypes of apathy and is suitable for use in patient groups with motor dysfunction. The subtypes include *executive*, associated with problems of organisation, attention and planning; *emotional*, refers to the integration of emotional behaviours; and cognitive/behavioural *initiation*, which is independent of motor function and reflects initiation and sustained response to tasks (Radakovic & Abrahams, 2014). Items were scored using a 4-point Likert scale based on the frequency of occurrence in the last month. The minimum score for each subscale is 0 (least apathy), the maximum score is 24 (most apathy), and the total score is 72. Abnormality cut-offs for each dimension are 14/24 for the executive subscale, 15/24 for the emotional subscale, 16/24 for the initiation subscale and 39/72 for the total score (Radakovic et al., 2016).

2.6.4 Psychiatric Rating Scales

2.6.4.1 Carer-reports

Psychosis manifestations across the FTD-MND continuum have been well-established. However, despite evidence that more subtle features appear to predominate over overt hallucinations and delusions, previous research has predominantly used the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) to give an overall impression of psychopathology in patients. Specifically developed to assess neuropsychiatric symptoms and psychopathology in patients with dementia and other neurodegenerative conditions, the NPI is both valid and reliable, assessing 12 behavioural disturbances as rated by someone who knows the patient well and is familiar with the patient's behaviour, together with the interviewer. A total score was calculated based on multiplying the severity and frequency rating. An additional psychosis index was calculated by combining the two overt psychosis items: *Delusions* and *Hallucinations*.

To detect features suggestive of psychiatric behaviour and overt psychosis, the Cambridge Behavioural Inventory-Revised (CBI-R) (Wear et al., 2008) was included. The full version of the CBI was not used, rather a 36-item version excluding the activities of daily living, as this is measured in other scales and is often inappropriate for many cases of MND who no longer undertake such activities. The CBI-R was developed as an abbreviated version of the original CBI and accurately evaluates behavioural change associated with various forms of dementia, proving effective differentiation between Huntington's disease, Parkinson's disease, Alzheimer's disease, semantic dementia and behaviour variant FTD (Wear et al., 2008). A total score was calculated by summing the frequency of each item, sub-total scores calculated by summing sub-section frequency scores, and a psychosis index calculated by combining the three psychosis-related sub-sections: *Abnormal Behaviour*, *Beliefs* and *Stereotypical and Motor Behaviours*. Abnormal behaviour and stereotypical motor behaviours were included in the psychosis index score because of their association

with other psychosis disorders, but note that they partially overlap with frontotemporal dementia criteria. Additionally, *broad* behavioural features suggestive of or potentially caused by overt psychosis may include such behaviours as *agitation*, *temper outbursts*, *uncooperative*, *fixed ideas*, which were intended to be captured in the current MND cohort.

2.6.4.2 Interviewer-reports

Due to its wide use in early psychosis groups, included in the test battery is the 18-item Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), which combines ratings based on patients' self-report, observed behaviour and observed behaviour *and* speech as rated by the interviewer. A total score was calculated by summing each item. A score of 1 is assigned to each behaviour that is not present, thus the minimum score, indicating no psychiatric behaviour involvement, is 18.

The Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005) was included based on available psychiatric literature showing it reliably measures across the psychosis phenotypic expression that encompasses subclinical levels of psychosis and recognises the prodrome of a first psychosis episode prospectively. The CAARMS aims to determine if an individual meets the criteria for an at-risk mental state and aims to rule out or confirm criteria for acute psychosis and does so with good to excellent reliability. The CAARMS was withdrawn after the first 20 MND participants as the final outcome was to categorize participants as "at-risk" or "not at-risk", of which one of the main criteria was a positive family history of a psychiatric condition, in addition to experiencing various symptoms for a specified time period. Adhering to such strict criteria of a tool developed for psychiatric conditions does not transfer well when applying to a neurodegenerative cohort that does not use the same labels. Data are not presented from the CAARMS.

2.6.5 Computerised Cognitive Tasks

The three following computer tasks were performed on either a DELL Latitude E5440 laptop or an ASUS Transformer Mini T102HA touchscreen laptop. Participants sat, unconstrained, approximately 60 centimetres from the screen.

2.6.5.1 Fish Decision Task

The Fish Decision Task was administered on the ASUS touchscreen laptop. This novel task (Figure 6) was designed by collaborators Dr Anna Ermakova and Dr Graham Murray (2018) in the Department of Psychiatry, Cambridge University. The task was based on previously published tasks (Garety et al., 1991; Huq et al., 1988) of reasoning in psychosis, however was updated according to decision-making theory, whereby the amount of evidence sought is inversely proportional to the costs of information sampling. These costs include the high subjective cost of uncertainty and the cost to self-esteem as well as other factors (Moutoussis et al., 2011). The task is a probabilistic reasoning task that measures the cognitive bias of jumping to conclusions (JTC), which has been strongly associated with psychosis symptoms and specifically delusions (Broome et al., 2007; Langdon et al., 2014; Woodward et al., 2009). It involves four stages with varying levels of manipulation of motivation. Participants were told there are two lakes each with black and gold fish in two different ratios (60:40). All fish were drawn from one lake per trial and all the previously 'caught' fish were displayed on the screen in order to reduce working memory load. Instructions informed participants that fish were being caught at random from either of the two lakes and then allowed to 'swim away'. Decisions of which lake the fish came from (black or gold) could be made after just seeing one fish or after seeing an incremental amount up to 20 fish. Fish were presented in a pseudorandomised order yet the same order for all participants and the lake from where the fish were drawn was also pseudorandomised.

The four self-paced blocked stages consisted of 10 trials each with a predetermined sequence, in order to increase reliability. Stage one was similar to the classic beads in the jar task (Garety et al., 1991), with the addition of providing feedback ('correct' or 'incorrect') after every trial. Stage two progresses to include a win (positive feedback) for a correct decision (100 points) and a loss for an incorrect decision (-100 points). Stage three introduces a cost (negative feedback) for each extra fish viewed after the first (-5 points), which is subtracted from the possible win or loss of 100 points. Finally stage four, similar to stage three, incrementally increases the cost for each extra fish viewed after the first. The first fish cost 0 points, the second -5 points, the third -15 points etc. Thus, the more information sampled, the higher the cost and points lost.

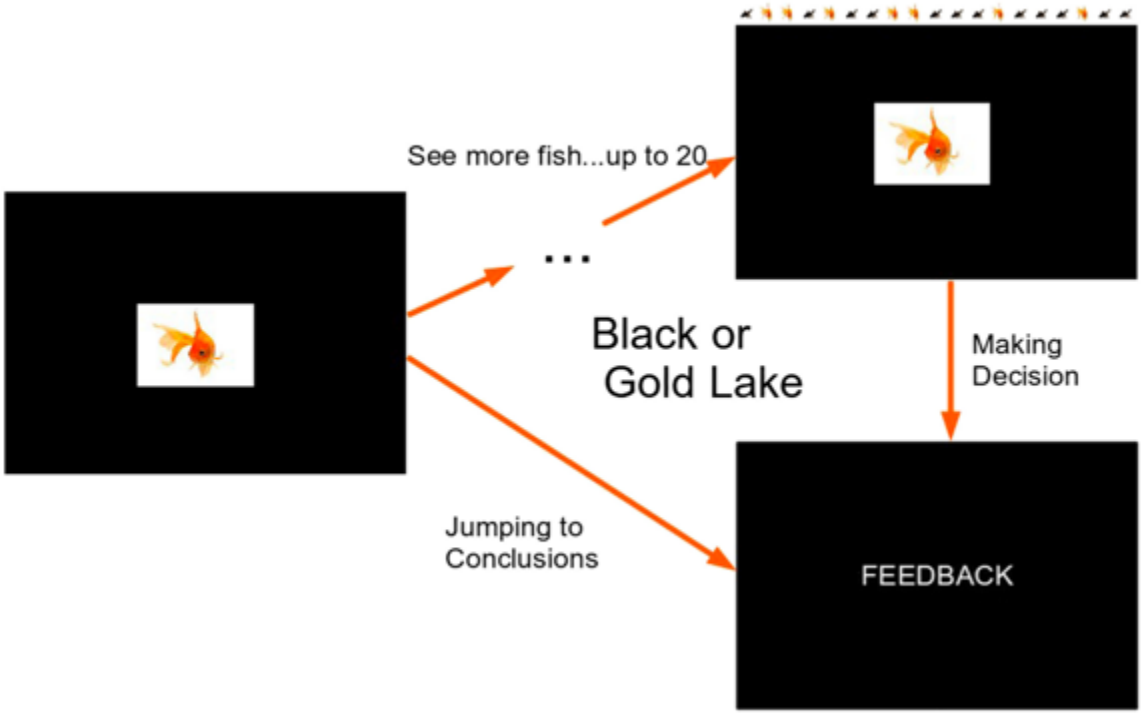

Figure 6: Fish Decision Task. Experimental design of a single trial. Image credit: Dr Anna Ermakova (2018) *Computational Psychiatry*.

The primary outcome measure was the number of fish sampled (draws to decision (DTD)) during each stage, which reflected whether or not the participant had jumped to conclusions

on which lake the fish belong to after having seen too few fish even though they can see any number of fish (up to 20) before making a decision. Secondary outcome measures across each stage included accuracy of the decision, which was calculated according to Baye's theorem as the probability of being correct based on how many fish the participant viewed (Etz & Vandekerckhove, 2018), and the extreme JTC variable, which is defined as making a decision after 2 or fewer pieces of information. Summary composite and difference scores were calculated to reflect a general JTC when sampling information was not costly (stage 1 draws + stage 2 draws), cost sensitivity (stage 3-4 composite draws – stage 1-2 composite draws) and increasing cost sensitivity (stage 4 draws – stage 3 draws).

2.6.5.2 CANTAB Intra/Extra Dimensional Set Shift (IDED)

The IDED was administered in the clinical mode on the ASUS touchscreen laptop using the CANTABeclipse software package (Cambridge Cognition LTD) (Robbins et al., 1994). This is a test of rule acquisition, association and reversal learning, comparable to the demands of the Wisconsin Card Sorting Test (Berg, 1948). Participants were presented with two artificial dimensions and required to learn which one is correct. Initially, the stimuli presented represent only one stimulus dimension (e.g. shape), then progress to two dimensions apiece (e.g. line and shape) (Figure 7). Participants were required to learn which dimension was correct based on feedback from the computer and make this correct choice consecutively before the rules and/or stimuli were changed after a specific number of correct responses. The shifts in correct stimuli were initially intra-dimensional (e.g. within the shape dimension) and then later extra-dimensional, which required a category shift (e.g. from the shape to the line dimension).

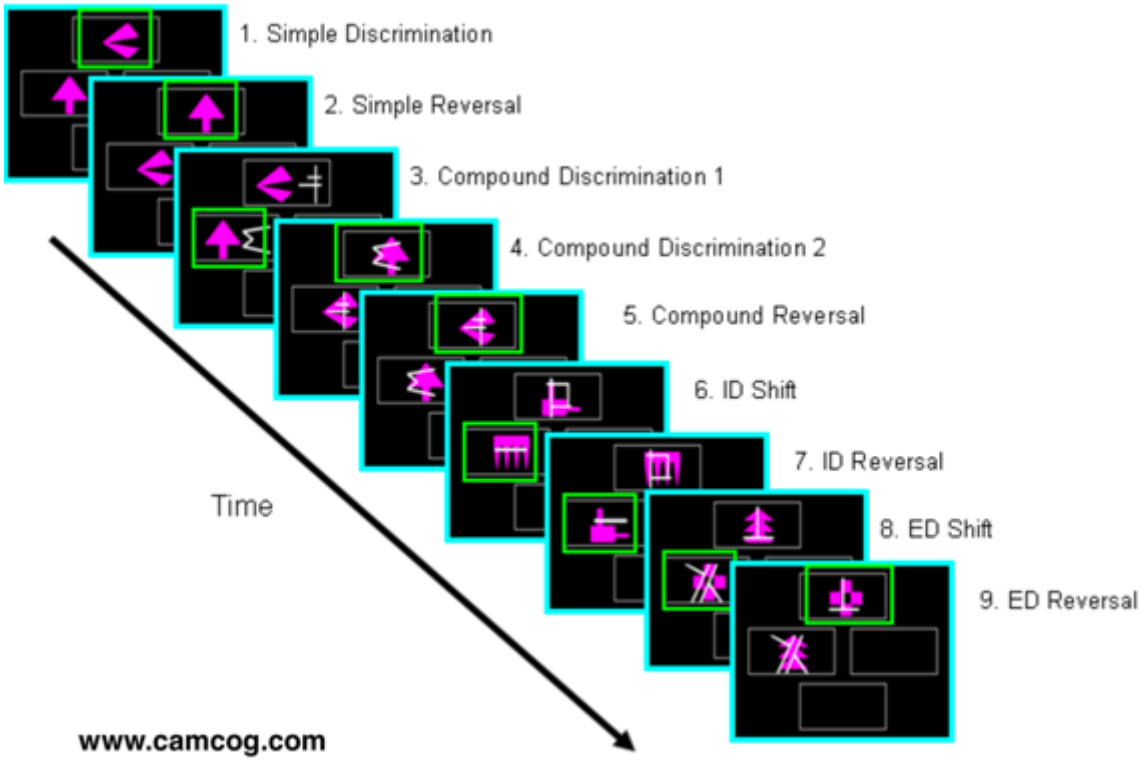

Figure 7: CANTAB's Intra/Extra Dimensional Set Shift task. Image credit: Professor Trevor Robbins (2015) https://www.cambridgecognition.com/downloads/Trevor_Robbins.pdf

2.6.5.3 Perceptual Processing Task

The perceptual processing task was designed and validated by collaborators Dr Christoph Teufel and Professor Paul Fletcher (2015) in the Department of Psychiatry, Cambridge University. The computerised experiment was carried out on the DELL laptop using Matlab R2016b (The MathsWorks) with the PsychToolbox Version 3 (Brainard, 1997). Each experiment began with a practice trial to ensure that participants became familiar with the structure of the task. The practice trial consisted of one session, which was identical to the experimental sessions (Figure 8a), except a shorter version of 4 instead of 10 trials were presented. The main experiment consisted of 8 sessions, including a final session of rating the complexity of each two-tone image on a sliding scale of Very Unclear to Very Clear. Each session commenced with a Before Block, in which the participants saw 10 two-tone

black and white images. Without prior knowledge, these two-tone images are ambiguous and depict meaningless two-dimensional black and white patches (Figure 8b).

Figure 8: Perceptual Processing Task. 8a: Example of test stimuli (two-toned ambiguous image and its picture template). 8b: example of a two-tone ambiguous image that has an embedded animal and/or person without its picture template.

In each trial, a two-tone image was presented with a brief appearance of a red dot located somewhere on the picture and after ~2 seconds the image disappears and the participant is presented with a prompt to make a decision during a participant-paced response window. The participants were asked to decide on whether they thought the red dot had appeared on a person/animal or the background. After 10 trials of two-tone images, participants were presented with each matching colour image three times each followed by a trial consisting of each two-tone image gradually morphing into its respective colour image. These two phases are where knowledge is provided to the participant to ensure ample prior knowledge was provided about image content. The colour images were the templates from which the two-tone images were generated, shown in the Before Block of the sessions. These colour images could then be used to disambiguate the two-tone images the next time these were viewed. Finally, the last block of each session, the After Block, is identical to the Before Block with the exception of a new randomisation for the order of two-tone image presentation. Again, participants were presented with the same 10 two-tone images as in

the Before Block and were asked to make a decision on whether they thought the red dot was located on a person/animal or the background.

Two-tone images were presented in blocks of 10, rather than one individual two-tone image with its respective colour image back-to-back as Teufel et al. (2015) argue this type of design is susceptible to alternative interpretations regarding purely bottom-up priming rather than top-down processing. By presenting 10 two-tone images in a block of random ordering before presenting their respective colour images, the effects of purely bottom-up processing are minimized.

Responses were transformed into yes/no data, from which outcome measures were computed, including discrimination sensitivity (*d*-prime), hit rates and false alarm rates, and response bias (criterion) for the Before and After Blocks separately, using a script developed by my collaborators. A higher *d*-prime indicated the participants were better able to identify the person/animal or were more accurate with responses (fewer misses or false alarms).

In all tasks, one has to consider the role of global cognitive impairment, memory impairment and executive impairment. It is possible that the task instructions may not be remembered, or are remembered but unable to organise behaviour according, which is reflected in task performance but does not accurately reflect performance on which the task was designed to measure. This problem is partially overcome by inclusion of control conditions. The computer tasks are not “pure” and examine multiple cognitive processes. For example, to successfully perform and complete the CANTAB’s Intra/Extra Dimensional Set Shift task, a number of complex cognitive processes are required, such as working memory, problem solving, reasoning and inhibition, which makes it difficult to determine which cognitive skills contribute to deficit observed in patients. However, the tasks afford multiple output measures and incorporate baseline control conditions, making it possible to dissociate performance errors that arise from different response strategies (or response error patterns).

In the experimental chapters, correlations with global cognition as measured by the ECAS will be performed, to assess the potential confounding effect of cognitive impairment.

2.7 Imaging

The imaging acquisition and sequences are provided below, followed by an overview of pre-processing of T1, volumetric T2 and diffusion-weighted images (DWI).

2.7.1 Image acquisition

Multiple MRI images were acquired from each participant recruited into Tier 3, and took place at the Wolfson Brain Imaging Centre (WBIC) using a PRISMA 3T Siemens scanner (Siemens, Germany https://www.siemens-healthineers.com/magnetic-resonance-imaging/3t-mri-scanner/magnetom-prisma) with a 64-channel head coil. Image acquisition lasted less than 60 minutes and followed the Genetic Frontotemporal Dementia Initiative (GENFI) MRI protocol (Cambridge GENFI Protocol v1.2 1st March 2017, REC Reference: 17/EE/0032), which includes several sequences to investigate brain function (EPI functional MRI sequences) and structure (MPRAGE and DWI) and arterial spin labelling perfusion (ASL), plus quality control and localiser sequences. The following is a comprehensive list of sequences (starred sequences were used in the current analyses):

- Localizer
- Sagittal MPRAGE non-distorted*
- Sagittal MPRAGE
- T2_spc_ns_sag_p2_iso*
- Resting State fMRI (eyes closed but instructed to remain awake)

- Field map (gre_field_mapping)
- ep2d_diff_FREE68+1_p2FAD_2.5mm_iso*
- ep2d_diff_FREE68+1_p2FAD_2.5mm_iso*
- Perfusion Weighted
- ASL3D_oblique
- ASL3D_TI1s
- ASL3D_TI2s
- ASL3D_TI5s

The most common MRI sequences, which were used in the current thesis, are T1- and T2-weighted magnetisation-prepared rapid acquisition gradient echo (MPRAGE) structural images. Both providing excellent tissue contrast (grey matter, white matter and CSF) per unit of acquisition time. Both are highly sensitive to pathological changes in tissue (T1) and tissue *and* water (T2) and differ in their characteristic tissue signal intensities/brightness (Radue et al., 2016).

The T1-weighted 3D structural images were acquired with repetition time (TR) = 2000ms, echo time (TE) = 2.93ms, resolution matrix of 256x256, 208 slices of 1.1mm thickness, inversion time = 850ms and flip angle = 8^{o}. Distorted-uncorrected T1 images were used.

The T2-weighted images were acquired with TR = 3200ms, TE = 401ms, resolution matrix of 256x256, 176 slices of 1.1mm thickness and flip angle = 120^{o}.

Diffusion-weighted images are designed to detect the random movements of and differences in the magnitude of water molecules within the brain. Water diffusion is expected to be restricted (i.e. anisotropic) within intact neuronal pathways and more diffuse (i.e. isotropic) in regions of reduced integrity (Soares et al., 2013), both of which provide information about anatomical connectivity in the brain. DWI 2D images were acquired

(ep2d_diff_FREE68+1_p2FAD_2.5mm_iso) using a posterior-anterior direction gradient sequence with the following parameters: *b* value 1000s/mm^2; TR = 7300ms; TE = 90ms; axial in-plane acquisition matrix of 96x96, 2.5mm slice thickness (with no gap), flip angle = 90^o.

Safety of participants was paramount. Participants underwent rigorous MRI contraindication checks at the recruitment stage and with further secondary safety checks immediately prior to entering the scanning facility. The WBIC uses independent qualified radiographers who are experienced and trained in lifting techniques and in ensuring participant comfort throughout the scanning. Standard WBIC procedures were followed for incidental findings on MRI.

2.7.2 Image pre-processing

2.7.2.1 T1 and T2-weighted images

To perform statistical analyses of grey matter volume across multiple MRI scans from patient and healthy control individuals, T1 and T2 images underwent pre-processing in preparation for volumetric parcellation. Pre-processing involved neck cropping and realignment using automated scripts in the Statistical Parametric Mapping software package version 12 (SPM-12), and manual identification and labelling of participants with big ventricles.

The neck crop is required to remove shoulder and neck signal, which can disrupt registration and normalisation. Depending on the posture of the participant when they are supine on the MRI scanner table during image acquisition, the raw images are almost always in different orientations. T1-weighted images were aligned to anterior and posterior commissures (two anatomical landmarks of the same axial plane in the brain). The automated script 1. Aligned

the T1-weighed scans to the first scan, 2. Resliced each scan to 1mm isotropic voxels, 3. Averaged the scans, 4. Saved the averaged realigned and resliced nifty file. The rotation matrix within this function is automatically generated, however, an averaged reference image as well as each scan were checked to ensure that the rotation matrix was correct. Big ventricles were subjectively identified in SPM-12 software with an MRI analysis specialist within the research group. Cortical reconstruction and volumetric parcellation were performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/).

2.7.2.2 FreeSurfer parcellation

Cortical reconstruction and volumetric parcellation were performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). Processing involved motion correction and averaging of T1 and T2 weighted images, the 3-step procedure to intensity normalise the data, skull stripping, and removal of non-brain structures. Followed by the construction of models of the boundary between white matter and cortical grey matter as well as the pial surface (grey matter to CSF). T2 images were used in combination with T1 to increase pial definition of cortical areas. Surfaces were visually inspected for each participant, under the guidance of an imaging expert in the research group, to ensure thorough quality control. Manually added control points were not required. Once these surfaces were identified, cortical volume reconstruction and parcellation, and subcortical segmentation were performed using the automated *recon-all* script, applying the cortical labels from the Desikan-Killiany Cortical Atlas. Cortical parcellation assigns a neuroanatomical label to each location on the cortical surface, incorporating both geometrical information (sulcus and curvature) and neuroanatomical convention.

Cortical parcellation output for each structure included hemispheric volumes (mm^3/1000 to ml), which were combined to include bilateral average volumes in analyses. Total intracranial volume was calculated separately using Statistical Parametric Mapping (SPM).

2.7.2.3 Diffusion weighted images

To perform statistical analyses of white matter tracts of MRI scans from patient and healthy control individuals, DWI images underwent rigorous processing using automated scripts that called on FMRIB Software Library (FSL) diffusion toolbox (version 5.0.9; www.fmrib.ox.ac.uk/fsl). Each participant had between 2-4 DWI images, due to sequence repetition if the participant moved during this acquisition. After inspection of the number of slices in each DWI image, two images per participant were selected to realign and combine. Fieldmaps were created, however were not included in the final pre-processed images due to a significant motion anomaly after applying eddy correction.

The procedure for obtaining FA and MD was as follows:

1. Images were corrected for eddy currents and participant motion by affine registration to the first b0 volume image, using FSL *eddy_correct* script.
2. The b0 image was extracted and a brain mask created, using the FSL Brain Extraction Tool (*BET*), which additionally excludes voxels outside the skull.
3. Diffusion tensors were fitted for the remaining voxels, using the *dtifit* script to create FA and MD maps.
4. FA maps from twenty participants each from the patient group and control group were nonlinearly registered to the FMRIB58_FA_1mm target, using the *tbss_2_reg* script.

5. Using the *tbss_3_postreg* script, the warped FA images were averaged to produce a study-specific FA template.
6. Registration was repeated for all participants using this study-specific FA template as the target, bringing all participants into the same 1x1x1mm standard anatomical space.
7. From the study-specific FA template, a mean FA skeleton was produced, and individual FA skeletons were mapped to it, applying a threshold of 0.2 with the *tbss_4_prestats* script.
8. Finally, the transformations putting the individual FA maps into the skeletonised standard space were applied to MD maps.

2.8 Statistical analyses

2.8.1 Demographics, clinical features, psychiatric behaviour and experimental tasks

Statistical analyses of group difference and correlations used the freely available R Studio version 3.6.1 (2019-07-05). Parametric *t*-tests and ANOVAs were used to compare within-group MND differences stratified by imaged status (imaged versus non-imaged), by tier and by group (MND versus healthy control group differences). More detailed group differences between MND and healthy controls used ANCOVA's and linear mixed models. Pearson's *r* correlations and partial correlations were used for within MND group associations. Principal component analysis (PCA) was applied to combine overlapping neuropsychiatric measures, and logistic regression, using JASP (version 0.12.2), was applied to explore predictors of psychosis status.

False Discovery Rate (FDR) corrections were applied when correcting for multiple comparisons. This controls for expected proportion of false positives amongst reflected hypotheses and is less stringent than other correction methods, such as Family Wise Error correction.

Assumptions were tested using Shapiro Wilk test of normality and inspecting histograms/boxplots and Q-Q Normality Plots, together with Bartlett's test of homogeneity of variance (where outcome measures were non-normal, Levene's test of homogeneity of variance was applied). Where appropriate, when data was significantly non-gaussian, non-parametric Wilcoxon test and Spearman's *rho* correlations were applied, otherwise variables were arcsine transformed and included in parametric tests.

Each participant was recruited and tested by me, as such I am acutely aware of the very few missing data points. For the PCA in chapter 3, three MND participants were missing one questionnaire each. These participants had completed the Tier 3 MRI scan and were considered too valuable to remove from the analysis. Therefore, their disease severity (ALS-FRS-R and FTD-FRS) and global cognitive (ECAS total) scores were visually inspected on scatter plots (labelled to identify each of the three participants) and standard deviation of scores from the group mean assessed. Disease severity and global cognition were deemed to be consistent with the group means and thus mean-replacement method on the missing total questionnaire score was applied to complete observations. *N*=9 MND participants did not complete one of the computer tasks, due to the task crashing during their testing visit (*N*=5) or fatigue after a long MRI and testing session in the same day (*N*=4). These participants were removed from descriptive and group difference analyses on this task.

2.8.2 Imaging analysis overview

The neural correlates of psychosis symptoms, the extracted neuropsychiatric behavioural components and cognitive task outcome measures were analysed using the freely available software package FreeSurfer version 6.0.0 development (http://surfer.nmr.mgh.harvard.edu/), which provides a full processing stream for cortical and subcortical reconstruction and volume segmentation of structural MRI data (analysis details in chapter 5) and the FMRIB Software Library (FSL) version 5.0.9 Tract-Based Spatial Statistics (TBSS) (analysis details in chapter 6). Specifically, using the combined T1 and T2-weighted structural MR images, analysis of grey matter volume was performed with FreeSurfer. Volumetric output from this analysis was then imported to R Studio to determine group differences and investigate the differential relationship of psychiatric and cognitive outcome measures on regional brain volume. Analysis of white matter diffusion metrics was performed using TBSS in the FSL diffusion toolbox and the automated FSL *randomise* script. TOPUP for susceptibility-induced distortions was not applied as the two DWI images used were not obtained in opposing PE-directions, thus this step was negligible.

Covariates included in regional volume linear mixed models and partial correlations were age and total intracranial volume (TIV), which gave more powerful and/or interpretable results. Diffusion tensor imaging (DTI) analyses covaried for age and disease severity as TIV does not influence the DTI metrics for white matter. FDR and Threshold-Free Cluster Enhancement (TFCE) correction were applied for multiple comparisons of FreeSurfer output and TBSS respectively.

2.9 Genetics

92/111 participants underwent blood/saliva sampling for the C9*orf*72 hexanucleotide expansion as per the GOLDeN Study protocol (Version 8 01 May 2019, REC Reference: 15/EE/0270). The normalised DNA samples were due to be sent for genotyping early 2020, however due to the COVID-19 pandemic this was obstructed and unable to be carried out. As such, the MND participants in the current thesis do not have confirmation of C9*orf*72 status and planned analyses to stratify by gene status were not performed.

2.10 Conclusion

The assessment battery measured key areas of global cognition, disease severity, psychosis behaviour, mood, apathy and specific cognitive mechanisms underlying psychosis risk. The following empirical chapters (3-6) employ these measures and exploit state of the art imaging techniques to assess the cognitive and neural mechanisms of psychosis risk in MND patients.

Chapter 3 Study population characteristics

This chapter describes the wider patient sample (Tier 0) from which the main screening (Tier 1) and testing sub-samples (Tiers 2 and 3) were drawn on demographic and disease characteristics. Followed by a detailed summary, including descriptives and group differences on cognitive and neuropsychiatric measures, of the main MND and control samples across Tiers 1 – 3. Finally, findings from the principal component analysis are presented, to identify components that best explain the variability in neuropsychiatric behaviour within the dataset.

I address the prediction that overt psychosis symptoms will be present in up to a third of MND participants but that subclinical psychosis symptoms will be more frequent. Additionally, it was expected that there would be significant group differences on the cognitive screening, neuropsychiatric and disease severity measures.

3.1 Introduction

The clinical presentation of MND is varied and a number of phenotypes exist, each with varying trajectories of prognosis and survival, these are outlined in section 1.1.

Cognitive and behavioural deficits, commonly mirroring those of behavioural variant FTD (bvFTD), may initially have a subtle appearance, with executive dysfunction (especially verbal fluency and social cognition), and changes in personality or language most prominent. With appropriate neuropsychological investigation, cognitive and behavioural deficits are shown to be present in up to half of patients with MND (Abrahams et al., 2014; Beeldman et al., 2016; Hsieh et al., 2016; Phukan et al., 2012b; Raaphorst et al., 2012b; Ringholz et al.,

2005), with frank dementia and overt cognitive and behavioural symptoms diagnosed as concurrent FTD in 5 to 15% of MND patients (Bock et al., 2016; Ringholz et al., 2005).

Behaviourally, reports of psychosis in MND are commonly associated with concurrent FTD (Lillo et al., 2010b; Saxon et al., 2017) and in particular with C9*orf*72 expansion carriers occurring in 6.6% up to 68.6% of C9*orf*72 cases (see review: Patel & Sampson, 2015). In MND alone, prevalence rates of psychosis symptoms have not been well established due to the overlap with FTD. Rather, descriptions of a close time relationship with typical MND symptom onset (Mioshi et al., 2014; Turner et al., 2016), increased risk and prevalence of psychiatric disorders among kindred of MND families (Byrne et al., 2013; Longinetti et al., 2017; O'Brien et al., 2017), and established genetic links between MND and primary psychosis illness (McLaughlin et al., 2017) are common among investigations relating to psychosis.

When psychosis symptoms present clinically in MND, or in FTD-MND, there are less frequent observations of florid psychosis symptoms (delusions and/or hallucinations). However, when psychosis symptoms are overtly present it can result in initial primary psychiatric diagnoses such as schizophrenia, delusional psychosis, somatoform psychosis or paranoid schizophrenia. More commonly observed are milder, subthreshold behavioural and psychiatric symptoms resembling odd behaviours such as complex repetitive behaviours, suspiciousness, paranoid and irrational ideation, somatisations ("crawling" sensation on or beneath the skin), fixed or overvalued ideas about comorbid illness (Devenney et al., 2014; Snowden et al., 2012). The nature of such subthreshold psychosis symptoms reflects delusional thinking more so than hallucinations. These symptoms are subtler than those observed in typical primary psychosis patients and more commonly fall below the threshold for a comorbid clinical diagnosis of psychosis.

Broader neuropsychiatric behaviours include apathy, depression and anxiety. Apathy is found in 29 – 88% of MND patients (Caga et al., 2018; Lillo et al., 2011; Raaphorst et al., 2012; Witgert et al., 2010) and considered the most prominent behavioural symptom of MND, although such large prevalence ranges indicate considerable heterogeneity. Beyond emotional adjustment following such a diagnosis, depressive disorders are not necessarily to be expected in MND, rather there is a higher risk of development (Roos et al., 2016). The literature reports large variation in prevalence and severity of depression and anxiety in MND. Prevalence ranges of depression are reported as significantly high from 48-75% of patients (Carvalho et al., 2016; Kawada et al., 2016; Körner et al., 2013; McElhiney et al., 2009; Menke et al., 2014; Zucchi et al., 2019) to as low as 0.9 – 12% (Carvalho et al., 2016; Rabkin et al., 2015; Zucchi et al., 2019). Prevalence rates of anxiety range from 8 to 48% (Benbrika et al., 2019; Kawada et al., 2016; Wicks et al., 2007). Similarly, severity of depression and anxiety largely varies with majority of patients (20 – over 50%) experiencing mild to moderate severity of depression (Atassi et al., 2011; Benbrika et al., 2019; Carvalho et al., 2016; Lillo et al., 2011; Wicks et al., 2007). These highly variable prevalence and severity rates can be explained partly by different measures (structured clinical interview as opposed to self-report questionnaires), concomitant cognitive symptoms, or even confusion with other behavioural alterations demonstrated in MND, such as apathy. Many traditional diagnostic nomenclature and measures, including the DSM-IV, treated apathy as an aspect of depression but the two have been shown to be clinically (Aarsland et al., 2001; Lillo et al., 2011) and neurobiologically (Hollocks et al., 2015) discriminable constructs. In MND, apathy and depression are found to be related (Caga et al., 2018), yet conversely, many reports show low levels of depression compared to higher levels of apathy (Kasper et al., 2015; Lillo et al., 2011; Radakovic et al., 2016).

These detailed phenotypic descriptions in the literature emphasise the physical complexities of MND, which are further compromised by the involvement of cognitive impairments and

disruptive behaviours, such as psychosis. Patients who experience a complex array of symptoms, require careful delineation of additional cognitive and behavioural symptoms, as these compound the physical symptoms in different ways. For example, the disorganised behaviours of psychosis may be detrimental to adherence to treatment such as maintaining a vital PEG feed, apathy may impact on social connectedness, and changes in personality may add to carer stress, additionally compromising the care the patient receives. Psychosis symptoms can be very confronting and threaten the control of one's own behaviour, consequently inciting unfamiliar personal experience and damage trust and familiarity between patients and their carers (Mythri & Ebenezer, 2018).

3.2 Methods

3.2.1 Participants

Between the period of September 2016 and September 2019, 186 MND patients were active and recorded to either visit the Neurology Clinics in person or, for those too unwell to travel, undertake a phone consultation. For 100% of those patients, basic demographic data (age, sex), diagnosis and where appropriate a date of death were recorded, and in 97% (*N*=176) symptom onset date recorded. Diagnosis of MND was based on the standard diagnostic criteria for MND (Brooks et al., 2000) as per the senior neurology consultant and included MND limb onset, MND bulbar onset, and MND PLS. Diagnoses of FTD-MND adhered to the ALS-FTD revised diagnostic criteria (Strong et al., 2017) as per the senior neurology consultant. Patients were excluded if they had a diagnosis other than MND (*N*=5). After applying this exclusion criteria, a total of 181 patients with a diagnosis of an MND sub-type of limb onset, bulbar onset, PLS, or FTD-MND were included. Disease duration was calculated from symptom onset as reported by the patient and in medical records, to the

date of cognitive screen in months. Demographic and diagnostic characteristics of the final overarching patient sample (Tier 0) are summarised in Table 3 of results.

Details on consent and recruitment of patient participants and healthy controls to Tier 1 to Tier 3 of the study are outlined in chapter 2 General Methods (section 2.2).

3.2.2 Cognitive and behavioural measures

The cognitive and behavioural measures presented in this chapter are described in detail in chapter 2 (section 2.6).

3.2.3 Analyses

Descriptive statistics were applied to the Tier 0 and Tier 1 MND group. Descriptives, ANOVAs, *t*-tests (Wilcoxon for non-parametric variables), and Pearson's *r* correlations (Spearman's *rho* for non-parametric variables) were applied to MND and healthy control groups in Tier 2 to ascertain group differences and relationships between variables. A principal component analysis (PCA) was conducted on the total scores of neuropsychiatric measures within the MND group. For appropriate comparison across difference psychiatric, mood and apathy questionnaires, total scores and psychosis index scores were converted to percentages of respective total scores (CBI-R, NPI, BDI and HADS) or the minimum to maximum score (BPRS), where the minimum score was not zero. The ALS-FRS-R score was similarly converted to a percentage of its total score to aid comparison with the percentage score derived from the logit score of the FTD-FRS. Using the PCA components as predictor variables, logistic regression was carried out using JASP (version 0.12.2) to predict psychosis status as rated by someone who knows the patient well on the ECAS carer report. This allowed for the suitable inclusion in analyses of the binary variable from the

ECAS where patients were classified as overtly “psychotic” (1) or “non-psychotic” (0) based on whether the carer had ticked at least one psychosis symptom as present. Overall fit of the model was determined by the loglikelihood statistic and its associated chi-square statistic, using a threshold of $p<0.05$. Tjur’s R^2 values provided additional indication of model effect size. The influence of the independent component scores on predicting psychosis status were determined by the significance of the Wald statistic ($p<0.05$). Odds ratio provided information regarding the directionality of the effect with values >1 indicating increased odds of psychosis status while values <1 indicated decreased odds of psychosis status (non-psychotic). Sensitivity (the percentage of cases correctly predicted as psychotic (true positives)) and specificity (the percentage of cases correctly predicted as non-psychotic (true negatives)) were also calculated and graphically presented.

3.3 Results

Table 3 shows the total number of MND participants across each tier, means and standard deviations for age, education, disease duration, severity and survival, count of male and female, percentage of MND participants with diagnosis sub-types, deceased and psychosis involvement.

3.3.1 Tier 0 patient demographic and disease characteristics

As indicated in Table 3, the majority of the overall Tier 0 MND patients clinically presented with limb onset MND, approximately one quarter (25%) with bulbar onset, and much smaller proportions with the less frequent PLS phenotype and MND with FTD. Not indicated in the table, yet noteworthy, 4% of the overall patient sample ($N=7$) experienced significant respiratory difficulties at the time of their clinic visit and were on non-invasive ventilation.

Disease duration in years was calculated from symptom onset, which was estimated based on recall of initial relevant symptoms.

To ensure the main testing sample of MND participants in each tier were representative of the overarching sample (Tier 0) and remained consistent across demographics (age and sex) and diagnoses, within-group *t*-tests and ANOVAs stratified by tier (T0 v T1 v T2 v T3) indicated no differences in age or sex ($p>0.05$). Additional *t*-tests were performed on all MND participants who had completed in-depth cognition (Tier 2 + Tier 3) compared to all MND participants who had only completed the cognitive screen (Tier 1). The results showed no group differences in age or sex ($p>0.05$). A within-group *t*-test was performed on all MND participants who had completed the MRI scan (Tier 3) and all MND participants who had not completed the MRI scan (sub-sample of Tier 2 + Tier 1). The results showed no group differences in age or sex ($p>0.05$). In summary, patients were demographically representative across all tiers of the study.

Table 3: Psychosis prevalence, demographic, diagnosis, severity and survival descriptives and group differences across Tiers 0-3.

Demographic and clinical data	Clinic	Study Tier						
	Tier 0	Tier 1	Tier 2			Tier 3		
	MND	MND	MND	Control	Difference	MND	Control	Difference
N	181	111	60	30	-	30	20	-
Age (y)	66.28 ±11.59	66.04 ±10.57	64.98 ±9.72	68.17 ±5.74	ns	64.22 ±9.38	68.39 ±5.49	ns
(min-max)	(28.90-90.95)	(35.53-87.27)	(44.47-76.68)	(57.39-79.18)		(44.47-76.68)	(57.39-79.18)	
Sex (m:f)	96:85	63:48	35:25	15:15	*p*=0.042	16:14	12:8	ns
Education (y)	-	-	12.37 ±2.81	13.89 ±3.31	ns	11.55 ±2.29	14.56 ±3.43	*p*=0.003
Diagnosis (*N*(%))								
Limb	114(63)	77(69)	50(84)	-	-	25(86)	-	-
Bulbar	45(25)	22(20)	9(16)	-	-	3(13)	-	-
PLS	7(4)	6(5)	3(5)	-	-	1(3)	-	-
FTD-MND	7(4)	4(3)	1(2)	-	-	1(3)	-	-
ALS-FRS-R[a]	-	-	35.68 ±8.30	47.57 ±0.97	*p*<0.001	37.67 ±5.93	47.35 ±1.14	*p*<0.001
FTD-FRS[b]	-	-	0.72 ±0.25	0.93 ±0.10	*p*<0.001	0.71 ±0.25	0.93 ±0.10	*p*<0.001
Disease duration (y)[c]	2.82	4.04 ±11.99	1.95 ±3.09	-	-	1.71 ±2.60	-	-
Survival (y)		-2.82 ±1.27	-3.13 ±1.43	-	-	-2.70 ±0.73	-	-
Deceased (%) at 01/07/2020	42	38	32	-	-	10	-	-
Family hx MND (*N*)	-	-	14	-	-	8	-	-
Family hx Psy[d] **(*N*)**	-	-	11	-	-	7	-	-
ECAS Psychosis (*N(%)*)	-	11(10)	6(10)	-	-	2(6)	-	-
Beliefs (*N*)	-	6	5	-	-	2	-	-
Hallucinations (*N*)	-	5	5	-	-	2	-	-
Suspiciousness (*N*)	-	6	5	-	-	2	-	-

[a]ALS-FRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised. [b]FTD-FRS = Frontotemporal Dementia Functional Rating Scale, a score in the 70th percentile indicates moderate functional impairment. [c]Calculated from symptom onset. [d]Psy = Psychosis

3.3.2 Tier 1 cognitive, psychosis and behaviour screening

N=111 patients underwent cognitive, psychosis and behavioural screening in clinic using the ECAS and the CBI-R (see Table 3 for demographic information). Figure 9 shows the spread of ECAS cognitive screen total scores and sub scores for individual MND participants overlaid onto group average scores.

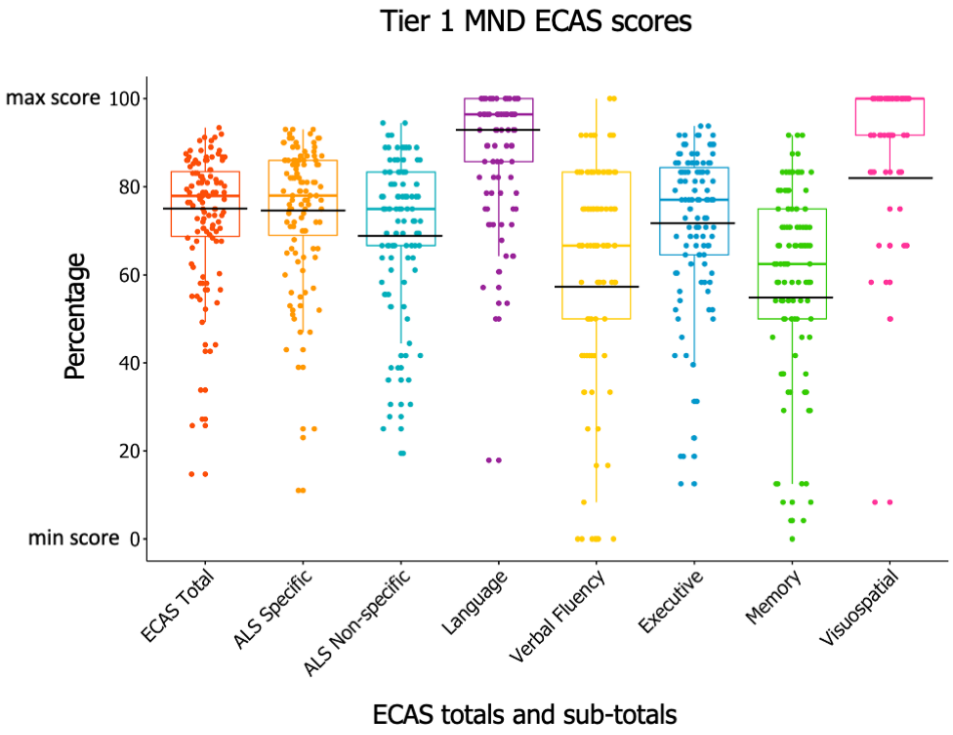

Figure 9: MND individual (scatterplot) ECAS total and sub-total scores, converted to percentages, overlaid onto group mean scores (boxplot). Scores closer to 100 indicate a good performance. Black lines indicate threshold for impaired performance.

Table 4 highlights the cut-off scores for each ECAS total, sub-total, and domain-specific scores, and percentage of Tier 1 cognitive screened patients who scored *below* those cut-offs. Around half of patients (48%) scored below the cut-off for intact global cognitive function, including 44% who showed specific involvement of cognitive domains commonly affected in MND, which include verbal fluency, language (spelling, confrontation naming and

comprehension) and executive functions (working memory, mental flexibility and sustained attention, inhibition, impulsivity and social cognition (empathy)). The ALS non-specific score, comprised of memory (unstructured verbal encoding, immediate and delayed recall, and recognition) and visuospatial skills, showed memory and visuospatial impairment in some MND patients (29% and 9% respectively) (Table 4), although there was great variation in memory impairment (Figure 9).

Table 4: Percentage of patients in Tier 1 scoring below the ECAS cut-off scores for intact cognitive function.

ECAS score	Cut off score (/total)	% patients scoring below cut off
Total	105 (/136)	48
ALS specific	77 (/100	44
ALS non-specific	24 (/36)	25
Language	26 (/28)	36
Verbal Fluency	14 (/24)	28
Executive	33 (/48)	31
Memory	13 (/24)	29
Visuospatial	10 (/12)	9

The carer report on the ECAS cognitive screen showed almost 10% of MND patients who were cognitive screened were described as endorsing at least one overt psychosis feature of the 3 screening items: “has strange and/or bizarre beliefs and behaviours”, “hears or sees things that are not there, and/or feels the presence of someone who is not there”, and “Is overly suspicious, and/or feels persecuted” (see Figure 10).

Additional behavioural items from the ECAS are presented in Figure 10. Behavioural change, as observed by someone who knows the patient well, was noted in 40% of the current MND cohort. *Apathy* was the most pronounced behavioural change in 23%. While *altered food preferences* was noted in 18% of our MND cohort, qualitatively many carers and patients reported this as forced changes due to difficulties eating and swallowing rather than the typical eating habit changes associated with behavioural variant FTD, such as food cramming or preference for sweet foods. Similarly, *loss of manners/decorum* was more due to difficulty in handling cutlery as usual. Smaller, yet notable, proportions of MND patients showed other odd and bizarre behaviours, such as social inappropriateness, perseverate, repetitive movements and compulsive behaviours.

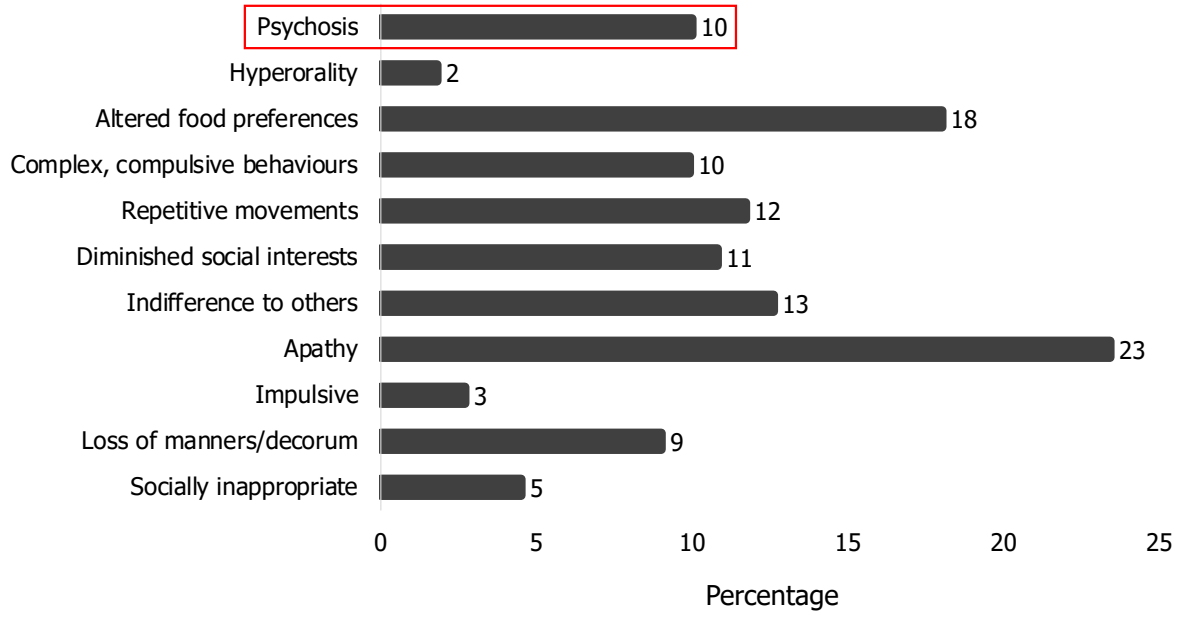

Figure 10: Percentage of Tier 1 MND participants endorsing various behaviours from the ECAS, as reported by someone who knows the patient well.

3.3.3 Tier 2 psychiatric and cognitive findings

Table 3 shows the relevant Tier 2 and 3 MND versus control group differences for age, education, disease duration, severity and survival, count of male and female, in addition to percentage of MND participants with diagnosis sub-types, deceased and psychosis involvement.

In the main Tier 2 testing sample, MND and healthy controls were matched for age and education, however sex demonstrated a significant group difference reflecting the much larger number of male MND participants than female (Table 3). In Tier 3 participants were matched on age and sex but not education due to the higher educational attainment achieved by healthy controls (Table 3). Sex and age were included as covariates in subsequent analyses to account for any possible residual confounding effects associated with variability in these demographics. Patients demonstrated functional impairment, denoted by reduced ALS-FRS-R and FTD-FRS scores, compared to healthy controls.

Table 5 shows the mean and standard deviation scores for total psychiatric, mood and apathy scores according to each questionnaire, including psychosis index scores for the CBI-R and NPI and group difference statistic, strength and uncorrected significance for Tier 2 study participants.

Table 5: Tier 2 mean and standard deviation scores on psychiatric, behaviour, mood and apathy measures.

	Measure	MND (*N*=60)	Controls (*N*=30)	Statistic	Cohen's *d*	Group difference
Psychiatric	Cambridge Behavioural Inventory-Revised					
	Total (range 0-92)	18.44 ±22.90	6.95 ±5.63	*W*=688.5	-0.56	***p*=0.030**
	Psychosis Index (range 0-52)	5.64 ±10.68	1.84 ±2.77	*W*=889	-0.41	*p*=0.042
	Neuropsychiatric Inventory					
	Total (range 0-120)	7.11 ±10.04	1.07 ±2.11	*W*=513.5	-0.74	***p*<0.001**
	Psychosis Index (range 0-36)	0.59 ±2.18	0.00	*W*=826.5	-0.33	*p*=0.039
	Brief Psychiatric Rating Scale (range 18-126)	24.23 ±6.03	19.12 ±2.07	*W*=405.5	-0.98	***p*<0.001**
Mood	Beck Depression Inventory	13.81 ±9.58	5.57 ±5.57	*t*=-5.04	-0.96	***p*<0.001**
	Hospital Anxiety & Depression Scale					
	Depression	5.07 ±4.03	2.45 ±2.37	*t*=-3.82	-0.73	*p*<0.001
	Anxiety	5.20 ±4.46	3.07 ±2.14	*t*=-3.15	-0.58	*p*=0.002
Apathy	Dimensional Apathy Scale					
	Executive	7.35 ±5.65	5.24 ±3.40	*t*=-2.15	-0.41	*p*=0.035
	Initiation	11.42 ±5.56	8.31 ±3.43	*t*=-3.21	-0.62	*p*=0.002
	Emotional	8.45 ±3.82	8.17 ±3.21	*t*=-0.35	-0.07	ns
	CamQuAIT					
	Total (range 22-88)	40.03 ±9.62	32.04 ±6.49	*t*=-4.67	-0.93	***p*<0.001**
	Executive skills (range 21-44)	37.94 ±9.16	30.19 ±6.21	*t*=-4.73	-0.94	*p*<0.001

	Complex behaviours (range 17-36)	30.17 ±7.38	24.41 ±4.68	*t*=-4.56	-0.89	*p*<0.001
	Friends (range 2-8)	3.57 ±1.72	3.15 ±1.29	*t*=-1.35	-0.28	ns
Impulsivity	ECAS Disinhibition	9.78 ±2.58	10.69 ±1.54	*t*=1.76	0.39	ns
	ECAS Impulsivity (*N*)	3	0	χ^2=0.42	-	ns
	NPI Disinhibition	0.48 ±1.87	0.00	*W*=798.5	-0.33	ns

W=Wilcoxon non-parametric test. *t*=two-sample parametric test. χ^2=Chi-square for categorical variables. *p*-values are uncorrected due to the nesting of subscales within total test score but total scores are FDR-corrected and highlighted in bold if survived at 0.05.

As expected, at the time of testing, across the three psychiatric and behaviour scales (CBI-R, NPI and BPRS), significant group differences were shown in all total and psychosis index scores for Tier 2 participants (Table 5). Figure 11 illustrates the variation in scores from each MND and control participant in Tier 2 overlaid onto group average scores, and specifically captures approximately 12-16% of MND participants reported to have mild to moderate features suggestive of psychosis (CBI-R and NPI psychosis indices), as reported by someone who knows them well in combination with structured interview.

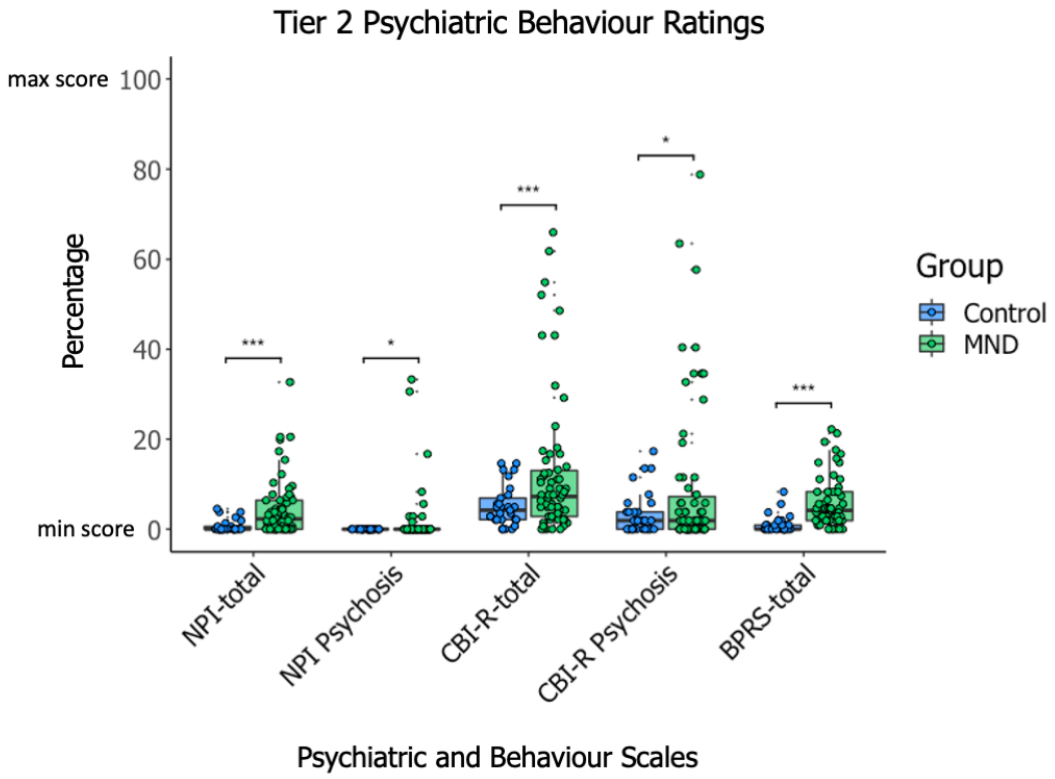

Figure 11: Tier 2 variation in percentage of psychiatric and behaviour ratings across three psychiatric and behavioural scales for MND and control participants (scatter plot) overlaid onto group average ratings (boxplot). Ratings converted to percentage of total score of respective scales and rescaled from minimum 0 to maximum 100. Ratings closer to 100 indicate a higher involvement of psychiatric behaviour. NPI-total=Neuropsychiatric Inventory (total score), NPI Psychosis=NPI psychosis index, CBI-R-total=Cambridge Behavioural Inventory-R (total score), CBI-R Psychosis=CBI-R psychosis index, BPRS-total=Brief Psychiatric Rating Scale (total score). *p<0.05, ***p<0.001.

The MND group experienced lower mood and increased anxiety compared to controls and these differences were significant (Table 5 and Figure 12a). On average, the MND group scored on the threshold for minimal mood involvement on the BDI (a score between 0-13) and on the HADS for both depression and anxiety scored within the range indicating normal levels (a score between 0-7). Nonetheless, on the HADS the MND group scored at the higher end of the normal range, hence the significant difference from controls, who scored on average toward the lower end of the normal range indicating almost nil involvement of

depression or anxiety symptoms. Similarly, differences in specific dimensions across apathy measures were shown to be significant (Table 5 and Figure 12b), indicating a much higher involvement of apathy and/or more heterogeneity within groups. Specifically, the MND group showed higher scores (more involvement) on all components of apathy across the two scales used, except the *Emotional* apathy component from the DAS and the *Friends* component from the Cam-QuAIT.

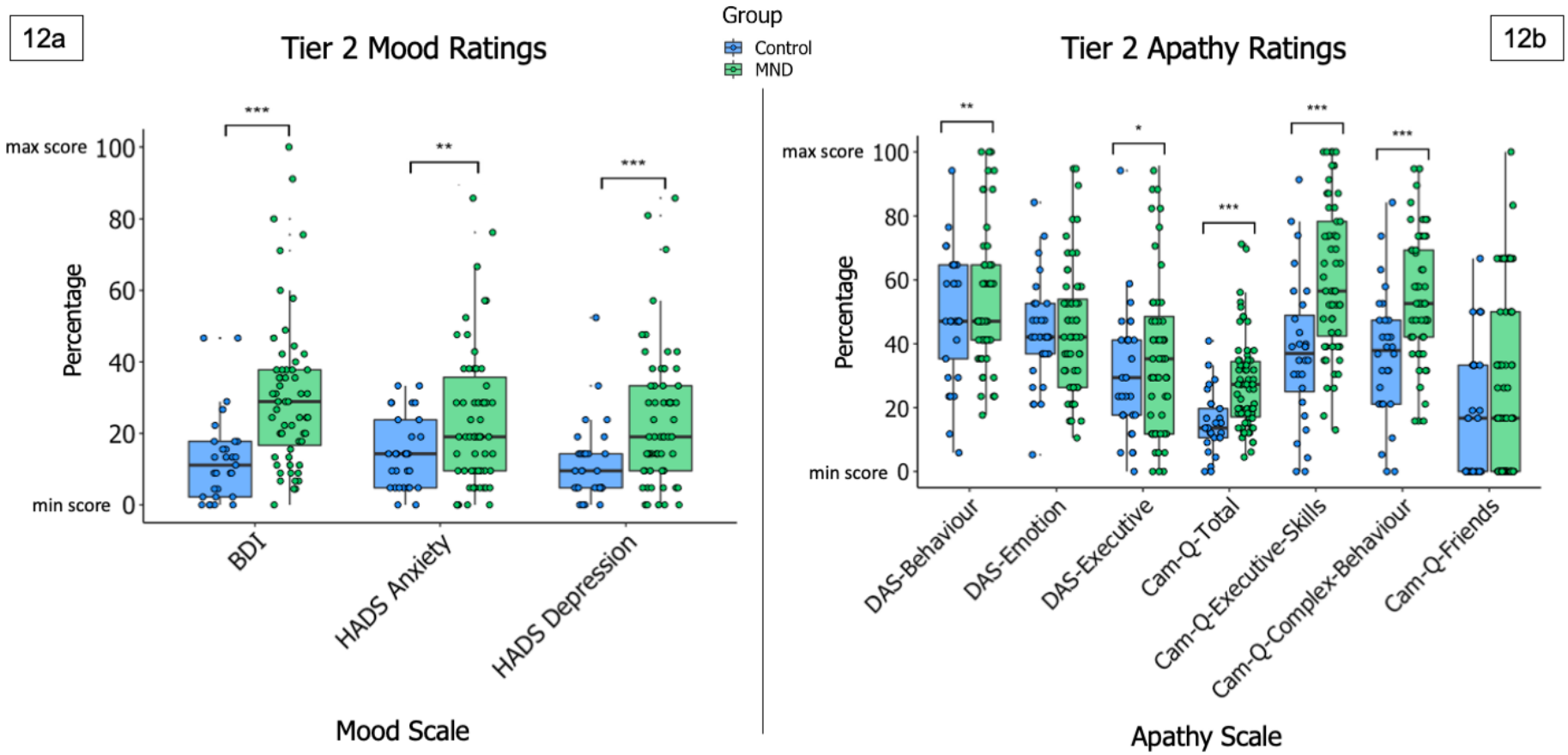

Figure 12: Mood (12a) and apathy (12b) ratings for MND and control participants (scatter plot) overlaid onto group average ratings (boxplot). Ratings converted to percentage of total score of respective scales and rescaled from minimum 0 to maximum 100. Ratings closer to 100 reflect a higher endorsement of mood and apathy symptoms. DAS=Dimensional Apathy Scale, Cam-Q=Cambridge Questionnaire for Apathy and Impulsivity (Cam-QuAIT), *p<0.05, **p<0.01, ***p<0.001.

On measures of cognition, Tier 2 MND patients showed a distinct performance compared to controls on the cognitive screening measures. Table 6 presents the mean and standard deviation scores across cognitive total and sub-scores and the group difference statistic, strength and uncorrected significance. In addition to the group difference, the Tier 2 MND group showed increasingly variable scores and on average scored below the threshold (Table 4) for intact cognitive function on the ECAS total score and ALS-specific total score and either below (Language) or on the border (Verbal Fluency, Executive) of the ALS-specific sub-scores. While the sub-scores of Memory and Visuospatial skills from the ECAS showed scores above the threshold for intact functioning, as expected for these domains, the variability in scores is the likely cause of the ALS-non-specific total score falling just below the threshold. Average scores on the ACE indicated intact functioning for Attention, Memory and Language, however scores on Verbal Fluency reflected typical poor performance in this domain with Visuospatial ability showing impairment, likely due to the physical nature (drawing) of these visuospatial tasks on the ACE.

Table 6: Tier 2 mean and standard deviation scores on cognitive screen measures.

Measure	MND (*N*=60)	Controls (*N*=30)	*t*-statistic	Cohen's *d*	Group difference
ECAS-Total	100.14 ±19.42	118.00 ±9.13	6.03	1.06	***p*<0.001**
ECAS-ALS-Specific	74.40 ±15.53	88.70 ±7.65	5.95	1.06	*p*<0.001
Language	25.32 ±3.99	27.33 ±0.96	3.79	0.60	*p*<0.001
Verbal Fluency	14.89 ±5.65	19.93 ±4.02	4.93	0.97	*p*<0.001
Executive	34.19 ±8.10	41.43 ±4.20	5.67	1.02	*p*<0.001
ECAS-ALS-non-Specific	25.75 ±5.67	29.30 ±3.91	3.52	0.69	*p*=0.001
Memory	14.43 ±4.89	17.33 ±3.87	3.10	0.63	*p*=0.004
Visuospatial	11.32 ±1.20	11.97 ±0.18	1.18	0.65	ns
ACE-R	86.49 ±14.93	93.87 ±13.16	2.39	0.51	***p*=0.026**
ACE-III	84.89 ±18.15	92.63 ±17.05	1.99	0.44	ns
Attention	16.02 ±3.67	17.10 ±3.33	1.41	0.30	ns
Memory	21.90 ±5.15	23.20 ±4.73	1.19	0.23	ns
Verbal Fluency	10.16 ±3.17	12.03 ±2.76	2.89	0.61	*p*=0.008
Language	22.98 ±5.32	24.87 ±4.75	1.71	0.37	ns
Visuospatial	13.82 ±3.23	15.43 ±2.19	2.80	0.55	*p*=0.007

p-values are uncorrected due to the nesting of subscales within total test scores but total scores are FDR-corrected and highlighted in bold if survived at 0.05.

3.3.4 Tier 3 psychiatric and cognitive findings

Tier 3 was a subset of MND patients and healthy controls from Tier 2 on which psychiatric and cognitive data are presented separately in Tables 7 and 8, respectively. Behaviourally, significant group differences were seen on measures of psychiatric behaviour, mood and apathy (Table 7). However, no group differences were seen on the mean CBI-R or NPI

psychosis index scores (Table 7). Figure 13 shows the variation in psychiatric and behavioural involvement for each Tier 3 participant and indicates a group of MND participants scored well above the group mean and strongly endorsed these features. Significant group differences in Tier 3 remained across global cognition and specific areas of cognition (Table 8).

Table 7: Tier 3 mean and standard deviation scores on psychiatric, behaviour, mood and apathy measures.

	Measure	MND (*N*=30)	Controls (*N*=20)	Statistic	Cohen's *d*	Group difference
Psychiatric	Cambridge Behavioural Inventory-Revised					
	Total (range 0-92)	19.21 ±25.49	6.95 ±5.63	*W*=248	-0.52	***p*=0.02**
	Psychosis Index (range 0-52)	5.64 ±10.68	1.84 ±2.77	*W*=306	-0.39	ns
	Neuropsychiatric Inventory					
	Total (range 0-120)	7.32 ±11.61	0.84 ±1.71	*W*=162	-0.71	***p*=0.003**
	Psychosis Index (range 0-36)	0.93 ±3.02	0.00	*W*=270	-0.37	ns
	Brief Psychiatric Rating Scale (range 18-126)	23.41 ±5.87	19.10 ±2.34	*W*=126	-0.59	***p*<0.001**
Mood	Beck Depression Inventory	13.89 ±9.53	4.25 ±4.05	*t*=-4.67	-1.19	***p*<0.001**
	Hospital Anxiety & Depression Scale					
	Depression	5.22 ±3.97	1.90 ±1.45	*t*=-4.04	-1.02	*p*<0.001
	Anxiety	5.59 ±4.97	2.70 ±2.03	*t*=-2.84	-0.72	*p*=0.014
Apathy	Dimensional Apathy Scale					
	Executive	8.07 ±5.26	4.45 ±2.74	*t*=-2.79	-0.73	*p*=0.015
	Initiation	11.63 ±4.81	8.00 ±3.40	*t*=-2.71	-0.73	*p*=0.008
	Emotional	8.11 ±3.69	7.55 ±2.28	*t*=-0.38	-0.10	ns
	CamQuAIT					
	Total (range 22-88)	38.93 ±8.21	31.74 ±6.98	*t*=-3.25	-0.91	***p*=0.004**
	Executive skills (range 21-44)	37.32 ±7.93	29.74 ±6.68	*t*=-3.55	-0.99	*p*=0.002

	Complex behaviours (range 17-36)	29.50 ±6.57	24.32 ±5.14	*t*=-3.02	-0.83	*p*=0.008
	Friends (range 2-8)	3.39 ±1.59	3.26 ±1.37	*t*=-0.32	-0.09	ns
Impulsivity	ECAS Disinhibition	9.48 ±3.19	10.70 ±1.69	*t*=1.52	0.45	ns
	ECAS Impulsivity (*N*)	3	0	χ^2=2.37	-	ns
	NPI Disinhibition	0.54 ±2.32	0.00	*W*=260	-0.27	ns

W=Wilcoxon non-parametric test. *t*=two-sample parametric test. χ^2=Chi-square for categorical variables. *p*-values are uncorrected due to the nesting of subscales within total test scores but total scores are FDR-corrected and highlighted in bold if survived at 0.05.

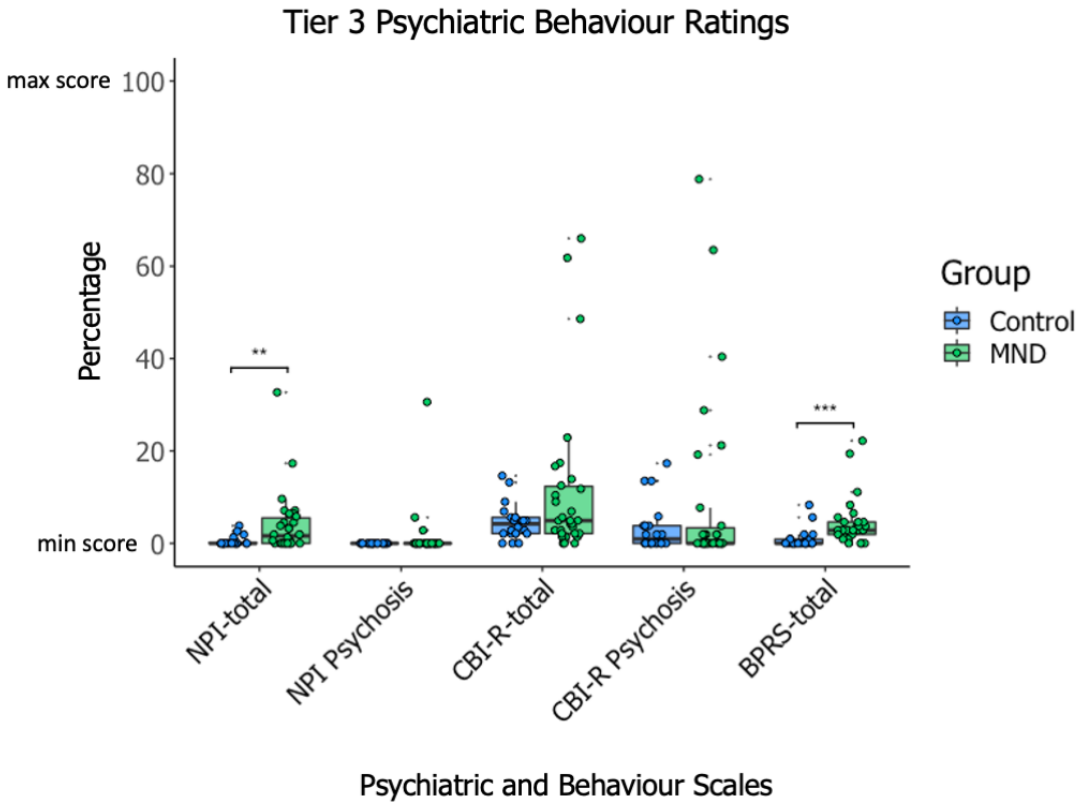

Figure 13: Tier 3 variation in percentage of psychiatric and behaviour ratings across three psychiatric and behavioural scales for MND and control participants (scatter plot) overlaid onto group average ratings (boxplot). Ratings converted to percentage of total score of respective scales and rescaled from minimum 0 to maximum 100. Ratings closer to 100 indicate a higher involvement of psychiatric behaviour. NPI-total=Neuropsychiatric Inventory (total score), NPI Psychosis=NPI psychosis index, CBI-R-total=Cambridge Behavioural Inventory-R (total score), CBI-R Psychosis=CBI-R psychosis index, BPRS-total=Brief Psychiatric Rating Scale (total score). **p<0.01, ***p<0.001.

The Tier 3 MND group experienced lower mood and increased anxiety compared to controls and these differences were significant (Table 7 and Figure 14a). On average, the MND group scores remained on the threshold for minimal mood involvement on the BDI (a score between 0-13) and on the HADS for both depression and anxiety score within the range indicating normal levels (a score between 0-7). Similar to the Tier 2 sub-sample, on the HADS the Tier 3 MND group scored at the higher end of the normal range, hence the significant difference from controls, who scored on average toward the lower end of the

normal range indicating almost nil involvement of depression or anxiety. Similarly, group differences in specific dimensions across apathy measures remained significant in the Tier 3 subset (Table 7 and Figure 14b), indicating a much higher involvement of apathy and/or more heterogeneity within groups. Specifically, the Tier 3 MND group showed higher scores (more involvement) on all components of apathy across the two scales used, except the *Emotional* apathy component from the DAS and the *Friends* component from the Cam-QuAIT.

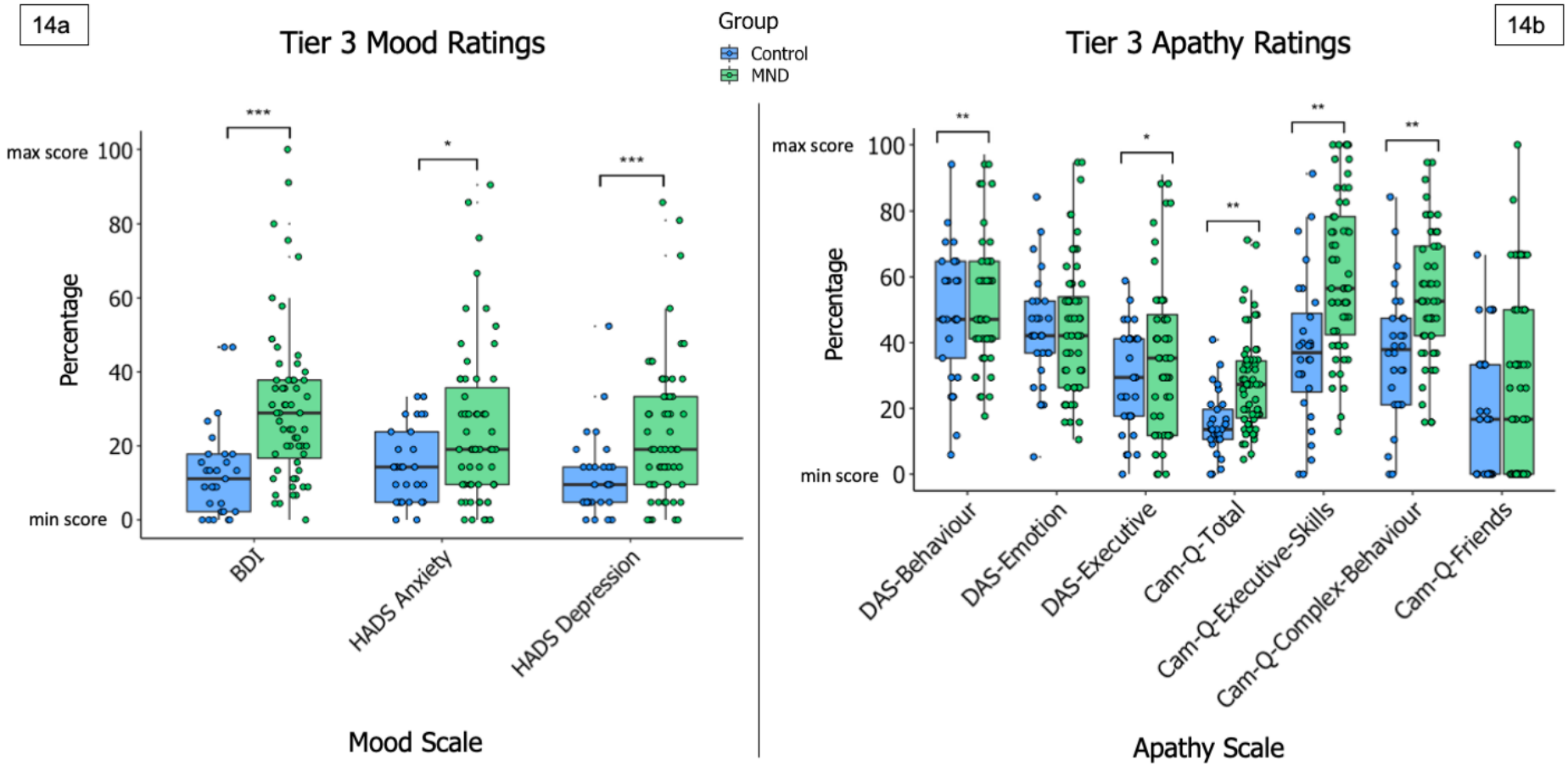

Figure 14: Mood (14a) and apathy (14b) ratings for MND and control participants (scatter plot) overlaid onto group average ratings (boxplot). Ratings converted to percentage of total score of respective scales and rescaled from minimum 0 to maximum. Ratings closer to 100 reflect a higher endorsement of mood and apathy symptoms. DAS=Dimensional Apathy Scale, Cam-Q=Cambridge Questionnaire for Apathy and Impulsivity (Cam-QuAIT), *p<0.05, **p<0.01, ***p<0.001.

Table 8: Tier 3 mean and standard deviation scores on cognitive screen measures.

Measure	MND (*N*=30)	Controls (*N*=20)	*t*-value	Cohen's *d*	Group difference
ECAS-Total	99.14 ±23.47	118.60 ±9.07	4.05	1.02	***p*<0.001**
ECAS-ALS-Specific	74.03 ±18.65	88.65 ±7.94	3.76	0.96	*p*<0.001
Language	25.28 ±4.96	27.50 ±0.69	2.38	0.58	*p*=0.039
Verbal Fluency	14.34 ±6.00	19.60 ±4.66	3.44	0.96	*p*=0.001
Executive	34.41 ±9.59	41.55 ±3.59	3.65	0.92	*p*<0.001
ECAS-ALS-non-Specific	25.10 ±6.46	29.95 ±2.48	3.67	0.93	*p*=0.001
Memory	13.83 ±5.40	18.00 ±2.38	3.67	0.94	*p*=0.001
Visuospatial	11.28 ±1.36	11.95 ±0.22	2.62	0.64	ns
ACE-R	87.52 ±12.55	96.05 ±3.33	3.38	0.87	***p*=0.001**
ACE-III	84.28 ±19.79	95.60 ±3.49	3.01	0.73	***p*<0.001**
Attention	15.97 ±3.90	17.85 ±0.37	2.58	0.62	*p*=0.004
Memory	21.34 ±5.16	23.80 ±2.02	2.32	0.59	*p*=0.032
Verbal Fluency	9.79 ±3.49	12.25 ±1.71	3.26	0.85	*p*=0.003
Language	23.10 ±5.94	25.90 ±0.31	2.53	0.61	*p*=0.011
Visuospatial	14.07 ±3.32	15.80 ±0.41	2.78	0.67	*p*=0.002

p-values are uncorrected due to the nesting of subscales within total test scores but total scores are FDR-corrected and highlighted in bold if survived at 0.05.

3.3.5 Correlation analysis

Within-group MND (*N*=57) Pearson's *r* correlation analyses, and Spearman's *rho* for comparison, were carried out to explore the relationship between total scores on psychiatric behaviour (NPI, CBI-R, BPRS), cognition (ECAS and ACE-III), mood (HADS and BDI, apathy (DAS-self report and Cam-QuAIT-carer report total scores) and functional severity (ALS-FRS-R and FTD-FRS) scales. On the ACE-III score, three outliers were identified in

the MND group that significantly exceeded a ±2 standard deviation threshold and were subsequently removed from the analysis. Two of these patients became very disengaged from the testing session and the third was too physically impaired to complete cognitive testing and was also excluded from the ECAS score in the correlation analyses.

Figure 15 (Pearson and Spearman correlations) illustrates the cross-correlations between key cognitive and psychiatric, mood and apathy total scores within Tier 2 MND participants. Significant negative correlations were shown between the well-established measure of psychiatric and behaviour symptoms (CBI-R) and cognition (both ECAS and ACE-III) such that the higher the endorsement of psychiatric behaviour (higher scores) in MND participants, the more impaired their cognitive ability (lower scores). No significant results were shown between the NPI or the BPRS total scores and the cognitive total scores. The psychiatric and behaviour total scores from the CBI-R and NPI showed significant negative correlations with disease severity on the FTD-FRS and the BPRS showed a positive correlation with the ALS-FRS-R. Of note, higher scores on the ALS-FRS-R and FTD-FRS indicates good function whereas lower scores indicate greater functional impairment. Additionally, these functional measures capture different aspects of functioning. ALS-FRS-R emphasises physical disability whereas the FTD-FRS encompasses more behavioural and cognitive aspects as well as a range of day-to-day functions and activities. The CBI-R and NPI total scores were positively correlated with the BDI score, and the BPRS total score showed significant positive correlations with both mood scores (BDI and HADS). The positive correlations suggest a higher endorsement of psychiatric behaviour, on the psychiatric and behaviour scales in MND participants, is related to a higher endorsement of depressed mood and anxiety. However, no significant correlations were shown between the CBI-R and NPI total scores and the HADS scale. All three psychiatric and behaviour total scores showed significant positive correlations with both apathy scales (CAM-Q and DAS). These significant correlations, specifically among the psychiatric behaviour, mood and

apathy scores are expected given many overlapping questions within each scale. For this reason, these variables will be included in the following PCA to reduce the number of contrasts in the following chapters with experimental computer tasks and imaging parameters.

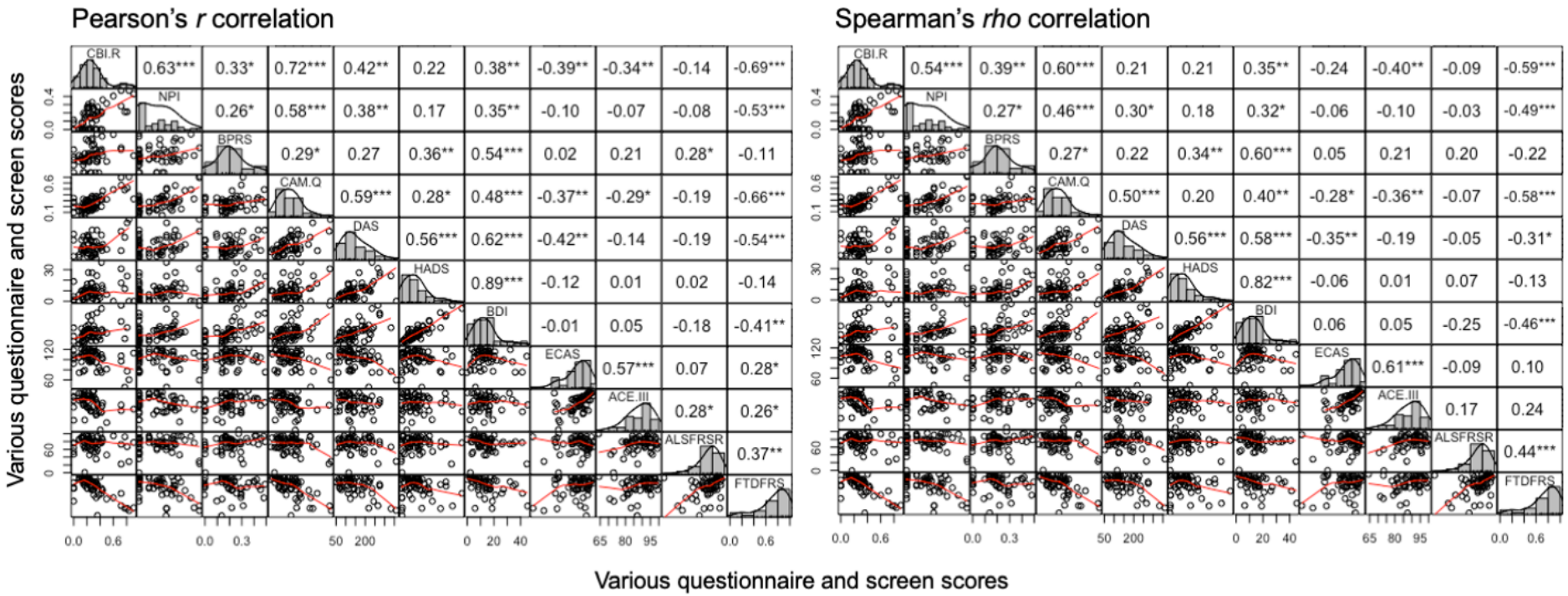

Figure 15: Tier 2 within-group MND cognitive and psychiatric behaviour correlations. Pearson's *r* (left) and Spearman's *rho* (right) correlations between cognitive screening (ECAS, ACE-III), psychiatric behaviour (CBI-R, NPI, BPRS), mood (HADS, BDI), apathy (Cam-Q and DAS) total scores, and disease severity (ALSFRSR and FTDFRS) for the Tier 2 MND participants. Scatter matrix on the lower diagonal, questionnaire/screening name with histogram on middle diagonal, correlation values on the upper diagonal with significant correlations denoted by stars (p*<0.05, ***p*<0.01, ****p*<0.001, uncorrected).**

3.3.6 Principal component analysis

Individual scales were not planned to be included in every comparison in subsequent chapters. Instead, a PCA was carried out on the total scores of the psychiatric, mood and apathy measures. The aim was to reduce the dimensionality of the data, to minimise the number of comparisons with cognitive task and brain imaging data, maximise the variance explained with minimised information loss. The MND group are considered as a continuous spectrum of severity and a PCA accommodated the phenotypic variation. Due to the non-Gaussian nature of a number of the neuropsychiatric and behavioural scales (CBI-R-total, NPI-total and BPRS-total), these proportion scores were arcsine transformed before proceeding to the principal component analysis. Arcsine transformation was required to stabilise the variance and normalise the non-Gaussian distributions of these variables. Psychiatric and behavioural measures entered into the principal component analysis included total scores from the BDI, HADS, DAS, Cam-QuAIT, and arcsine transformed CBI-R, NPI and BPRS total scores. The extracted components will be used in subsequent chapters along with CBI-R and NPI psychosis index scores.

Principal component analysis was carried out on Tier 2 MND data (N=60). The sample size was adequate for the analysis using Kaiser-Meyer-Olkin (KMO = 0.760) and Bartlett's test of sphericity (approximate χ^2= 219.74, p < 0.001), indicating correlations between items were sufficiently large for PCA. Varimax rotation was used and the correlation matrix extracted components meeting Kaiser's and/or Cattell's criteria (whichever was more inclusive) and scores were generated using the regression method.

Two components were extracted from the PCA accounting for 74.38% of the variance. The scree plot is presented in Figure 16 and the rotated component matrix is presented in Table 9. Expectedly, assessments that are traditionally associated with measuring mood and apathetic behaviour (HADS, BDI, DAS) by way of self-report loaded onto the same factor

(component 1), which was labelled '*Patient-rated Mood & Behaviour'*. High scores on component 1 reflect increased endorsement of anxiety, depression and dimensions of apathy (emotional, behavioural and executive). Similarly, higher scores on component 2 reflect increased endorsement of a variety of psychiatric and apathetic behaviour, as rate by someone else (clinician, researcher or carer). These component 2 loadings (NPI, CBI-R and Cam-QuAIT) were labelled '*Carer-rated Behaviour'*.

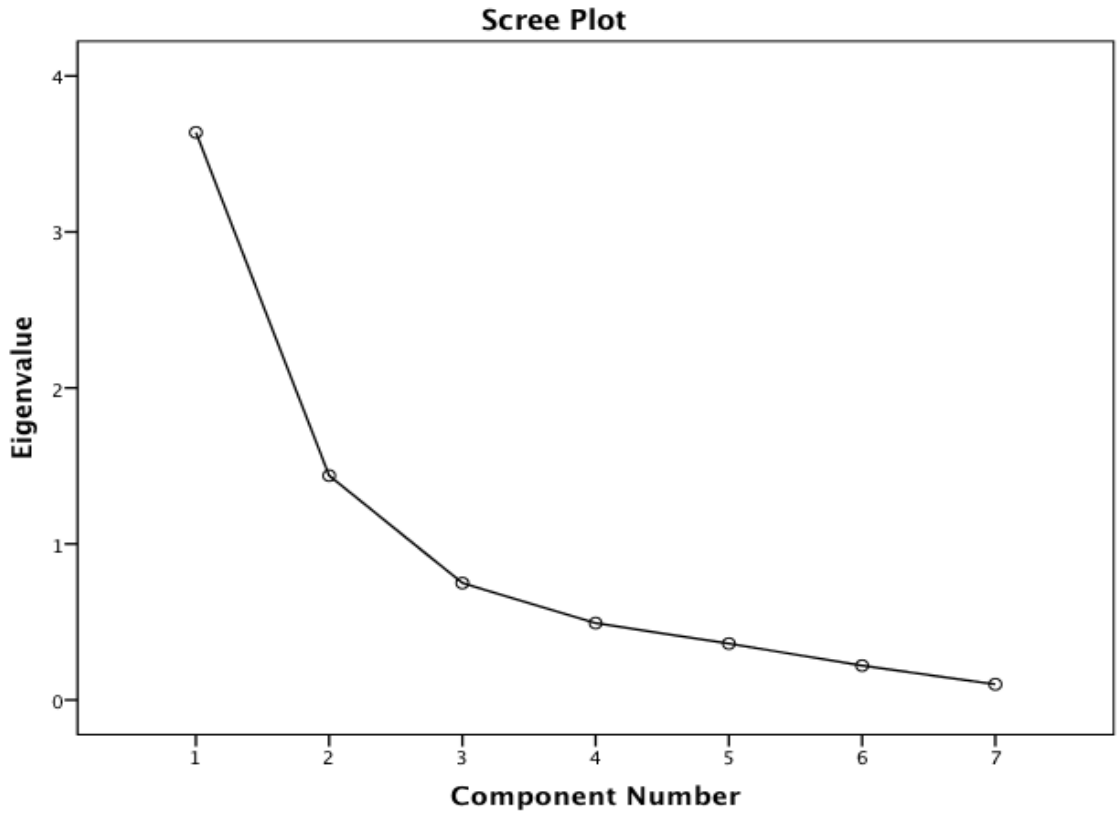

Figure 16: PCA scree plot. Scree plot demonstrating the number of components above 1 eigenvalue to be extracted from the PCA.

Table 9: Final rotated component matrix extracted from principal component analysis.

Input variable	Component Structure	
	C1 Patient-rated Mood & Behaviour	**C2** Carer-rated Behaviour
Eigenvalue I/R[a]	*3.638/2.694*	*1.438/2.382*
Variance (%)	38.47	35.90
Hospital Anxiety & Depression Scale	**.938**	.118
Beck Depression Inventory	**.937**	.127
Dimensional Apathy Scale	**.704**	.276
Brief Psychiatric Rating Scale	**.529**	.327
Cambridge Behavioural Inventory-R	.176	**.895**
Neuropsychiatric Inventory	.102	**.864**
Cam-QuAIT	.345	**.793**

[a]Initial (I) and rotated (R) eigenvalues

3.3.6.1 Component scores within MND group

Figure 17 shows the distribution of component scores 1 and 2 in the MND group.

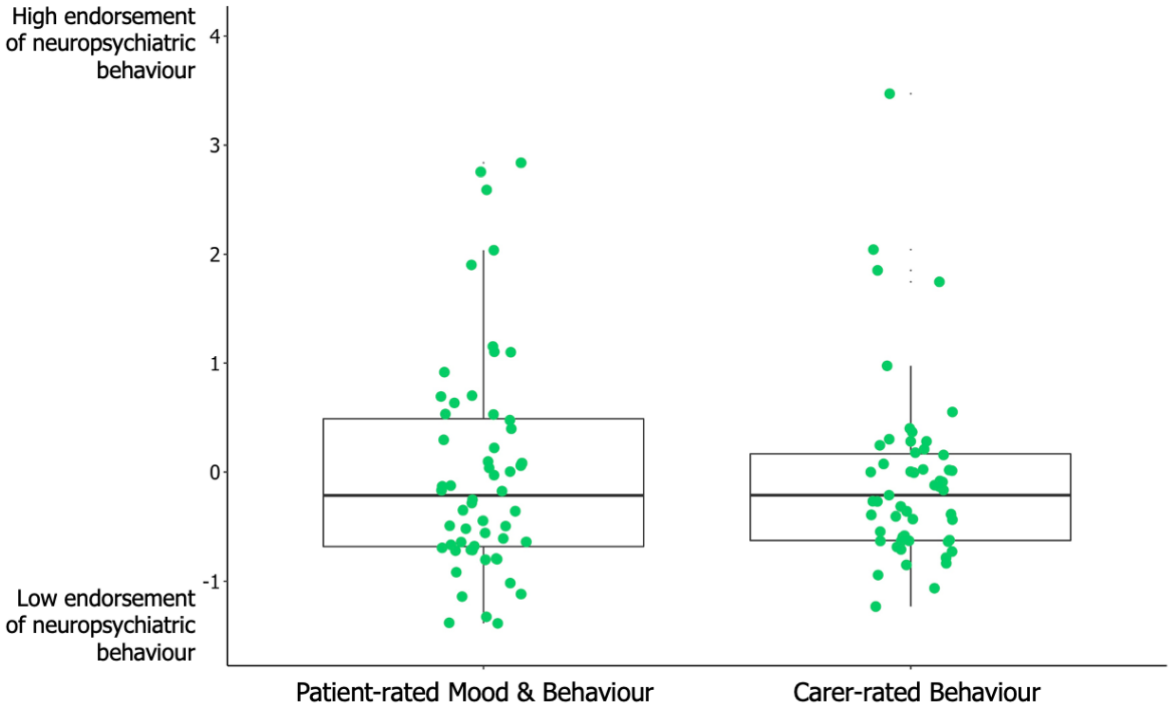

Figure 17: MND distribution of PCA component scores. Individual MND participants (scatter plot) overlaid onto MND group average (box plot) to illustrate their endorsement of neuropsychiatric behaviour on Patient-rated scales of Mood & Behaviour (component 1) compared to Carer-rated Behaviour (component 2).

Pearson's correlation analyses within the MND group (see Table 10) revealed that Carer-rated Behaviour showed significant moderate correlations with greater cognitive involvement (ECAS total and sub-total scores) and disease severity (FTD-FRS). Whereas no significant correlations were revealed with Patient-rated Mood and Behaviour. Both the CBI-R and NPI psychosis index scores showed moderate negative correlations with the ECAS total and sub-total scores reflecting a higher endorsement of overt psychosis symptoms relating to lower cognitive performance. Table 10 also shows moderate correlations with the psychosis index scores and measures of functional severity. The FTD-FRS revealed moderate to

strong negative associations with both psychosis index scores suggesting patients who endorsed more overt psychosis symptoms (higher psychosis score) were rated as being more functionally impaired (lower functional score) by their carer. No significant correlation was revealed with ALS-FRS-R and the psychosis index scores. Neither PCA components nor psychosis index scores were significantly related to age.

Table 10: Pearson's *r* correlation between the two components identified by principal components analysis and CBI-R and NPI psychosis index scores with age, cognitive performance and disease severity ratings for the MND group.

	Age	ECAS Total	ALS-specific	ALS-nonspecific	ALS-FRS-R	FTD-FRS
Patient-rated Mood & Behaviour	-0.16	0.04	0.05	-0.16	-0.17	-0.25
Carer-rated Behaviour	-0.13	**-0.48****	**-0.44****	**-0.40****	-0.09	**-0.69*****
CBI-R Psychosis	0.10	**-0.53*****	**-0.50*****	**-0.46*****	-0.05	**-0.72*****
NPI Psychosis	0.01	**-0.65*****	**-0.61*****	**-0.56*****	0.14	**-0.49*****

*p<0.05, **p < 0.01, ***p < 0.001. Uncorrected p-values presented and the boldened values remained highly significant after FDR correction (p<0.001).

3.3.7 Logistic regression by psychosis status

A logistic regression was performed to investigate whether the ECAS psychosis status could be predicted by the proportion scores on the CBI-R and NPI psychosis indices and/or the two PCA components. The model that included PCA Carer-rated Behaviour (component 2) was significant, $\chi^2(53)=8.68$, $p=0.003$, Tjur $R^2=0.51$. The model correctly classified 100% of patients who were reported as having symptoms suggestive of psychosis on the ECAS and correctly predicted 62.5% of patients who were not reported to have psychosis symptoms on

the ECAS. This is unsurprising given the overlapping items in some of the carer report measures. A higher endorsement of psychosis and broader behaviour, mood and apathy symptoms as reported by someone who knows the patient well was associated with increased likelihood of being classified on the ECAS as having psychosis symptoms. Figure 18 illustrates the fitted sigmoidal logistic regression curve. There were no significant predictions of PCA Patient-rated Mood and Behaviour (component 1), CBI-R or NPI psychosis indices on the ECAS status of psychosis.

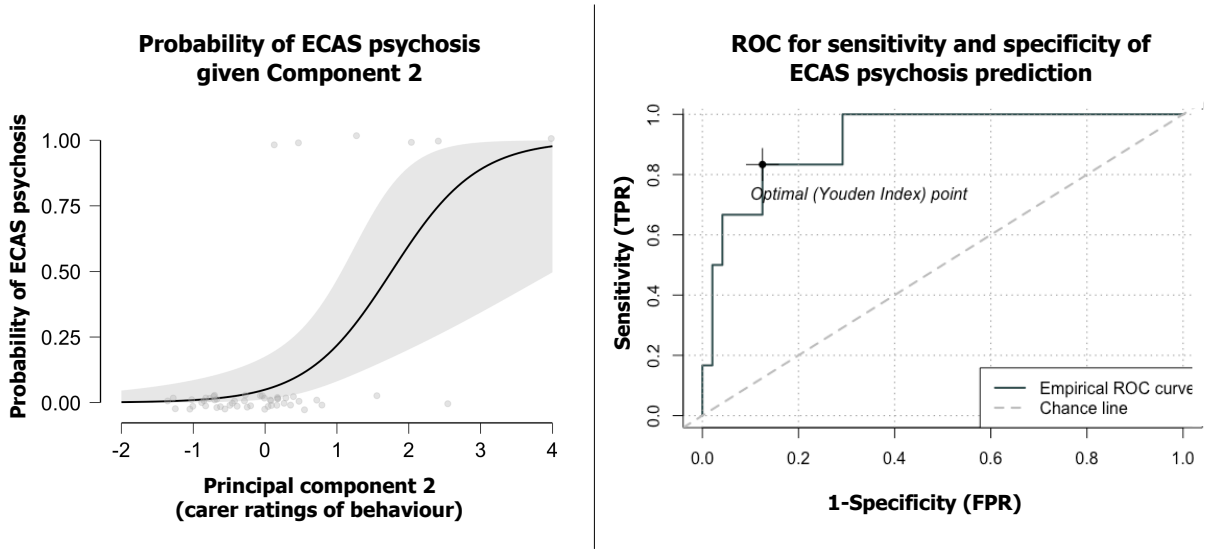

Figure 18: Fitted sigmoidal logistic regression curve to the prediction of continuous variable principal component 2 (carers rating of patient's behaviour) on the likelihood of being categorised as showing psychosis symptoms or not (binary variable). TPR=True Positive Rate. FPR=False Positive Rate.

3.4 Discussion

The sample characteristic data described above first and foremost provide necessary insight into the physical, demographic, psychiatric, behavioural and cognitive profile of the current MND cohort, which is important in two ways: first the description confirms patients in the current study typically resembled other similar studies in MND, and second the current MND group were comparable in disease characteristics and demographics across all tiers of the current study.

These are important and necessary features of a study that combines multi-factorial investigations in which vulnerable patients vary in their ability to participate. Second, the data provide insight into the prevalence of overt psychosis and subclinical psychosis symptoms in the current MND sample. The heterogeneity of these symptoms is evident and indicates symptoms suggestive of psychosis in MND do not have to be overt to warrant attention. Third, the psychosis insights extend into broader neuropsychiatric symptoms, including mood and components of apathy, which load onto components that not only indicate consistent measurement of behavioural symptoms but that distinguish patient ratings of their own behaviour from those based on carer observations. The fourth and final insight gained from this data is that the carer observations of broader neuropsychiatric patient behaviour predicted patient psychosis status.

3.4.1 A representative MND sample

In this study, the data provide confirmatory disease, demographic and cognitive descriptions that support the current MND cohort is mostly typical of MND cohorts studied in similar research.

Site of onset is one defining disease characteristic at clinical presentation. Consistent with the general population of MND patients who develop signs and symptoms that indicate the predominant limb onset presentation (Kiernan et al., 2011) and similar research studies (Consonni et al., 2018; Hsieh et al., 2016; Lillo et al., 2011; Tan et al., 2014), 63% of my overarching MND cohort presented with limb onset. Across the main testing tiers, this increased to between 70-86%, reflecting the general ability and resilience of limb onset patients compared to bulbar onset. A decreasing number of bulbar onset patients were captured due to being more vulnerable as a result of increased fatigue when speaking and risk of choking and/or aspiration when lying flat on their back, which was necessary for the MRI scan. In the current MND cohort, average disease duration, calculated from first symptom described by the patient, was around four years in the cognitive screened group and in the main testing groups remained just below two years, which is consistent with other similar studies (Leslie et al., 2015; Mioshi et al., 2013). On the ALS-FRS-R scale, the mean functional severity scores for the current MND cohort were similar to those in other similar studies (Silva et al., 2016; Hsieh et al., 2016; Mioshi et al., 2013) with mean scores falling in the mid to high thirties (total score 48 indicating intact function). This score is entirely weighted on the physical obstructions of MND of bulbar, fine and gross motor function (for example, swallowing, handling utensils, and climbing stairs). Included in the current study was the FTD-FRS measure, which is complimentary in that it weighs more on behavioural disturbances and the organisation of daily activities, such as impulsivity, lacking interest, organising finances, and independent shopping. Studies comparing across clinical groups that span the FTD-MND continuum will commonly include the FTD-FRS as the primary measure of functional severity in FTD syndromes (For example: De Silva et al., 2016; Devenney et al., 2017). The current MND cohort scored in the mild to moderate range of functional severity based on the FTD-FRS, which is consistent across similar studies that also include this measure (De Silva et al., 2016).

Demographically, the mean age of the current MND cohort ranged from 63 – 66 years and was a few years older than the general MND population peak age at onset (58-63 years (Kiernan et al., 2011)) and other similar studies where the mean ages commonly fell in the fifth decade (Hsieh et al., 2016; Leslie et al., 2015; Mioshi et al., 2013; Tan et al., 2014). Many previous studies commonly include comparison diagnoses of FTD-MND, those with familial disease or genetic phenotypes where the mean age is often younger in the late fourth to early fifth decade. Nevertheless, the mean age range in the current MND sample was consistent with large MND population studies (Chiò et al., 2019; Phukan et al., 2012) and few similar studies (De Silva et al., 2016; Machts et al., 2015) and importantly, was accurately represented to that of the overarching clinic population (~66 years) from which the main testing sample was recruited. MND has a slight male predominance (Al-Chalabi & Hardiman, 2013) and the current MND clinic population reflected this. The sex imbalance occurred across all tiers until Tier 3 where the sex difference within the MND group converged to minimise imaging confounds involving brain size and sex. The slight imbalance in sex is frequently seen in other similar studies (Crockford et al., 2018; Lillo et al., 2011; Machts et al., 2015; Tan et al., 2014). Consistent with other similar studies (De Silva et al., 2016; Machts et al., 2015; Mioshi et al., 2013), mean years of education were generally in the same range of 11 – 13 years in the current study.

The current MND sample was analysed as a continuous group rather than sub-dividing according to the consensus criteria into MND, MND-cognitive impairment or MND-behavioural impairment categories (commonly referred to as ALSci and ALSbi, respectively (Strong et al., 2017) in the literature). Reasons pertaining to significantly reduced group numbers if the sample were to be split and the limitations of employing the consensus criteria when patients commonly experience *both* cognitive and behavioural symptoms but insufficiently for the MND-FTD diagnosis. Importantly, stratifying patients would result in a loss of the variation in the experience of psychosis symptoms across the group.

Cognitively, approximately half (48%) of the Tier 1 sample scored below the cut-off on the ECAS for intact global cognitive function, consistent with well-recognised evidence indicating cognitive impairment occurs in up to half of MND patients (Bock et al., 2016; Phukan et al., 2012; Ringholz et al., 2005). Just under half of the current MND cohort showed deficits in the MND-specific sub-domains of executive, language and verbal fluency, consistent with MND cohorts also assessed with the ECAS (Abrahams et al., 2014) and studies using a broad range of neuropsychological assessments (Massman et al., 1996; Phukan et al., 2012; Ringholz et al., 2005). Within the executive sub-domain, impulsivity in MND was in line with controls and reported by carers as present in only *N*=3 people with MND on the ECAS and minimally rated as frequent on the NPI. The most prevalent deficit occurred in language function (35%) consistent with findings that suggest language impairment is more prevalent than executive impairment (Phukan et al., 2012b; Taylor et al., 2013), and unrelated to bulbar features in some MND patients. The majority of the literature report verbal fluency as the predominant area of cognitive impairment in MND (Abrahams et al., 2000; Abrahams et al., 2005; Crockford et al., 2018; Massman et al., 1996) and consider it a sensitive marker to general cognitive impairment, and specifically executive impairment. Executive deficits are part of the ALS-FTD revised diagnostic criteria (Strong et al., 2017), which recognises executive (and behavioural and perceptual) impairments are manifestations of the spectrum of deficits resulting from frontotemporal dysfunction. The current results pertain to cross-sectional data, however it is worth noting that although patients may initially have lower performance than controls, cognitive deficits tend to remain stable over time (Benbrika et al., 2019). Even in patients who have stable cognition, behavioural impairments may still appear (Bock et al., 2017). Furthermore, the initial presence of even mild cognitive or behavioural impairment is considered an increased risk factor for later developing concomitant dementia (FTD) (Elamin et al., 2013).

These cognitive deficits have been associated with changes in extra-motor regions that are involved in higher order cognitive processes and behavioural control, for example executive and verbal fluency have been related to the dorsolateral, orbitofrontal and medial prefrontal dysfunction (Schoenberg & Scott, 2011). Since verbal fluency and executive deficits tend to occur early in the disease process (Beeldman et al., 2016; Phukan et al., 2012) the association with structural and functional changes in the prefrontal cortex suggest the involvement of early pathological processes in this area. Certainly, in genetic forms of FTD and MND, pathological changes have been documented 5-10 years before symptom onset (Rohrer et al., 2015). In contrast, memory dysfunction is less commonly reported thought due to the exclusion of patients with end-stage MND from research studies (Crockford et al., 2018). However, it is a known cognitive deficit in MND, unrelated to dementia, (Phukan et al., 2012) and evident in 29% of the current MND cohort who scored below the cut-off for intact (verbal) memory function, a rate higher than that reported in other studies (Abrahams et al., 2014; Consonni et al., 2016; Crockford et al., 2018; McHutchison et al., 2019; Phukan et al., 2012). It may be that these studies are excluding end-stage patients, for example due to respiratory insufficiency, and hence are not capturing memory impairment that almost certainly arises with disease progression. Alternatively, the range of memory tests applied in research, or lack thereof, may not be capturing all the components of memory, such as encoding, retrieval and recognition, as well as visual versus verbal domain. Memory deficits in MND rarely occur in isolation. Encoding of material hinges on the prerequisite skill of attention, however, on average the current MND cohort demonstrated intact attentional ability as measured by the ACE-III. Executive processes subserved by frontal-striatal circuitry, particularly the medial and dorsal frontal connections, in the brain are thought to also contribute to encoding and retrieval (Schoenberg & Scott, 2011). Up to a third of the MND cohort (31%) show impairment in executive function, thus it is reasonable to assume the involvement of the frontal-striatal system in its interplay in executive dysfunction and subsequent higher rate of memory dysfunction in this proportion of the MND cohort.

Cognitive impairment is not a universal feature of MND and its manifestations are highly heterogeneous. The current MND sample did not significantly diverge in the cognitive deficits or behavioural involvement from other similar studies in MND.

In addition to the above disease, demographic and cognitive consistencies between the current MND group and similar groups studied in the wider research community, important comparisons were made within the MND sample and between the specific tiers in which they participated in the current study. First, those who completed in-depth neuropsychology versus those who did not and second, those who completed the MRI scan and those who did not. There were no differences among the MND participants in each of these stages on the fundamental demographic metrics of age and sex, ensuring group consistency spanning across all tiers of the current study. This importantly confirms representation on these basic demographic metrics of the main testing groups (Tiers 1-3) to the overall clinic population (Tier 0) from which the cognitive screened and main testing group were recruited. Progressing into the following chapters of this thesis, this is an important and necessary feature of a study that combines multi-factorial investigations in which vulnerable patients vary in their ability to participate.

3.4.2 Psychosis prevalence in MND

Most interesting in the descriptive data, are the insights gained from the behavioural measures. The behavioural data informs the prevalence of overt psychosis and subclinical psychosis symptoms in the current MND cohort, such that these symptoms do not have to be common to warrant attention. Approximately 10% of the MND sample who were screened with the ECAS (*N*=111) were described by someone who knows them well as having overt psychosis symptoms, based on the three questions referring to visual/auditory hallucinations, bizarre beliefs or behaviours and persecutory ideation. This falls short of the

hypothesis that up to one third (*N*~37) would show overt psychosis symptoms. Compared to the studies which have documented psychosis in MND, this rate is higher than rates reported in Lillo et al., (2011) (5%), Crockford et al., (2018) (2.9%), and Abrahams et al., (2014) and McHutchison et al., (2019) (both *N*=1). It was also predicted that milder psychosis symptoms would be observed in a much larger proportion of our MND participants. I observed features suggestive of psychosis in a larger proportion but not substantially larger (16%). Psychosis more commonly occurs at the bvFTD end of the FTD-MND continuum, with increasing prevalence associated with C9*orf*72 gene expansion, found to be present in a third up to 60% (Devenney et al., 2017; Snowden et al., 2013). Thus, the studies that report on psychosis symptoms almost always involve groups where psychosis is more prominent, that is in diagnoses of FTD-MND, bvFTD and/or are stratified by C9*orf*72 gene expansion status. The overriding research into the phenotypic profile of C9*orf*72 is largely warranted by the importance in recognising and understanding this profile for diagnostic accuracy. However, inclusion of sporadic MND participants without C9*orf*72 in these studies is often minimal and when psychosis symptoms are reported, it is often unclear which group they belong to.

The current rate of overt psychosis (~10%) was consistent with some studies that included FTD-MND and/or C9*orf*72 patients (Sha et al., 2012), whereas other FTD-MND cohorts showed rates unsurprisingly above the current MND cohort ranging from 14 – 38% (Chiò et al., 2012; Devenney et al., 2017a, 2019; Saxon et al., 2017; Snowden et al., 2012; Takada & Sha, 2012), likely due to the predominant overlapping diagnosis of FTD. Conversely, some studies report a far lower incidence of less than 5% (Mahoney et al., 2012; Simón-Sánchez et al., 2012), or even in one study including FTD-MND and MND groups where individuals initially presented with psychosis symptoms and misdiagnosed as Alzheimer's disease with dementia or schizophrenia, these few would subsequently be diagnosed as bvFTD (Hsiung et al., 2012). Yet this study, and few others (Grossman et al., 2007; Lillo et al., 2011; Mioshi

et al., 2014) demonstrate in the absence of fulfilling diagnostic criteria for concomitant FTD, the frequency of neuropsychiatric symptoms, as identified by someone who knows the patient well, can be quite prominent in sporadic MND alone.

The dichotomous score from the ECAS screen may have detected overt psychosis symptoms in less than one third of the current MND patients, however results from broader psychiatric and behavioural scales (CBI-R, NPI and BPRS) clearly demonstrated large variation in psychosis and neuropsychiatric symptoms (Figures 11 and 13). These results reflect the current diagnostic classification of MND with FTD (Strong et al., 2017), which thoroughly recognises the behavioural and cognitive changes that are present in a substantial proportion of MND patients and recognises that MND patients more commonly experience psychosis symptoms at subclinical levels, as evidenced in the current study. The current study did not seek to diagnose individuals in the MND group with a comorbid psychosis condition, rather to capture the milder symptoms suggestive of psychosis present in some.

3.4.3 Apathy and mood

Extending to additional neuropsychiatric involvement, apathy was unsurprisingly the main behavioural symptom to emerge, given it is an established pervasive behavioural feature of MND (Grossman et al., 2007; Lillo et al., 2011; Mioshi et al., 2014; Witgert et al., 2010). Specifically, the current MND cohort demonstrated the dimension of initiation apathy to be most increased, similar to a previous MND group on which the same multidimensional apathy scale was applied (Radakovic et al., 2017). Apathy is also a core symptom of depression and FTD, and in the context of being given a life-limiting diagnosis, it is reasonable to assume low mood and anxiety to have a prominent presence in MND patients. This is certainly expected soon after diagnosis (Benbrika et al., 2019; Rabkin et al., 2005)

and their co-occurrence is noted in the literature (Caga et al., 2018; Radakovic et al., 2016). The co-occurrence was similarly observed in the current MND cohort, albeit at opposing levels of involvement with apathy. The current MND group showed a significantly higher involvement of depression and anxiety compared to controls, however on average they scored within or on the threshold of normal limits on both scales (below 7 on the HADS and on the threshold of 13 on the BDI). Consistent with previous research of low depression and anxiety rates alongside significant involvement of apathy, the current findings support the evidence of a dissociation between depression and apathy (Levy et al., 1998; Lillo et al., 2011; Rabkin et al., 2016; Radakovic et al., 2017).

3.4.4 Principal components

The data revealed that behavioural, mood and apathy measures were positively correlated in MND. This was shown through the PCA, where measures loaded onto the same components (Table 9). The two components that emerged succinctly distinguished two perspectives on the neuropsychiatric aspects of MND: patients' own ratings of behaviour from carers' and observer/carers' observations of patient behaviours. The components reflected clear abnormalities in patient behaviour but the two perspectives (patient versus carer) did not correlate. Patient-rated Mood and Behaviour (component 1) reflected increased patient rated anxiety, depression (HADS and BDI) and apathy (DAS), while Carer-rated Behaviour (component 2) reflected clinician and carer loadings from the NPI, CBI-R and Cam-QuAIT. The difference in these two component loadings is likely due to the difference in awareness and observations of certain behavioural symptoms between the patient, their carer and researcher and this is succinctly reflected in the two components.

The separation may additionally reflect to some degree patients' lack of insight into behavioural changes. Impaired insight is a core diagnostic criterion for establishing a

diagnosis of FTD-MND (Strong et al., 2017), however in MND alone, the little research into insight has found that MND patients without concomitant FTD have normal insight (Woolley et al., 2010), although even in the absence of a concomitant FTD diagnosis, MND patients can still present with mild behavioural changes that might reflect a psychological response to their condition. As expected, component 2 (carer's perspective of patient behaviour) correctly predicted patients' psychosis status, indicating consistency in carers' appraisals of behaviours and accuracy in their ability to identify odd psychosis-like behaviour.

Carer-rated Behaviour was mildly and negatively correlated with global cognition and specifically MND-specific cognitive performance (executive, verbal fluency and language deficits) (Table 10). This supports a relationship emphasising the interplay of cognition and neuropsychiatric behaviour on performance, such that significant involvement of abnormal behaviour, mood, and apathy can further compound cognitive performance. Carer-rated Behaviour was also associated with disease severity. Conversely, patients' perspective of their own behaviour was not associated with their cognitive performance or disease severity, further implying patients' difference in opinion on their own neuropsychiatric behaviour.

Although this chapter did not directly measure the involvement of neural circuitry, the negative correlation between carer perspective of patient behaviour and executive cognition suggests a common network of structural and functional disruption in the brain. Known pathways affected in constituents of executive function include the prefrontal cortex and its frontal-striatal network involving the dorsolateral and medial-frontal cortices, specifically the inferior frontal gyrus with the caudate and nucleus accumbens are similarly affected in the regulation of behaviour (Barbagallo et al., 2014; Christidi et al., 2018; Goldstein & Abrahams, 2013; Machts et al., 2015; Schoenberg & Scott, 2011). Neural correlates of cognition and behaviour processes specifically underlying the emergence of psychosis will be explored in chapters 5 and 6 of the thesis.

The current study sought to obtain focused information about the prevalence of psychosis symptoms and extended aspects of neuropsychiatric behaviour in the current MND sample, whilst bearing in mind the tolerance and frailty of people living with MND. The conclusions drawn from this necessarily selective neuropsychological test battery can only relate to the patient participants studied and the domains of cognition and psychiatric behaviour assessed. The test battery included representative assessment types (questionnaires, objective and observer elements) and assessments that are widely used in the MND and psychosis literature to capture varying degrees of psychosis symptoms. However, questionnaires are limited in their ability to determine the underlying *cause* of behavioural evolution and change. For example, psychosis-related questions in the CBI-R, such as *"Sees things that are not really there",* or *"Has odd or bizarre ideas that cannot be true"* attempt to assess changes in perceptual experience yet these experiences may be confounded by compromised executive function, or a learned coping strategy in an attempt to understand physical changes associated with their condition. Key cognitive processes implicated in the emergence of psychosis symptoms will be explored in more detail in chapter 4. Here, it is suggested that the extracted components reflecting neuropsychiatric behaviour more accurately capture behavioural change, which is distinct from overt psychosis symptoms rather than applying multiple single questionnaires in isolation.

3.4.5 Limitations

This study has limitations. First, as is common in primary data collection, there can be recruitment bias and in the current study the patients are heterogeneous in disease severity and duration as recruitment occurred at different progressive stages of their condition. There is a known time relationship with psychosis symptoms and typical motor symptom onset (Mioshi et al., 2014; Turner et al., 2016), thus investigating patients at their earliest

point in diagnosis bodes ideal for studying these symptoms. Recruitment efforts were focused on capturing patients at their first clinic visit, however most patients are delayed in receiving a diagnosis from first symptom onset (Al-Chalabi & Hardiman, 2013), impeding investigation of early disease processes. Varying progressive stages meant that through the tiers, patients who were more physically able to complete all investigations, especially a lengthy MRI scan, predominated, thus likely not representative of many bulbar patients or cognitively impaired patients (Elamin et al., 2013). However, this is unavoidable due to the swallowing/breathing difficulties bulbar patients experience in supine position.

Second, replication in a larger cohort is necessary to capture a larger number of patients with overt and subclinical psychosis symptoms to then stratify for sub-group analyses and maintain the statistical power. Valuable insights could be revealed from stratifying groups not only based on their diagnoses but also based on their psychosis symptoms, such as delusions and hallucinations separately. The small numbers of MND participants who showed psychosis symptoms in the current study restricted further stratification and was therefore outside the scope of this study.

Third, not all assessment tools were selected based on disease-specific development. The ECAS cognitive screen, the DAS apathy scale and the CBI-R were designed or adjusted to account for the physical limitations that many MND patients experience. Similarly, the NPI does not include any items affected by a physical disability. Items from other questionnaires, such as the HADS *"I feel I have slowed down"* are simply not appropriate for individuals living with a movement disorder and at times fail to accurately capture the specific behaviours it was developed to. There is only one mood scale to my knowledge developed for individuals with MND, the 12-item ALS Depression Inventory (ADI-12 (Hammer et al., 2008) that eliminates the emphasis on any physical limitations of the condition that could be misinterpreted as an underlying depression process. However, this scale does not include an anxiety sub-scale and has been recommended for use as a screen in primary care, rather

than a comprehensive assessment of depression (and anxiety) as the combination of the BDI and HADS provided in the current study.

The use of the two extracted dimensions across the psychiatric behaviour, mood and apathy scales more accurately represents the essence of these behavioural changes than the use of single questionnaires in isolation. Applying these components also provides a more principled means to accommodate phenotypic variation in the current MND cohort without bias since the group is being treated as one group rather than stratifying by cognitive and/or behavioural involvement. The standard screening measure used widely in cognitive neurology, the ACE-III (or Revised version) was included in the test battery for comparative purposes, however it is well acknowledged here that this test is not entirely suitable in MND patients. It does not take into account the language impairment that occurs in MND, which commonly exaggerates performance decrements more than expected in the absence of physical disability. The widely used cognitive screening measure, included in this thesis, the ECAS, was designed to allow for verbal and motor disability in MND, for example during verbal fluency providing the option of speaking or writing words (with a time adjustment included). Such specific adaptions to traditional cognitive screening assessments more accurately captures ability rather than inadvertently magnifying disability. Therefore, the subsequent analyses in this thesis, only include the ECAS as the representative measure of global cognition.

Detecting subtle subthreshold psychosis symptoms in a cohort where this symptom is not prominent proved challenging. Screening measures identify obvious symptoms, however even tools used in early psychosis or at-risk psychosis groups (such as the BPRS and CAARMS) whose symptoms theoretically are not unlike the mild symptoms experienced by some MND and FTD-MND patients, are inappropriate. The CAARMS was withdrawn after the first 20 MND participants as the final outcome was to categorize participants as at-risk or not at-risk, of which one of the main criteria was a positive family history of a psychiatric

condition, in addition to experiencing various symptoms for a specified time period. These criteria are simply not transferable to such a neurodegenerative sample. For example, previous family history of a psychosis condition is not solely considered to be a primary risk factor to developing psychosis, rather additional emphasis is placed on family history of FTD or MND and C9*orf*72 gene expansion status. I argue that specific aberrant cognitive processes will indicate stronger vulnerability in MND for the development of psychosis, thus manipulating the current MND sample into an "at-risk" tick box based on the utility of a psychiatric tool suited to psychiatric populations and conditions was in hindsight deemed counter intuitive. It was initially anticipated that including the tool would provide broader descriptions of psychosis symptoms, however the language used throughout was focused on overt symptoms reflecting typical psychosis delusion and perceptual experience.

3.4.6 Change in practice

The cognitive and behavioural status of patients is commonly unknown in a clinic setting and minimally considered in clinical management, often due to a lack of personnel in clinic to conduct the existing assessments, especially in a busy multi-disciplinary clinic, or restricted resources for extended clinical neuropsychology. In many multidisciplinary MND clinics and care centres, most often physical symptoms are considered a priority (to the patient/families and clinicians alike), given these are usually the overriding and presenting symptoms in MND. Since the commencement of this project, cognitive screening is now well established in the Cambridge MND Care Centre. It is an integral part of the patients' clinical care and an essential step in managing cognitive and behavioural symptoms.

3.4.7 Future directions

This study was focused at the MND end of the FTD-MND continuum largely due to the crater in the literature investigating the prevalence and cognitive and neural correlates of psychosis symptoms in sporadic MND. This is one of few studies that have reported on prevalence of psychosis symptoms in sporadic MND. However, it is plausible to argue that an exploration of psychosis in a comprehensive inclusion of participants representing the full span of the FTD-MND continuum would be highly valuable. It is surprising the lack of formal investigations with large representative groups across the FTD-MND continuum, given the significant overlap of FTD-like symptoms in MND. This would allow for comparison of type, frequency and severity of psychosis symptoms as disease evolution changes along the continuum as well as vital comparisons at the extreme ends of the continuum (bvFTD and pure MND). Given the limited number of MND patients who experience overt psychosis symptoms, it would have been detrimental to the sample size and subsequent statistical power to only include patients showing these symptoms on initial screening in clinic.

3.5 Conclusion

In conclusion, in the absence of fulfilling diagnostic criteria for concomitant FTD, the frequency of psychosis symptoms is prominent in 10% of the current MND cohort. The main testing group is representative of the overarching clinic population by demographic and disease characteristics, and the main testing group is not unlike similar groups studied in similar previous research with regards to cognition and psychiatric behaviour changes. These are important and necessary features of a study that combines multi-factorial investigations in which vulnerable patients vary in their ability to participate. The reduction of the multiple psychiatric and behavioural questionnaire scores using individual loadings from a PCA is argued to more accurately represent neuropsychiatric change in the current MND

group. The measures are separate from the indices that represent psychosis symptoms and will be used in the following chapters in regression analyses with experimental cognitive outcome measures and structural MRI parameters.

Chapter 4 Tier 2: experimental neuropsychology

This chapter examines the cognitive basis of pre-psychosis cognitive features in this cohort of MND participants compared to healthy controls, drawing on insights from collaborations in Department of Psychiatry. The findings from unique neurocognitive paradigms that have previously detected and informed the emergence of psychosis symptoms in early primary psychosis conditions will be presented, as applied for the first time in an MND sample.

I predicted that abnormal cognitive processing in key decision-making, attentional control and perceptual inference that predispose to psychosis will be affected in this MND cohort compared to healthy controls, in the context of subthreshold psychosis symptomology.

4.1 Introduction

To identify and characterise psychosis symptoms in MND and across the FTD-MND continuum, historical studies have predominantly relied on classical personality inventories and later, now widely used, gold standard neuropsychiatric inventories that encompass broader psychiatric behaviours (Cummings et al., 1994; Wear et al., 2008). Both retrospective and prospective studies alike have employed structured proformas, which address individual behaviour systematically, while other assessments of psychosis in MND have employed psychiatrists (e.g. Howland, 1990), who traditionally characterise psychosis symptoms with conventional psychiatric diagnostic tools and labels. These measures may be inappropriately applied to a neurodegenerative sample, such as MND, although they have been used in neurodegenerative conditions with overt psychosis symptoms. Such measures often aim to achieve a categorical diagnosis of psychosis, rather than aiming to

detect subtler signs of complex, abnormal behaviours or cognitive processes that may indicate risk for the development of psychosis or worsening of current psychiatric symptoms. The utility of conventional inventories in a busy multidisciplinary clinic setting is valid for identification of psychosis symptoms but insufficient for detailed examination and interrogation of underlying processes that may put patients at-risk for psychosis. It is important to understand the wider at-risk population if neuroprotective interventions are to be usefully applied, and to support the management of psychiatric well-being in MND.

Under the psychosis continuum framework (Van Os et al., 2009) many at-risk and psychosis-prone groups who do not have a primary psychosis disorder, can be investigated on the same symptoms and underlying cognitive deficits that are observed in patients with primary psychosis disorders, such as schizophrenia. The study of psychosis-prone groups allows for the measurement of manifestations of the subclinical psychosis phenotype and the dimensions of subclinical psychosis symptoms, including vulnerable cognitive processes. I consider, the subtle subclinical symptoms experienced by some patients with MND to be informed by those experienced by early psychosis phenotypes. In these groups the prevalence of clinical disorder is low, but the prevalence of subclinical symptoms can conceivably be much higher. This formed my rationale in seeking tools that have previously been applied in early psychosis groups to identify underlying cognitive mechanisms by which psychosis phenomena emerge. An advantage of employing a cognitive marker is that it attempts to reflect behaviours and processes that have been implicated in the emergence of psychosis, and advances insight into other processes that have not previously been included when investigating psychosis in MND and FTD-MND. The next sections will detail three cognitive mechanisms by which psychosis symptoms have emerged and are maintained in early psychosis groups.

4.1.1 Cognitive mechanisms and experimental paradigms

Previous investigations of the emergence of psychosis symptoms, such as visual hallucinations and delusions, have identified aberrant cognitive processes and psychological constructs as underlying cognitive mechanisms to the emergence of such symptoms (Dudley et al., 2016; Garety et al., 2001; Griffin & Fletcher, 2017; Hemsley & Garety, 1986). The three novel neurocognitive paradigms applied in the current thesis have been applied in treatment-naïve, young adult psychosis groups who represent at-risk and early psychosis phenotypes. These paradigms have informed how specific cognitive alterations may underly delusion formation and perceptual abnormalities and importantly, may represent a state of vulnerability prior to the emergence and persistence of psychosis symptoms and clinical disorder. The three cognitive processes outlined in the next three sections are: 1. decision-making ("jumping to conclusions" and positive-negative feedback processing), 2. attentional control (attentional switching and associative learning) and 3. perceptual inference (top-down bottom-up information processing).

4.1.1.1 Decision-making processes

Decision-making is impaired in primary psychosis conditions due to suboptimal performance on one or many decision-making processes (Ermakova et al., 2019; Falcone et al., 2015; Hutton et al., 2002; Larquet et al., 2010; Woodrow et al., 2018). A consistent psychological finding in patients with schizophrenia, especially those with delusions, is a tendency to gather less information before making a decision. Known as the "jumping to conclusions" (JTC) bias, this data gathering summary metric directly informs Garety and Freeman's (1999:131) conclusion that people with psychosis, and specifically delusions, are more willing to accept a hypothesis on the basis of less evidence and further, more readily abandon existing hypotheses and form new ones on the basis of little evidence. Using a

version of the classic probabilistic reasoning “beads task” (Huq et al., 1988), Ermakova et al. (2019) demonstrated a JTC decision-making style in connection with sampling significantly less information and increased positive symptom scores in their early psychosis group compared to controls. Their results were thoroughly consistent with a wider body of research suggesting that a reduced amount of evidence gathered when formulating a decision may be most strongly associated with presence of delusions (Dudley et al., 2016; Fine et al., 2007; Langdon et al., 2014). There is preliminary evidence that the JTC bias is demonstrated in subthreshold psychosis groups such as those who score highly for delusion ideation on psychiatric inventories (Warman et al., 2007) and established evidence in those considered at-risk (Broome et al., 2007; Ormrod et al., 2012) and in patients with chronic schizophrenia (Garety & Freeman, 1999). The presence of the JTC bias across all stages of psychosis-proneness and clinical psychosis illness indicates that the JTC bias may be related to a general predisposition towards delusions and indeed play a causal role in the formation of delusions in some patients.

The Ermakova et al. (2019) version of the beads task used in the current thesis incorporates positive and negative feedback learning features: points gain (positive) and loss (negative) for correct and incorrect decisions, and eventually trial-by-trial cost (negative) feedback for sampling each item of information. Therefore, the task requires an ability to learn action-outcome information, evaluate performance based on feedback and adjust behaviour accordingly. The integrity of such processes may mediate the JTC decision-making style. The ability to accurately monitor one’s own performance and integrate internal with external performance feedback are critical aspects of cognition, as positive-negative processing and learning guides adaptive decision-making (Botvinick et al., 2004; Holroyd & Coles, 2002; O’Doherty et al., 2017). Impulsivity has been reported in patients with MND (Lillo, Mioshi, & Hodges, 2012; Woolley et al., 2018) and may impact on task performance. However, it is important to differentiate motor impulsivity from cognitive impulsivity, the latter which allows

for false inferences and judgements, which can underlie psychosis. There is no timed component in this task, which alleviates the pressure to make a hasty motor response.

General decision-making impairments have been identified in patients with schizophrenia (Woodrow et al., 2018), with specific behavioural impairments in performance monitoring (Farreny et al., 2016; Perez et al., 2012; Turken et al., 2003), however results are mixed when investigating the specific motivational and affect driven constituents of decision-making in early psychosis. Studies investigating positive and negative feedback processing at various stages of psychosis are mixed. In the early stage of psychosis, some have shown that both positive and negative feedback sensitivity are diminished (Martin et al., 2018), with positive feedback insensitivity more apparent with disease progression (Chang et al., 2016; Martin et al., 2018; Strauss et al., 2014). This is consistent with the widely replicated finding of reward insensitivity in schizophrenia (see review: Strauss et al., 2014). Simultaneously, previous research has demonstrated negative feedback insensitivity in schizophrenia patients (Alain et al., 2002; Bates et al., 2002; Farreny et al., 2016).

In MND, previous research in decision-making has focused on decisional capacity with conclusions about decision-making cognitive processes drawn indirectly from evidence of executive impairment (Witgert et al., 2010), with very few having formal capacity assessments. Few studies have directly investigated cognitive processes underlying decision-making in MND, therefore results are limited yet superficially suggest altered decision-making ability (Lillo et al., 2012; Meier et al., 2010), even in MND patients without cognitive impairment (Meier et al., 2010). Additional measurement of behavioural adjustment from positive and negative feedback in the context of attentional control is demonstrated on related associative learning tasks described next.

4.1.1.2 Attentional control

One of the most common neuropsychological findings in the psychosis literature is impairment in attentional set-shifting, or cognitive flexibility (Elliott et al., 1995). Applications of the local Cambridge Cognition CANTAB modern version of a classic attentional control task (the Wisconsin Card Sorting Test (Grant & Berg, 1948)) have observed abnormal cognitive flexibility in established schizophrenia (Kim et al., 2014; McKirdy et al., 2009; Pantelis et al., 2009; Waltz & Gold, 2007) and first episode psychosis (Leeson et al., 2009; Murray et al., 2008; Pantelis et al., 2009). Importantly, this deficit has been noted in some early psychosis patients to present near the time of initial presentation to psychiatric services (Joyce et al., 2002; Murray et al., 2008) and is a strong predictor of a primary psychosis diagnosis as disease progresses (Peña et al., 2011).

The relationship between early psychosis symptoms and poor attentional control is supported by evidence of early global cognitive impairment before the onset of psychosis symptoms, which continues to decline (Sheffield et al., 2018), and in other psychosis disorders, such as bipolar, where minimal impairment in attentional control becomes apparent by the first psychosis episode (MacCabe et al., 2010). Research into prodromal psychosis states have specifically identified deficits in attentional control independent of impairments in other cognitive domains, compared to healthy controls, and that these appear before first positive symptoms (Frommann et al., 2011).

Together, this evidence suggests that early attentional control impairment in line with or prior to the emergence of overt psychosis symptoms may contribute to a vulnerable cognitive state and play a mechanistic role in the emergence of psychosis symptoms. Thus, the early involvement of executive function in MND, including impairments in tasks of attentional control, may contribute to a putative marker of psychosis vulnerability in MND. Previous research has documented executive dysfunction as an early and prominent cognitive feature

in many patients with MND (Abrahams et al., 2005), of which cognitive flexibility deficits have been reported (Beeldman et al., 2016; Evans et al., 2015; Goldstein & Abrahams, 2013; Lange et al., 2016), although not especially related to psychiatric behaviour. This will be ascertained in the current chapter.

4.1.1.3 Perceptual inference

The third cognitive mechanism by which psychosis may emerge involves imbalanced information processing that impacts perceptual integration and subsequent inference. In order to generate an unambiguous representation of the world, we integrate ambiguous incoming sensory information with prior knowledge of the environment (Fletcher & Frith, 2009). However, under the strain of a pathological state, an imbalance in this integration may represent a point of vulnerability and underly the emergence of incorrect perceptual inference. Under this cognitive model, it has been hypothesised that an imbalance between bottom-up sensory evidence and top-down prior knowledge is at the core of the altered state of mind observed in psychosis (Fletcher & Frith, 2009).

Performance on neurocognitive tasks in psychosis patients compared to controls is typically impaired. However, Teufel et al. (2015) observed a relative performance advantage in their psychosis-prone groups compared to controls. The mechanism proposed by Teufel and colleagues in the emergence of psychosis experience is an increased top-down processing in the construction of meaningful perceptions of ambiguous inputs. Using a locally designed visual perceptual processing task, Teufel et al. (2015) demonstrated a basic shift in visual information processing whereby an over-reliance on prior knowledge to discriminate between ambiguous images (incoming sensory information) was identified in their early psychosis and psychosis-prone groups compared to controls. Their studies show a core disturbance to the balance between bottom-up (sensory input) and top-down (prior

knowledge) processing is present in individuals with early psychosis and even associated with psychosis-proneness in the general population (Teufel et al., 2015). The latter group importantly were not experiencing psychosis symptoms or suffering from a primary psychosis diagnosis. Rather, those individuals scored highly on scales that identified a number of unusual perceptual experiences, an approach which reflects the description of psychosis symptoms in the absence of a formal psychosis disorder diagnosis in the current study.

The ambiguity of incoming sensory information requires the human visual system to integrate this information with prior knowledge of the environment to generate an unambiguous representation (Friston, 2010; Gilbert & Li, 2013). Under a Bayesian decision theory framework, a person's prior knowledge influences expectations that are fed back from higher to lower levels of information processing (top-down processing), subsequently shaping incoming sensory information. From Teufel et al.'s (2015) findings, it was argued that an over-reliance on prior knowledge may impose prior expectations on inputs to the extent that resulting perceptions may be generated with no direct sensory cause.

Alterations in perception integration and inference have not been investigated in MND nor across the FTD-MND continuum. However in a related neurodegenerative condition, dementia with Lewy-bodies (DLB), in which hallucinations are common, using a similar two-tone image visual perception task, recent research has corroborated an imbalance that favoured prior knowledge in DLB patients with hallucinations compared to those without (Zarkali et al., 2019). Importantly, Zarkali and colleagues observed an increased effect of prior knowledge with increased severity of visual hallucinations, suggesting that even a small effect relating to milder psychosis symptoms will nonetheless provide mechanistic insight into psychosis risk in MND.

Despite the clear co-occurrence of psychosis symptoms and cognitive and information processing impairment across the psychosis continuum, there is little evidence to suggest severity of psychosis experience is directly related with severity of these cognitive deficits (Bell et al., 1994; Heydebrand et al., 2004). However, based on the evidence above there should be no doubt that the specificity of a JTC bias in psychosis patients with delusions and poor performance monitoring in decision-making, the early presence of impaired attentional control, and aberrant perceptual information processing, confer risk or vulnerability to psychosis experience, independent of severity.

This chapter applied the local cognitive paradigms used by my collaborators to address the prediction that, given their milder experience of psychosis symptoms, similar alterations in these key cognitive processes relating to psychosis emergence will be observed in my MND group. Further, these alterations will be related to specific and broader neuropsychiatric behaviour in the MND group.

4.2 Methods

4.2.1 Tier 2 participants

Table 3 (chapter 3, page 113) outlines the demographic and disease characteristics for MND and healthy control participants included in Tier 2. MND participants demonstrated cognitive (Table 6) and functional (Table 3) impairment, as measured by the ECAS, ALS-FRS-R and FTD-FRS, compared to healthy controls. MND participants also showed higher endorsement of psychiatric behaviours, mood and apathy, as measured by the CBI-R, NPI, BPRS, BDI, HADS, Cam-QuAIT (all sub-scores except *Friends* component) and DAS (all sub-scores except *Emotional* component), compared to healthy controls. 12-20% of the MND participants were reported to have mild to moderate features suggestive of psychosis

as reported by someone who knows them well in combination with clinical interview by the researcher. The MND and control groups did not differ with regard to age or years of education but did on sex due to the higher number of male MND patients (Table 3). Of note, there were fewer MND participants (*N*=51) who completed the Perceptual Processing task due to fatigue and on occasion, faltering equipment.

4.2.2 Experimental tasks

The experimental tasks presented in this chapter are described in detail in chapter 2 (section 2.6.5 page 89).

4.2.3 Analyses

T-tests (Welch two-sample) and repeated-measures ANOVA (Type III and Satterthwaite's method, fit by restricted maximum likelihood (REML)) were applied to explore group differences on primary outcome measures for each task. Pearson's *r* correlation was applied to determine the relationship with task outcome measures and global cognition, disease severity, psychosis index scores, and PCA components 1 (Patient-rated Mood and Behaviour) and 2 (Carer-rated Behaviour) in the MND group. The Disinhibition item was selected from the ECAS as a scale estimate of impulsivity to correlated with JTC task performance. Logistic regression was performed to determine which outcome measures best predicted psychosis status as measured by the ECAS psychosis score from the carer report. This allowed for the binary variable from the ECAS to be suitably included in the analyses.

The outcome measures for the decision task and ID/ED were not normally distributed but showed homogeneity of variance. The outcome measure for the perceptual processing task was normally distributed and variance was homogenous. Since ANOVA is considered robust to deviations from normality and given the sample size of *N*=90 (*N*=81 for perceptual processing task), it was appropriately applied. Where the assumption of sphericity was violated, the Greenhouse-Geisser correction was applied.

4.3 Results

Mean, standard deviation and group difference for outcome scores for the Fish Decision Task are presented in Table 11. Summary composite and difference scores for the Fish Decision task are presented in Table 12. Percentages, means, standard deviations and group differences on outcome scores for the Perceptual Processing and ID/ED tasks are presented in Table 13.

Table 11: Mean, standard deviation and group differences on draws to decision and probability of being correct outcome scores for the Fish Decision Task.

Measure	MND (*N*=60)	Controls (*N*=30)	value	Group difference
Fish Decision Task				
Stage 1				
Draw to Decision	9.36 ±6.48	12.91 ±5.68	*t*=2.85	*p*=0.049
Probability of being correct (%)	67 ±11	75 ±11	*t*=3.32	*p*=0.016
Stage 2				
Draws to Decision	10.14 ±6.65	14.12 ±5.31	*t*=3.46	*p*=0.017
Probability of being correct (%)	69 ±12	78 ±9	*t*=4.09	*p*=0.001
Stage 3				
Draw to Decision	5.13 ±4.06	7.60 ±4.57	*t*=2.15	ns
Probability of being correct (%)	64 ±9	68 ±7	*t*=2.21	ns

Stage 4				
Draws to Decision	3.81 ±3.07	4.11 ±3.10	*t*=0.26	ns
Probability of being correct (%)	61 ±7	63 ±7	*t*=0.88	ns

p-values are FDR corrected.

Table 12: Mean, standard deviation, group differences and logistic regression on composite and difference draws to decision scores for the Fish Decision Task.

Measure	MND (*N*=60)	Controls (*N*=30)	value	Group difference	Logistic Regression ECAS psychosis status			
Fish Decision Task					**Odds Ratio**	***p*-value**	**Sensitivity (%)**	**Specificity (%)**
Summary Composite Scores								
Total Draws to Decision	7.11 ±4.57	9.53 ±3.86	*t*=2.61	*p*=0.012	-	-	-	-
First Half (stage 1 + 2)	19.50 ±13.03	26.58 ±10.51	*t*=3.15	*p*=0.004	0.83	*p*<0.001	0	100
Second Half (stage 3 + 4)	8.94 ±6.74	11.54 ±6.81	*t*=1.16	*p*=0.249	0.68	*p*<0.001	0	100
Interaction Composite (second half – first half)	-10.57 ±9.80	-15.04 ±8.67	*t*=-2.18	*p*=0.03	1.36	*p*<0.001	0	96
Summary Difference Scores								
Difference 1 (stage 2 draws – stage 1 draws)	0.78 ±1.63	1.25 ±2.95	*t*=0.82	*p*=0.415	0.38	*p*=0.004	33.3	74
Difference 2 (stage 4 draws – stage 3 draws)	-1.32 ±2.52	-3.10 ±3.35	*t*=-3.13	*p*=0.004	2.90	*p*=0.006	0	82
Interaction Difference (difference 2 – difference 1)	-2.10 ±3.32	-4.34 ±4.41	*t*=-2.66	*p*=0.009	2.65	*p*=0.001	33.3	82

p-values are FDR corrected.

Table 13: Percentages, means, standard deviations and group differences on outcome scores for the Perceptual Processing and the CANTAB ID/ED tasks.

	MND	Controls	value	Group difference
Perceptual Processing	**(*N*=51)**	**(*N*=30)**		
Before-After difference	1.27 ±0.75	1.34 ±0.61	*t*=0.48	ns
CANTAB Intra/Extra Dimensional Set Shift	**(*N*=60)**	**(*N*=30)**		
Successful task completion (%)	66.1	63.3	-	-
Stages completed (/9)	8.46 ±0.91	8.63 ±0.49	*t=0.99*	ns
Average total trials	10.75 ±2.97	10.22 ±2.59	-	-
Average total errors	2.65 ±1.81	2.30 ±1.54	*t*=-0.98	ns
Discrimination trials (stage 1-5)	8.65 ±2.74	8.84 ±3.22	-	-
Discrimination errors (stage 1-5)	1.51 ±1.34	1.49 ±1.46	*t*=0.10	ns
ID trials (stage 6)	7.48 ±4.16	6.57 ±0.73	-	-
ID errors (stage 6)	0.84 ±2.18	0.50 ±0.57	*t*=-0.05	ns
ED trials (stage 8)	25.86 ±17.07	24.90 ±17.84	-	-
ED errors (stage 8)	12.29 ±10.78	11.60 ±10.78	*t*=-1.53	ns
ED reversal trials (stage 9)	14.45 ±14.62	9.95 ±9.60	-	-
ED reversal errors (stage 9)	5.73 ±8.81	2.55 ±5.37	*t*=-1.73	ns

4.3.1 Fish Decision Task

4.3.1.1 Draws to decision

Overall, the MND group sampled less information than controls before making a decision (Table 10 *Total Draws to Decision*). Across the first two stages, MND and control participants performed differently (Table 11 and Figure 19a) on number of draws to decision (DTD), with MND participants choosing to sample significantly fewer items before making a

decision. As the cost of sampling information was introduced (stage 3) and increased (stage 4), the group differences became increasingly attenuated (p>0.05) (Table 11 and Figure 19a).

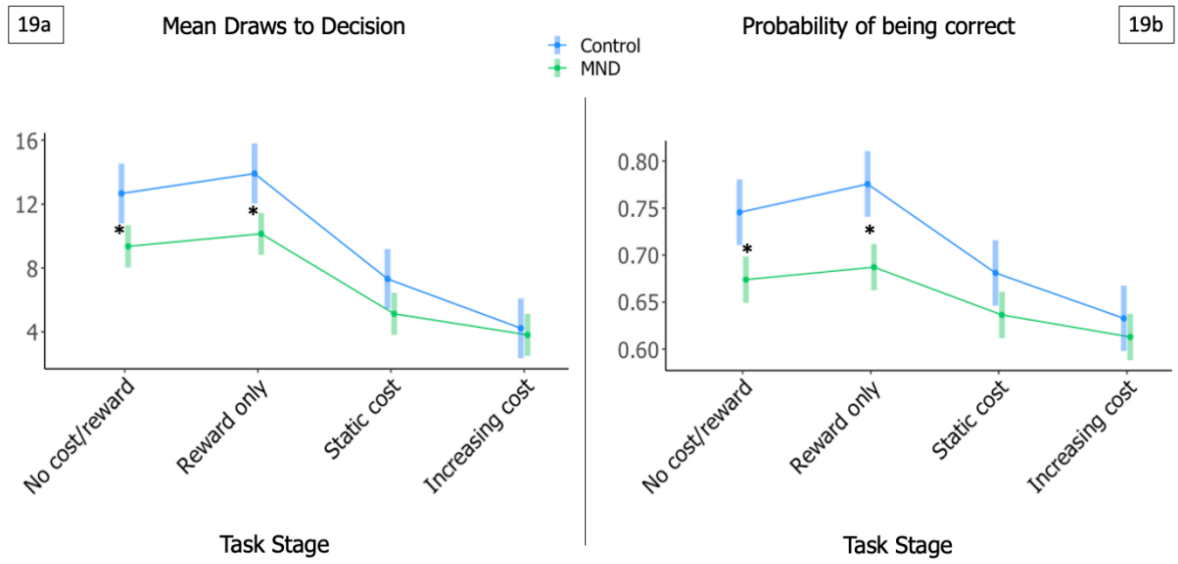

Figure 19: Mean draws to decision (19a) and mean probability of being correct (19b) for each stage of the Fish Decision Task. *denote significant difference between MND and Control groups.

Pearson correlation analyses explored the relationship between mean DTD from each stage with the psychosis index scores, the two PCA component scores, disease severity (ALS-FRS-R and FTD-FRS) and cognitive performance (ECAS total score), including correlation with the impulsivity item from the ECAS (disinhibition). Pearson's *r* and significance are presented in Table 14.

In the MND group, negative correlations were shown for Carer-rated Behaviour (component 2) and mean DTD in stage 1, stage 2 and stage 3. The CBI-R psychosis index negatively correlated with mean DTD in stage 2 and stage 3. No significant correlations were revealed

for Patient-rated Mood and Behaviour (component 1) or the NPI psychosis index scores with mean DTD across any of the task stages (p>0.05). No significant correlations were shown for disease severity (ALS-FRS-R or FTD-FRS) (p>0.05) or global cognitive performance (ECAS total) (p>0.05) with mean DTD in any of the task stages. In the control group, positive correlations were shown with global cognitive performance on the ECAS total score and mean DTD in stage 1 (r=0.47, p=0.010), stage 2 (r=0.43, p=0.020) and stage 3(r=0.39, p=0.038), with stage 4 (p>0.05). No significant correlations were revealed in the controls between the mean DTD in any stage with CBI-R or NPI psychosis index scores.

Table 14: Pearson's *r* correlations in the MND group between draws to decision in each stage of the Fish Decision Task and PCA components, psychosis index scores, disease severity and global cognition.

	DTD Stage 1	DTD Stage 2	DTD Stage 3	DTD Stage 4
Patient-rated Mood & Behaviour	-0.14	-0.15	-0.13	-0.07
Carer-rated Behaviour	-0.30*	-0.35*	-0.31*	-0.26
CBI-R Psychosis	-0.12	-0.29*	-0.31*	-0.18
NPI Psychosis	-0.12	-0.18	-0.13	-0.17
ALS-FRS-R	-0.01	0.00	-0.12	-0.21
FTD-FRS	0.11	0.17	0.22	0.16
ECAS Total	0.22	0.26	0.21	0.19
Disinhibition[a]	0.03	0.10	0.23	0.13

*p<0.05, unc, significance did not survive FDR correction. [a]Spearman's *rho* applied due to violation of normality.

4.3.1.2 Summary composite and difference scores

There was a clear step-down from the first half to the second half of the task, in terms of DTD (composite scores) and sensitivity to cost (difference scores) (Figure 20a and 20b, respectively). A repeated measures ANOVA was performed on the two composite and two difference scores (separately). On the composite scores, the analysis revealed a main effect of task stage ($F(1)=142.16$, $p<0.001$), main effect of group ($F(1)=6.57$, $p=0.012$) and task stage by group interaction ($F(1)=5.00$, $p=0.028$). Simple contrasts showed the MND group sampled less information than controls in the first half of the task but were comparable with controls in the second half (Table 12 and Figure 20a). The overall difference between the two composite scores was significantly different (Table 12). On the difference scores, the repeated-measures analysis revealed a main effect of task stage ($F(1)=58.64$, $p<0.001$) but no main effect for group ($p>0.05$). The interaction between group and task stage was significant ($F(1)=7.09$, $p=0.009$), shown in Figure 20b. Simple contrasts showed a comparable behavioural response to the introduction of a reward between MND patients and controls but a decreased sensitivity to the introduction of a cost as well as escalating cost for the MND group compared to controls (Table 12 and Figure 20b).

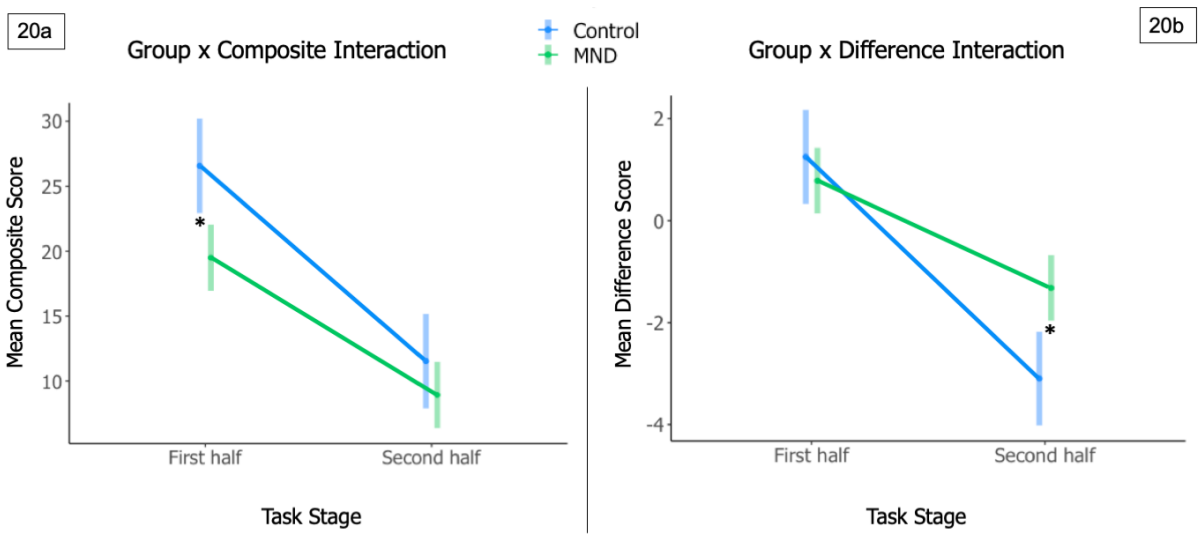

Figure 20: Interaction of Fish Decision Task stage. First half (stage 1 and 2) compared to second half (stage 3 and 4), change in evidence gathered (20a) and sensitivity to introduction of a cost and increasing cost (20b). *denotes significant interaction at *p*<0.05. 20a shows the MND group gathered less evidence than controls in the first half of the task. 20b shows the MND group were less sensitive than controls to the introduction of a cost to sampling information in the second half of the task.

In summary, the MND group sampled less information than controls in the first half of the task, which included the introduction of positive feedback (Figure 20a). However, when analysing the direct behaviour change in response to the introduction of positive feedback, patients' sensitivity to that reward was comparable to that of controls (Figure 20b). In the second half of the task, patients were less sensitive than controls to the introduction of a cost (negative feedback) and less sensitive to the added effects of an escalating cost (Figure 20b).

Within MND group logistic regressions were performed to investigate the extent to which the draws to decision composite and difference scores predicted psychosis status as measured by the ECAS carer report of presence of psychosis symptoms in patients. Table 12 details the odds ratio, significance, sensitivity and specificity percentages. While the specificity of correctly identifying patients who were not showing psychosis symptoms was strong, the

sensitivity of these scores did not correctly identify patients with psychosis symptoms. However, the inferential plots of the composite DTD scores each suggested that the psychosis group were scoring low on DTD in the first half and second half. The MND group was thus split by psychosis status and a repeated-measures ANOVA with the two composite DTD scores revealed a main effect for task stage ($F(1)=11.47$, $p=0.001$), group ($F(1)=8.23$, $p=0.006$) and group by task stage interaction ($F(1)=4.64$, $p=0.036$) such that the psychosis MND group, compared to the non-psychosis MND group, sampled less information before making a decision in the first half of the task. Figure 21 illustrates the interaction.

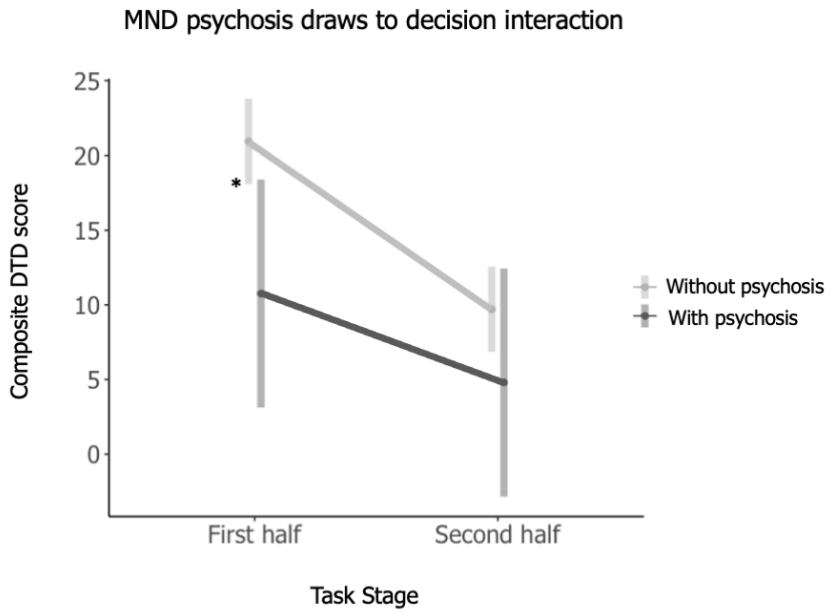

Figure 21: Interaction of Fish Decision Task stage by MND group stratified by ECAS psychosis status. *denotes significant interaction at $p<0.05$. The figure shows those classified by the carer report on the ECAS as overtly psychotic, gathered less information in the first half of the task compared to those not classified as psychotic.

4.3.1.3 Probability of being correct

Accuracy of decisions across the four stages was assessed by analysing the probability of being correct with a repeated-measures ANOVA. Mauchly's test of sphericity indicated a violation of the assumption ($W(5)=0.39$, $p<0.001$). Group differences in the probability of being correct were very similar to the results shown in the number of DTD (Table 11 and Figure 19b). The ANOVA revealed a main effect of group ($F(1)=9.53$, $p=0.003$) and of task stage ($F(3)=53.48$, $p<0.001$) on the probability of being correct. Simple contrasts showed that the MND group performed with a lower probability of being correct compared to controls ($t=-3.09$, $p=0.003$). The interaction between group and task stage was also significant ($F(3)=5.04$, $p=0.010$). Similar to number of DTD, group differences on decision accuracy were significant in the first two stages, whereas in stages 3 and 4, the group differences were increasingly attenuated (Table 11).

4.3.1.4 Points won/lost

Analysing points wont/lost in Stages 2-4 (Figure 22), two outliers (one from each group) were identified that significantly exceeded a ±2 standard deviation threshold. After removal of these participants, a repeated-measures ANOVA revealed a main effect of stage ($F(2)=126.23$, $p<0.001$) and a group by stage interaction ($F(2)=21.06$, $p=0.002$), such that patients won less points in stage 2 and lost less points in stage 4 compared to controls but did not differ from controls in points won/lost in stage 3 ($p>0.05$).

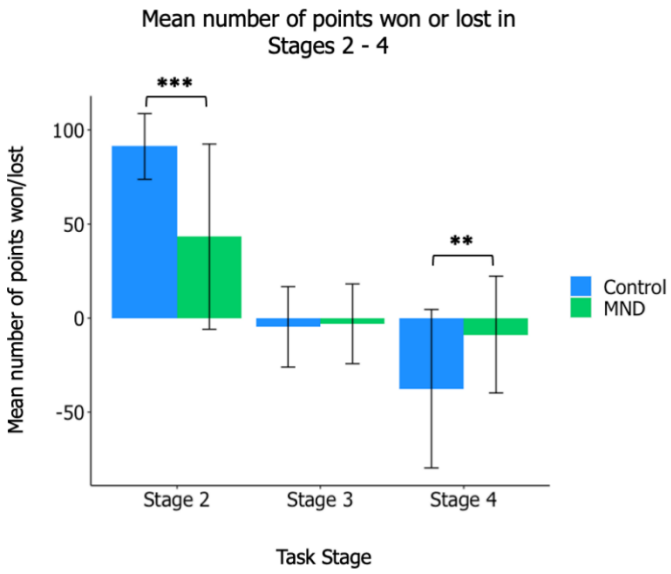

Figure 22: Mean number of points won or lost in Stages 2–4 of the Fish Decision Task. Error bar=standard deviation of the mean. ***p<0.001, **p<0.01.

4.3.1.5 Extreme jumping to conclusions

The dichotomous JTC variable is defined as making a decision after viewing two or fewer pieces of information. Table 15 presents the percentages and counts of participants displaying an extreme JTC reasoning style. As expected, as the task demands increased from stage 1 to 4, an increasing number of both MND patients and controls selected 2 or fewer items before making a decision. However, across all four stages only 16.07% (N=9) MND patients consistently chose two or fewer items before making their decisions.

Table 15: Count and percentage of participants who displayed extreme JTC reasoning style[a].

	MND (*N*=60) count (%)	Controls (*N*=30) count (%)
JTC stage 1	11 (19.64)	2 (6.67)
JTC stage 2	11 (19.64)	3 (10)
JTC stage 3	17 (30.35)	5 (16.67)
JTC stage 4	24 (42.85)	9 (30)
JTC across all stages	9 (16.07)	2 (6.67)

[a]extreme JTC reasoning style defined as making a decision after viewing 2 or fewer items.

4.3.2 Intra/Extra Dimensional Set Shift

66.1% and 63.3% of the MND and control groups, respectively, successfully completed all 9 stages of the ID/ED task. 100% of both groups successfully completed the discrimination stages (stages 1-5) and the ID stage (stage 6) as shown in the attrition graph in Figure 23. The increasing dimensional shift demand of the ED stage (stage 8) is where both MND and control groups began to fail to achieve the correct number of trials to criterion, however no significant group differences were seen in any of the error analyses (Table 13).

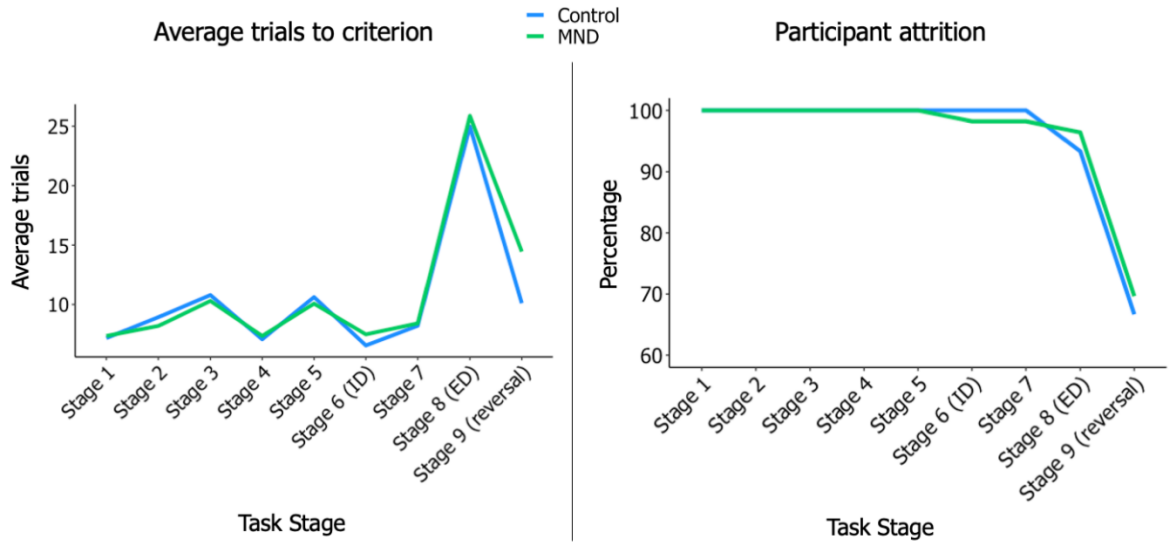

Figure 23: ID/ED average trials to criterion (left) and attrition (right) of MND and control groups across the 9 stages. The figure shows that the MND group performed in-line with controls, the deviations between the groups in the Participant attrition graph (right) were not significant.

Correlational analyses revealed no significant correlations (p>0.05) between any of the error scores on the ID/ED task and psychosis index scores, PCA component scores, disease severity, or cognitive performance.

4.3.3 Perceptual Processing

The perceptual processing task is represented by a sensitivity measure (*d*-prime) before knowledge is provided and after. The difference between the before and after *d*-prime was calculated for the MND and control groups and is presented in Figure 24. There were no significant group differences seen on the perceptual processing task (Table 13).

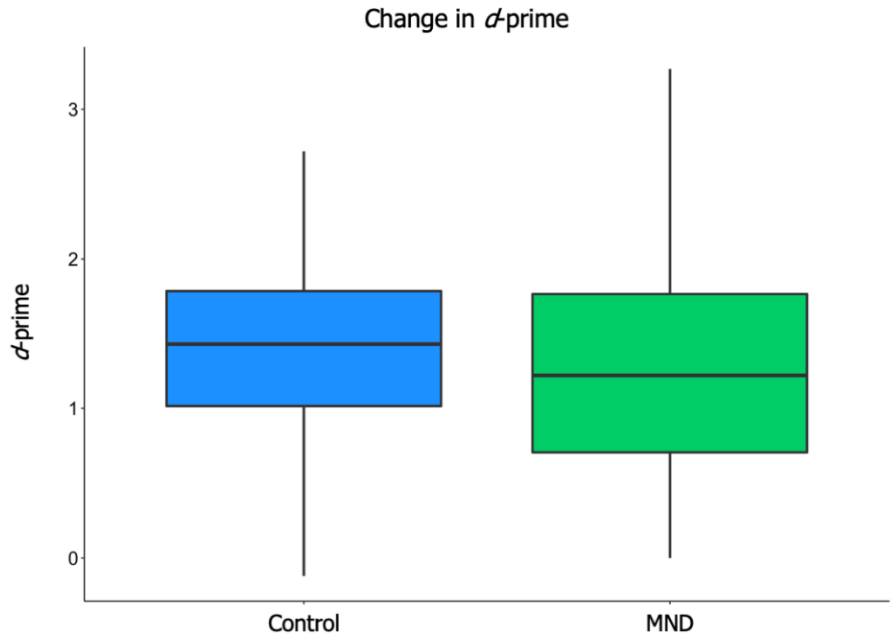

Figure 24: Perceptual processing task change in *d*-prime for controls and MND participants, representing the change in accuracy of response from ambiguous stimuli to post exposure to real picture knowledge. The figure shows no difference in task performance between MND and controls.

Correlations with the perceptual task sensitivity outcome measure, *Before-After Difference*, showed a positive correlation with cognitive performance on the ECAS (total score) (r=0.47, p<0.001), suggesting a positive influence of higher scores in cognition on task performance. There were no significant correlations between perceptual task performance and the psychosis indices, PCA component scores or disease severity.

4.3.4 Summary variables

Results from this chapter reveal three variables from the Fish Decision Task that represent suboptimal reasoning that will be continued to the following imaging chapters 5 and 6 to include in contrasts with grey and white matter imaging parameters. In addition to the two neuropsychiatric PCA components (Patient-rated Mood and Behaviour, and Carer-rated Behaviour), the two psychosis index scores, and disease severity (ALS-FRS-R and FTD-FRS), the following decision task summary variables will be applied: "JTC" (DTD composite score from stage 1 and 2), "cost sensitivity" (the difference between DTD in the first half compared to the second half), and "increasing cost sensitivity" (the difference between DTD in stage 3 and 4).

4.4 Discussion

The above data illustrate suboptimal decision-making in the current MND group. First, MND patients were more willing to make a decision based on inadequate information and this was related to psychosis-specific behaviour and broader neuropsychiatric behaviour. Second, patients were less sensitive to the cost of information and additionally did not adapt as well as controls in their decision-making behaviour in response to increasing cost of information. Attentional control and perceptual inference in the MND group were comparable with controls.

4.4.1 Reduced evidence gathering

The draws to decision analyses on the Fish Decision Task emphasised a suboptimal decision-making style in the MND group, whereby patients were more willing to make a

decision based on inadequate evidence. Both MND and control groups slightly increased their DTD in response to positive feedback when a reward for a correct answer was introduced (stage 2) and significantly decreased their DTD in response to negative feedback when an explicit cost was introduced (stage 3 and 4). The decrease was strongest in stage 4, which involved an escalating cost for each item viewed. These effects were stronger in controls than in the MND group as controls sampled significantly more information during the first two stages, whereas the MND group sampled significantly less information and thus had a lower baseline performance against which to exhibit a change in behaviour (number of DTD) with increasing cost. With less evidence gathered, the accuracy of decisions was compromised in the MND group (i.e. the probability of being correct at the time of making the decision), leading to subsequent poor inference. The limited data gathering and subsequent reduced accuracy findings are consistent with research from my collaborators in early psychosis groups using the same task (Ermakova et al., 2019) and in early psychosis groups who were administered the more traditional beads in the jar version (Broome et al., 2007; Fine et al., 2007; Langdon et al., 2014).

Across all four stages, 16% of MND participants displayed the extreme JTC reasoning bias as it is strictly defined (sampling two or fewer pieces of information before making a decision (Garety & Freeman, 2013), whereas only 0.06% of controls did so. The current proportion of MND patients performed consistently with the early psychosis group of my collaborators (Ermakova et al., 2019) and delusional groups at chronic (Garety & Freeman, 1999), early (Dudley et al., 2011; Langdon et al., 2014; Ward et al., 2018) and at-risk (Broome et al., 2007; Ormrod et al., 2012) stages of psychosis. However, the current results suggest majority of patients demonstrated a JTC bias that does not reflect the extreme bias. While the current results mostly align with previous psychosis research, the draws to decision results show inconsistencies with other experimental reasoning tasks in MND that observed no difference from controls in amount of information gathered before making a decision

(Meier et al., 2010; Štukovnik et al., 2010). The experimental tasks in these studies proposed to assess everyday reasoning and planning in the context of problems patients might need to address in day-to-day life, such as renting a holiday apartment and daily scheduling of medication, which may be more familiar to patients and subsequently maintain attention to the task rules and requirements.

In general, the current MND group were more willing to make a decision based on less evidence. However, this version of the traditional beads task used explicit costs and rewards, therefore, making a decision based on little evidence could be an advantageous strategy because sampling a large amount of very costly information would cancel out the potential gain from a correct response. Average group behaviour and differences across the blocks supported this: the group differences were especially strong in the first two stages when sampling information did not have a cost attached to it; in stage 3 a small stable cost was introduced and both groups responded to the change by lowering the number of items they viewed, and MND participants still applied fewer DTD; the final task manipulation of an increasing cost for each item of information sampled abolished the group differences. In the early stages of the task when information gathering is free, the group differences in DTD are consistent with previous research using the traditional version of the beads task that identifies decisions being made based on little evidence across all stages of psychosis from risk states (Broome et al., 2007; Rausch et al., 2016) and early psychosis (Dudley et al., 2013; Ermakova et al., 2019; Langdon et al., 2014; Ormrod et al., 2012) to clinical psychosis illness, such as chronic schizophrenia (Garety & Freeman, 1999; Langdon et al., 2010), compared to controls.

4.4.1.1 Relation to psychosis symptoms

In the psychosis literature, a JTC bias has specifically distinguished deluded from non-deluded psychosis patients (Garety et al., 1991) as well as shown a strong association with delusion symptom ratings (Dudley et al., 2016; Fine et al., 2007; Langdon et al., 2014). The current study similarly showed an association between tendency to JTC and behaviours suggestive of psychosis (CBI-R psychosis index score rated by someone who knows the patient well), such that fewer items of evidence gathered correlated with higher ratings of psychosis symptoms. The JTC tendency in the current study did not correctly identify the MND patients who were characterised by obvious psychosis symptoms. Despite this, when the MND group was split by psychosis status, within-group analyses showed the psychosis group to exhibit the JTC tendency in the first half of the task when information sampling was free. Perhaps not strongly related to a predisposition to delusions per se, the current results that identify a relation between JTC and behaviours suggestive of psychosis may pertain to a general predisposition towards a vulnerable state to developing psychosis in MND. In support of a more general predisposition to psychosis risk, in a meta-analysis Fine et al. (2007) discussed evidence that the JTC tendency may not be exclusively related to delusions and that some of the bias may in part arise from other psychosis symptoms or cognitive and behavioural impairments.

4.4.1.2 Influence of other cognitive and behavioural impairments

In light of the aforementioned meta-analysis evidence from Fine et al. (2007), in established schizophrenia, it has been suggested that poorer cognitive and neuropsychological functioning contribute to a JTC tendency independent of any specific relation to delusion-proneness (Bentall et al., 2009; Lincoln et al., 2010). Consistent with this view, non-delusional individuals with prefrontal lesions also show a JTC tendency relative to control

groups (Lunt et al., 2012). The contribution of poor cognition to a JTC tendency supports the current rationale in comparing JTC results from early psychosis groups to those from the current MND group, which both allow the investigation of probabilistic reasoning biases before the cognitive and neuropsychological decline that is typically associated with chronic illness in psychosis and in many patients with MND. Interestingly, the early psychosis patients in Ermakova et al.'s (2019) study who demonstrated impaired task performance showed preserved cognitive function (average IQ 102), whereas the current MND participants showed impaired global cognition (average ECAS = 100.14, cut off = 105) compared to controls. However, reduced DTD in the current MND group showed no correlation with global cognition. More detailed investigation of the association of cognitive domains on DTD may reveal otherwise. For example, impulsivity is a recognised cognitive deficit in MND (Benbrika et al., 2019; Lillo, Mioshi, & Hodges, 2012), however it was not a common or severe behaviour in the current MND cohort (chapter 3). Only 3% of people with MND in Tier 1 (Figure 10), who also continued to Tier 2 (*N*=3) were reported by someone who knows them well to show impulsive behaviour (as questioned on the ECAS carer interview). Additionally, analyses revealed that impulsivity was not correlated with performance on this task. The inclusion of a detailed measure for impulsivity in future studies will determine the impact of impulsivity on task performance.

Decision-making draws on components of executive functions and it is well-documented that executive functions are impaired in some patients with MND (Abrahams et al., 2000; Lomen-Hoerth, 2004), with many concluding that decision-making is critically affected as a result. Executive dysfunction is the most commonly cited facet of cognitive impairment in MND, however it is a broad umbrella term that encompasses several relatively distinct higher-order processes, such as behavioural control, cognitive flexibility, inhibitory control, goal-directed behaviour, decision-making when confronted with positive and negative outcomes in various novel, ambiguous or complex situations (Christidi et al., 2018). The current decision task

controlled for a number of cognitive processes required to successfully complete the task. For example, the current version reduced the impact on working memory by continually displaying each item as it was viewed. Perhaps impulsive decision-making may not be the result of an obvious limiting cognitive factor, a suggestion that is consistent with other research which indicates that a JTC tendency is not merely a secondary effect of cognitive deficits that are usually present in psychosis groups (Fine et al., 2007). The same can be argued for other behavioural impairments that may have impacted task performance. Apathy is particularly prominent in MND patients and may have at the least impacted on task engagement or impacted on additional neurocognitive mechanisms, such as representation of cost-benefit valuation and learning action-outcome contingency. Prior to any behaviour occurring, an individual must decide whether or not that behaviour is worth engaging in, which requires weighing up cost-benefit valuation. The apathy questionnaires were included in the PCA in chapter 2 and thus motivation was not separately investigated alongside this task. However, it is plausible to suggest that the high frequency and severity of apathy in component 2 (Carer-rated Behaviour) may be influencing the negative relationship with DTD in the first three stages of the task beyond the other neuropsychiatric behaviours included in that component.

4.4.2 Insensitivity to cost

The current results highlighted an insensitivity to the cost of sampling information in the MND group and emphasised difficulty in flexibly adapting their information sampling, integrating feedback and adjusting future decisions appropriately.

Insensitivity to negative feedback in the current MND sample is consistent with studies that demonstrate the same using different feedback tasks in schizophrenia (Alain et al., 2002; Bates et al., 2002; Farreny et al., 2016) and in earlier stages of psychosis (Martin et al.,

2018). The task in the current study had multiple consequences, some of which were positive points some of which were negative points and these positive and negative points varied depending on how many items were gathered. In the second half of the task, which included costs to sampling information, it became necessary to balance the weight of these positive and negative outcomes in order to integrate and inform a single decision. Ermakova et al. (2019) discussed value and appeal of feedback and argued that a given reward is not as appealing in situations in which it is accompanied by an associated penalty, and a given punishment is not as strong of a deterrent in situations in which it is associated with a rewarding outcome. Controls increased the number of items viewed when there was a reward for a correct response and decreased the number viewed when sampling became more costly (fixed and escalating cost). MND participants also decreased the number of DTD when information sampling became more costly, indicating a hasty decision-making style is not fixed, however their adjustment to negative feedback was not comparable to controls. This suggests that the MND participants were less sensitive to the cost of sampling information, failed to simultaneous neglect the information about the magnitude of the loss, and may have viewed information sampling generally as more costly.

It is plausible that, as suggested by Ermakova et al. (2019), gathering less information may be a functional way of reducing cognitive demand and the investment required to make the decision. In the context of MND, post diagnosis, patients have often insurmountable information to process and frequent decision-making is ever present for the duration of the illness from making decisions on adjustments to the home in response to changes in mobility; decisions regarding changes in food preparation and administration in response to bulbar changes in chewing and swallowing; medical decisions that are critically important to quality of life or potential life-prolonging decisions, among many others. The results across all four stages indicate that the MND participants had difficulty integrating feedback appropriately to update their future decisions. As a result, when decisions reach a certain

level of difficulty, participants may respond more randomly and with greater uncertainty because they can no longer effectively utilise the information available.

Alternatively, I propose two hypotheses: patients attribute insufficient value to the cost of information to drive an appropriate response. Or, after having demonstrated intact responses to positive feedback in the short term, the ability to retain positive-related information to guide future decisions is compromised, particularly if the most recent incoming stimuli is a cost to sampling each item of information requiring careful integration of this additional information. Evidence for the former hypothesis has been demonstrated in avolitional schizophrenia patients who show an inability to differentiate gains from avoiding loss, which correlated with negative symptoms (Waltz et al., 2018). The latter hypothesis has also been shown in schizophrenia patients who initially learned about reward feedback but the accessibility of this information was diminished subsequently affecting future decisions, which again was particularly prominent in patients with negative symptoms (Culbreth et al., 2020; Waltz et al., 2018). In the current MND sample, it is possible that the lack of sensitivity to the magnitude of the cost to sampling information may be influenced by the presence of apathy.

4.4.2.1 Insensitivity to cost and performance monitoring

Evidence of impaired behaviour adjustment according to costs has been shown by abnormal risk-taking in MND on gambling tasks, such as the Iowa Gambling Task (Bechara et al., 1994), which simulates reward and punishment. The gambling tasks are somewhat similar to the probabilistic task used in the current study, however, entails a higher degree of motivational and emotional decision-making with the inclusion of variable financial rewards and losses, and often require a broad range of intact cognitive functions. In MND, findings from gambling tasks have been mixed with some groups concluding an inability to avoid

negative consequences (Girardi et al., 2011), a similar insensitivity to negative feedback as observed in the current results, and others not finding any significant group differences from controls in negative avoidance (Lillo et al., 2012). Analogous results in poor performance monitoring and insensitivity to negative feedback have been observed in other neurological disorders, such as Parkinson's disease (Kobayakawa et al., 2010), and in drug-addiction (Ersche et al., 2016).

Decision-making, as measured by probabilistic reasoning and gambling tasks, tap into ventral medial prefrontal cortex (VMPFC) and orbitofrontal cortex function, areas in which gradient atrophy is shown across the FTD-MND continuum (Lillo, Mioshi, Burrell, et al., 2012). Whereas typical performance on these tasks in healthy individuals identifies a gradual learning over trials to maximise rewards, similar to the current MND group and early psychosis groups, VMPFC lesion patients generally fail to maximise rewards and avoid the contingencies with a high frequency of punishment (Bechara et al., 1994), likely due to insufficient top-down input to striatal regions. The insensitivity to negative feedback (cost of sampling information) evident in the current MND sample may reflect abnormalities in key regions that are involved in neural networks that process reward and punishment outcomes, such as the frontal-striatal pathways and prefrontal connections to the limbic system. The next two chapters will explore the neural correlates of the aberrant decision-making processes identified here.

4.4.3 Intact attentional and perceptual control

A JTC tendency with impaired feedback integration in decision-making is considered to be only one of a number of factors that potentially contribute to the emergence and maintenance of delusions and subsequent vulnerable risk state to developing psychosis. In light of the other proposed cognitive mechanisms by which psychosis symptoms may

emerge, the current findings did not show alterations in attentional control or perceptual inference in the current MND group.

My collaborators demonstrated an atypical perceptual information processing in psychosis-prone individuals whereby a distinct overreliance on prior knowledge reflected a risk state for imposing prior expectation on environmental stimuli on which ill-informed perceptions are generated (Teufel et al., 2015). The current MND group performed comparably to controls and did not demonstrate a performance benefit on this task that would suggest an imbalance in information processing. While average memory performance was lower in the MND group compared to controls (chapter 3, Table 6), it was above the threshold for normal performance. Therefore, relatively intact memory function in this cohort of MND patients (measured on the ECAS) may offer a plausible explanation for the comparable performance to controls on the perceptual processing task such that the MND and control groups alike showed good memory for the template information provided between the ambiguous stimuli. Not only was the performance between the current MND and control groups comparable after viewing the template information, the MND group were as comparable to controls in their ability to discriminate the ambiguous two-toned images without prior knowledge. This was also observed in the early psychosis and psychosis-prone groups in Teufel et al.'s (2015) study, which notably contrasts findings from established schizophrenia patients who show a reduced ability to disambiguate two-toned images of faces without prior knowledge (Grützner et al., 2013; Sun et al., 2013). Likely reflecting advanced cognitive and visual information processing deficits in established schizophrenia (Rajji et al., 2014; Sheffield et al., 2018), the same cannot be argued in the current MND cohort, given visual information processing and memory are affected in MND but to a lesser degree (Ringholz et al., 2005; Abrahams et al., 2014; Crockford et al., 2018) and these MND non-specific areas of cognition do not tend to become more frequent with advancing disease (Crockford et al., 2018).

Performance on the ID/ED from the CANTAB computerised battery, also demonstrated comparable results for the MND and control groups in attentional control. This was a surprising finding given several studies in the MND literature show evidence for impaired attentional control and mental flexibility (Massman et al., 1996; Abrahams et al., 1997; Witgert et al., 2010; Evans et al., 2015; Lange et al., 2016). Yet early psychosis groups, on the same ID/ED task, have shown to succeed in shifting among categories, whereas established psychosis patients tend to fail (commonly due to perseveration) (Orellana & Slachevsky, 2013).

Contrasting results may be due to differences in the set shifting task used within the MND literature. The current study used a computerised analogue of the previously more commonly used Wisconsin Card Sorting Test (Berg, 1948), which has shown demonstrably significant impairment in MND groups compared to controls (Beeldman et al., 2016; Lange et al., 2016). However, the precise cognitive processes underlying the WCST performance deficits in MND are not purely set shifting (or mental flexibility). This same notion can be applied to the computerised analogue administered in the current study (the ID/ED). Successful completion of the task requires the interplay of multiple additional cognitive processes such as working memory, rule inference and association and reversal learning.

The neural mechanisms underpinning these cognitive abilities extensively involve the frontal-striatal pathways (Li et al., 2011), particularly involving the nucleus accumbens and orbitofrontal cortex (Morris et al., 2016). An explanation for the absence of mental flexibility deficit in the current MND cohort may be that the integrity of these pathways has not yet been compromised by the neurodegenerative process, thus the preservation of the particular facets of executive skills reliant on them. The average disease duration in the current MND cohort was 1.95 years (Table 3 page 113), which falls close to the median disease duration of 30 months from symptom onset with less than 10% surviving beyond 10 years (Talbot, 2009; Kiernan et al., 2011). Thus, it is plausible to argue that MND is indeed associated with

attentional control deficits but that the decline in these abilities cannot be detected using such behavioural measures at relatively early stages of the condition.

4.4.4 Limitations

Conclusions here reflect inferential abnormalities and insensitivity to negative feedback, however the reported reduction in draws to decision and poor behaviour adjustment could simply reflect miscomprehension of the task instructions due to cognitive deficits, reduced task engagement due to apathy, or low tolerance to uncertainty. Apathy especially is prominent in MND, and as discussed earlier, the negative correlation with Carer-rated Behaviour and DTD may have been driven by the embedded high apathy scores. Future studies may wish to investigate motivation and apathy influence on task performance more closely. Similarly, correlations with a global measure of cognition were reported in the current study, whereas domain-specific measures of cognition may be more informative in delineating the impact of specific cognitive deficits on task performance.

4.4.5 Future research

To further define impairments in positive and negative feedback learning and decision-making, and to ascertain whether it is solely a data gathering deficit, confirm insensitivity to negative feedback, or an absolute deficit in probabilistic reasoning, it will be necessary to use instruments that more directly assess the separate components of positive and negative feedback processing. A condition in future experiments exploring evidence and inference in MND would include providing participants with more emotionally motivating stimulus, and varying predetermined probabilities in addition to participants freely choosing the amount of

evidence they see, a design similar to that by Dudley and colleagues (Dudley et al., 1997). Future research that includes MND participants with advancing cognitive or behavioural impairment should address the specific involvement of compromised executive cognitive processes or aberrant behaviours, such as apathy, that are affected early and later in the disease stage. This will be equally important to monitor the impact of compromised cognition on insight and decisional capacity when the processing and effective utilisation of information becomes vital in potential life-changing intervention decisions.

4.5 Conclusion

The current MND group demonstrated a suboptimal decision-making style compared to controls. This was not merely a deficit in performance but rather can be specified with some precision to sampling far less information prior to reaching a decision and failing to sufficiently modulate behaviour in response to the cost of gathering information. This decision-making style was related to observed psychosis-specific symptoms, supporting the hypothesis that aberrant cognitive processing may underlie a proneness to psychosis inference.

The current MND group displayed abnormalities in evidence gathering, which are qualitatively similar to those seen in early psychosis and at-risk mental state psychosis groups, and even in patients with more severe psychosis, but are quantitatively less severe. These results are similar to early psychosis and at-risk psychosis groups who also display abnormalities in reasoning and are related to psychosis symptoms, consequently compromising their judgements and ability to integrate feedback and make correct inferences. However, a direct relationship with psychosis symptoms does not simply reflect suboptimal decision-making processes or insensitivity to negative feedback and neither of which are direct correlates of psychosis. Compromised decision-making and insensitivity to

negative feedback are not necessarily specific to certain clinical groups, rather vary continuously across clinical categories within psychiatry and neurodegeneration and may represent a vulnerable psychosis risk state with advancing disease.

Chapter 5 Tier 3A: imaging – grey matter

This chapter examines the grey matter neural correlates of psychosis, behaviour suggestive of psychosis and the hypothesised cognitive mechanism which may put patients with MND at risk of psychosis. Parcellated regional volume was correlated with the psychosis index measures and the two neuropsychiatric components extracted from the PCA (patient and carer perspective) from chapter 3, and the significant cognitive outcome measures from the decision-making task from chapter 4.

First, findings are presented from group differences in grey matter volumes of hypothesis-driven regions of interest and from mixed model linear regressions investigating the influence of psychosis, broader neuropsychiatric behaviour and decision-making on regional volume. The same analyses are then extended to a wider range of exploratory brain regions.

I hypothesised that psychosis, neuropsychiatric behaviour and aberrant decision-making processes, from chapters 3 and 4 respectively, are related to abnormalities in key brain regions known to be affected in early psychosis and in MND: the amygdala (limbic system), frontal-striatal pathways involving the orbitofrontal cortex, nucleus accumbens, and caudate, and the cerebellum (Figure 25). The rationale for selection of these regions is based on their association with the three cognitive mechanisms of interest together with evidence of abnormalities in MND and in primary psychosis groups is provided in chapter 1 section 1.7. Region of interest selection did not rest on relevance to neural correlates of psychosis relating to FTD-MND C9*orf*72 or psychosis in a primary psychosis phenotype. The hypothesised cognitive mechanisms that may represent a cognitive risk in MND in relation to psychosis are subserved by select regions and the connections between them, and which

have also been shown to be involved in abnormal behaviour in MND, psychosis symptoms in primary psychosis conditions.

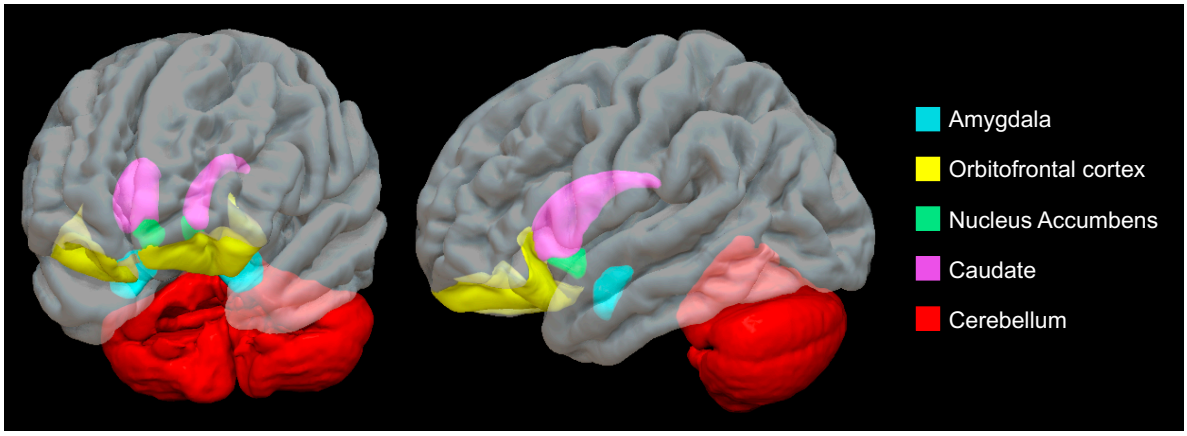

Figure 25: Regions of interest.

5.1 Introduction

5.1.1 Grey matter correlates in MND

In MND, grey matter atrophy is evident in motor regions (Turner et al., 2012) and are prominent in the early stages of disease (Chang et al., 2005). Extra-motor region abnormalities are also present and are related to illness chronicity (Agosta et al., 2016; Crockford et al., 2018; Ellis et al., 2001; Machts et al., 2015; Mioshi et al., 2013). Specifically, MRI studies have identified atrophy in frontal and temporal regions in line with the overlap with FTD features (Agosta et al., 2018; Turner et al., 2009; van der Burgh et al., 2020), in striatal structures (Bede et al., 2013), and the cerebellum (Gellersen et al., 2017; Tan et al., 2014). These findings are consistent with post-mortem pathological studies (Brettschneider et al., 2013; Wilson et al., 2001), however I will be focusing on the evidence from MRI findings.

The regional changes in MND depend on the behavioural and cognitive phenotype. For example, behaviourally, those who have apathy show atrophy in the orbitofrontal and dorsolateral prefrontal cortices (Consonni et al., 2019; Tsujimoto et al., 2011); those who have defective empathy show atrophy in the anterior cingulate and inferior frontal gyrus (Cerami et al., 2014), and those with broad neuropsychiatric symptoms show atrophy in the inferior lobules and vermis of the cerebellum (Tan et al., 2014). MND patients stratified by cognitive involvement show atrophy in the caudate and nucleus accumbens (Alruwaili et al., 2018; Machts et al., 2015), and those with specific attention and executive deficits show atrophy in prefrontal structures (Evans et al., 2015). Conversely, MND patients without cognitive or behavioural impairment show regional changes to a lesser extent (Christidi et al., 2018; Tsermentseli et al., 2012) suggesting grey matter abnormalities may precede variable phenotypic presentations, a finding consistent with demonstrated atrophy in pre-symptomatic FTD C9*orf*72 carriers 5-10 years before expected symptom presentation (Rohrer et al., 2015).

Psychosis in MND is largely overlooked due to its infrequency, especially compared to frequent behaviours such as apathy, and prominent motor features. However, two studies have explored the grey matter correlates of psychosis in patients diagnosed with FTD-MND and FTD, stratified by gene status (Devenney et al., 2017; Sellami et al., 2018). First, Devenney et al. (2017) explored the grey matter correlates of psychosis symptoms in FTD-MND patients stratified by C9*orf*72 gene status. Majority of patients in this study had a diagnosis of behavioural variant FTD (bvFTD) and a small proportion had concomitant MND. Devenney et al. (2017) demonstrated a higher psychosis score was associated with atrophy in a widespread network of cortical and subcortical regions in C9*orf*72 FTD-MND carriers, compared to non-carriers, including discrete regions of the frontal (medial frontal, anterior cingulate, orbitofrontal), temporal (middle, superior and fusiform gyrus) and occipital (lateral) cortices, the thalamus, insula, striatum (caudate, putamen) and cerebellum.

The second study by Sellami et al. (2018) stratified FTD patients by C9*orf*72, *MAPT* and *GRN* gene status, and found psychosis symptoms correlated with atrophy in similarly widespread cortical and subcortical structures of C9*orf*72 patients, with a specific association between delusions and left frontal cortical atrophy. The significant volume reductions identified in these two studies relating to psychosis, reflect the brain atrophy patterns identified in other neuroimaging studies of MND and FTD patients stratified by the C9*orf*72 gene, which highlight excessive subcortical atrophy in carriers compared to non-carriers including in the amygdala, hippocampus, caudate, nucleus accumbens, and thalamus (Bede et al., 2013; Bede, Elamin, et al., 2013; Byrne et al., 2012; Mahoney et al., 2012; van der Burgh et al., 2020). One major caveat in these investigations is the lack of representation of patients diagnosed with MND, which is a considerably large contribution of the current thesis.

The evidence here emphasises that little is known about the neural correlates of psychosis in MND, however insight can be gained from the evidence in primary psychosis conditions, outlined in sections 1.6 and 1.7. In brief, overlapping with MND, in chronic schizophrenia, widespread atrophy in frontal, temporal, limbic, striatal and cerebellar structures are also commonly reported (Andreasen & Pierson, 2008; Bois et al., 2015; Fornito, Yücel, & Pantelis, 2009; Laidi et al., 2015; Levitt et al., 2002; Shenton et al., 2001), and are identified at the early emergence of psychosis symptoms in first episode patients (Bogerts et al., 1990; Bois et al., 2015; Meisenzahl et al., 2008; Torres et al., 2016; Witthaus et al., 2009).

Further insight into psychosis symptoms in the context of MND can be gained from reviewing structural correlates with specific psychosis symptoms, such as delusions, hallucinations and thought disorder, and the hypothesised cognitive processes related to symptom emergence, reviewed in the next two sections.

5.1.2 Grey matter correlates with psychosis symptoms

Hallucinations and delusions in schizophrenia have most consistently been related to volume reductions in temporal and limbic structures (Barta et al., 1990; Modinos et al., 2013; Song et al., 2015; Takahashi et al., 2009). For example, auditory hallucinations have consistently been related to volume reductions in the medial and superior temporal lobe and adjacent insula (Levitan et al., 1999; Modinos et al., 2013; Shapleske et al., 2002; Van Tol et al., 2014). Delusions and related thought disorder have additionally been associated with prefrontal structures (orbitofrontal cortex and inferior frontal gyrus) (Horn et al., 2010; Nakamura et al., 2008; Song et al., 2015).

Frontal, temporal and limbic connections are part of an important network that integrates and discriminates internal/self-generated and external/sensory (visual and auditory) information with emotion and affect (Wylie & Tregellas, 2010). Evidence from at-risk psychosis groups indicate minimal to no involvement of the amygdala (Bois et al., 2015; Klauser et al., 2015; Velakoulis et al., 2006), whereas by chronic schizophrenia amygdala atrophy is pronounced (Ellison-Wright et al., 2008; Wright et al., 2000). Amygdala alterations after the onset of psychosis illness indicate the pathophysiological change may be secondarily related to the disease process.

Disruption to frontal, limbic, striatal and cerebellar structures is thought to additionally contribute to the emergence of delusions and hallucinations by disrupting the role these structures play in cognitive processes, such as decision-making, that allow for adaptive behaviour on the basis of previous experience and feedback (positive and negative) (Cohen et al., 2008; Robbins & Everitt, 1996). The following section will outline structural correlates of cognition, pertaining to decision-making processes and factors, in-line with the hypothesised cognitive mechanism, drawing on evidence from primary psychosis conditions.

5.1.3 Grey matter correlates of decision-making in MND and primary psychosis conditions

In chapter 1, I proposed three cognitive mechanisms which underly the emergence of psychosis symptoms: 1. decision-making ("jumping to conclusions" and positive-negative learning), 2. attentional control (poor executive control and associative learning) and 3. perceptual inference (an imbalance in visual perceptual information processing). In chapter 4, I showed a deficit in decision-making in the current MND patients, characterised by reduced data gathering and an insensitivity to the cost of gathering information.

Broadly, frontotemporal and frontal-striatal regions have been implicated in a range of cognitive processes, including decision-making, affected in MND (Agosta et al., 2016; Mioshi et al., 2013; Strong et al., 2017) and psychosis patients at all psychosis stages along the continuum (Antonova et al., 2004; Bang et al., 2015; Bora & Murray, 2014; Fusar-Poli, et al., 2012). Decision-making, with its many component processes, has been shown in few studies to be impaired in some patients with MND (Girardi et al., 2011) but not others (Meier et al., 2010; Štukovnik et al., 2010), and in many studies to be impaired in schizophrenia (Falcone et al., 2015; Hutton et al., 2002; Larquet et al., 2010; Shurman et al., 2005).

Lesion and PET studies have linked impaired decision-making to orbitofrontal dysfunction (e.g. Bechara et al., 1994; Rogers et al., 1999), which is important in decision-making for assigning value and updating action-outcome in the context of feedback (Fettes et al., 2017; Robbins & Everitt, 1996). Atrophy in the orbitofrontal cortex has been identified in MND (Bede et al., 2013; Christidi et al., 2018; Consonni et al., 2019; Trojsi et al., 2015), in schizophrenia (Nakamura et al., 2008), first episode psychosis (Meisenzahl et al., 2008; Takayanagi et al., 2010) and in prodromal psychosis stages (Borgwardt et al., 2008; Pantelis et al., 2003), and has specifically been linked to poor decision-making in MND (Meier et al., 2010) and primary psychosis conditions (Hutton et al., 2002; Larquet et al., 2010).

However, decision-making processes are not mediated by the orbitofrontal cortex alone, rather, from systems that include other cortical and sub-cortical components, such as the amygdala, striatal structures and cerebellum. The amygdala is important for integrating emotion and sensory information (Benes, 2010; Bogerts, 1997; Li et al., 2011), striatal structure (nucleus accumbens and caudate) for processing reward-punishment information (Haber & Knutson, 2010; Robbins et al., 1989) and its extensive dopaminergic inputs, and the cerebellum for associative learning and error detection in both movement and thought (Andreasen & Pierson, 2008; Becerril et al., 2011). As part of decision-making circuitry, the provision of adaptive feedback to the cortex to inform learning and to update and monitor future behaviours is reliant on intact function across the circuitry. Previous volumetric studies have reported atrophy in these structures in MND (e.g. Machts et al., 2015; Pinkhardt et al., 2006; Tan et al., 2014) and primary psychosis disorders (e.g. Fusar-Poli et al., 2012b; Keshavan et al., 1998; Kim et al., 2018; Scanlon et al., 2014; Westmoreland Corson et al., 1999), with some associating such atrophy to cognitive processes of decision-making in both groups (Fan et al., 2019; Girardi et al., 2011; Levitt et al., 2002).

5.1.4 Examining the neural correlates of psychosis and aberrant decision-making in MND

There is a lack of accurate assessment tools available to quantify less common neuropsychiatric behaviour changes observed in MND, particularly in the context of psychosis symptoms. This is an important caveat to consider when interpreting the single study that has included MND patients in their examination of associated brain changes with psychosis symptoms in FTD-MND (Devenney et al., 2017). The application of standard psychiatric assessments likely contributes to the variability in the detection of milder psychosis symptoms. This applies especially at the MND end of the FTD-MND continuum,

although it is duly recognised that these symptoms are typically less frequent in this patient population (6% from ECAS carer report). In the absence of accurate assessment tools to detect subtler psychosis symptoms, the current study also administered standard psychiatric assessments. Furthermore, in the Devenney et al. (2017) study, the existing subjective measures of psychosis phenomena are not matched with objective measures. It is acknowledged that this is difficult given the perceptual nature of psychosis phenomena, however, not impossible. Given these limitations and having applied multiple subjective psychiatric and behavioural questionnaires in chapter 2, I suggest a combination of subjective measures of psychiatric behaviour and objective representative metrics of pre-psychosis cognitive processes may be appropriate to assess the neural correlates of psychosis in MND in detail. Specifically, the combination of composite psychosis indices, broader neuropsychiatric behaviour constructs, and decision-making components will be employed separately as covariates of interest in mixed linear regression models with regional grey matter volume.

Previous imaging studies of psychosis (Devenney et al., 2017) or broader neuropsychiatric behaviour (Sellami et al., 2018) in FTD-MND have stratified their patient groups either by diagnosis within the FTD-MND continuum and/or by gene status, for example, bvFTD and FTD-MND (Devenney et al., 2017) but not MND, or groups stratified by gene status, for example C9*orf*72, *MAPT*, or *GRN*, irrespective of diagnosis (Sellami et al., 2018). These studies have particularly focused on groups in which psychosis symptoms have been commonly reported, namely bvFTD and/or those who are C9*orf*72 positive (Devenney et al., 2017; Snowden et al., 2012) despite the variable presence of psychosis symptoms across the FTD-MND continuum. These approaches risk overlooking patients with MND and MND with features of FTD in the absence of a concomitant FTD diagnosis, in which psychosis symptoms are also present.

While focusing on distinct diagnoses is valid when seeking to understand the complex relationship between brain changes and clinical features across overlapping groups to provide insights into common neural systems underlying a symptom, this method loses all the variability of psychosis behaviour as it presents across the disease continuum. The Tier 3 MND group did not differ in their mean CBI-psychosis index score, however the large standard deviation indicated great variability in these symptoms (beliefs, abnormal behaviour and stereotypical motor behaviours). To reflect the variability of cognition and behaviours suggestive of psychosis in the current Tier 3 imaged MND group and maintain statistical power, the group remained as one heterogeneous group rather than stratifying into subgroups of MND versus MND with FTD features or even those who experienced versus those who did not experience psychosis symptoms. In addition, an advantage of employing a concise combination of psychosis-specific index scores, dimensional weightings of broader neuropsychiatric behaviour and a cognitive marker is that it attempts to reflect behaviours and processes that have been implicated in the emergence of psychosis, and also maintains statistical power and insight into other processes that have not previously been included when investigating psychosis in FTD-MND.

5.2 Methods

5.2.1 Tier 3 participants

Table 3 (chapter 3, page 113) outlines the demographic and disease characteristics for the subset of MND and healthy control participants included in Tier 3. MND participants demonstrated cognitive (Table 8) and functional (Table 3) impairment, as measured by the ECAS, ALS-FRS-R and FTD-FRS, compared to healthy controls. However, no group differences were seen on the mean CBI-R or NPI psychosis index scores (Table 7), likely

due to the variation of psychiatric involvement seen in Figure 13 (page 128). 10-13% of the MND participants in Tier 3 were reported to have mild to moderate features suggestive of psychosis as reported by someone who knows them well in combination with clinical interview by the researcher. The imaged MND subset of participants did not significantly differ in age (t=0.67, p=0.504), sex (χ^2=0.01, p=0.947) or disease characteristics (site of onset: χ^2=0.61, p=0.435) compared to non-imaged MND subset.

5.2.2 Image processing and FreeSurfer parcellation

T1 and T2-weighted image processing, cortical reconstruction and volumetric parcellation is outlined in chapter 2 (page 98).

5.2.3 Analyses

Linear mixed models (Type III and Satterthwaite's method, fit by restricted maximum likelihood (REML)) were applied to explore group differences and interactions in regional brain volume. Pearson's partial correlations were used to explore relationships between variables. Mean-centred age and TIV were included as covariates to account for any possible residual confounding effects associated with variability in these measures. Sex was not included in final analyses as it did not consistently independently influence any of the models and it is supported that including TIV may accommodate the influence sex has on overall brain size (Barnes et al., 2010).

Group difference analyses were first performed on *a priori* regional volume of interest, which included the following: amygdala, orbitofrontal cortex, caudate, nucleus accumbens and cerebellum. These selected regions were believed to most accurately reflect the predictions

that volumetric differences would be apparent in the limbic and frontal-striatal structures, and the cerebellum that are similarly implicated in MND and early psychosis, and which underly key cognitive processes implicated in the development of psychosis. Analyses then extended to include broader experimental areas of frontal, temporal, parietal and occipital lobes, the thalamus, putamen, hippocampus and cingulate.

Cognitive and neuropsychiatric outcome measures included in the linear regressions with regional volume were arcsine transformed CBI-R and NPI psychosis index scores, the two neuropsychiatric behaviour components extracted from the PCA, and the three variables representing reasoning ability (JTC, cost sensitivity and increasing cost sensitivity). MND within-group investigations included disease severity measures of ALS-FRS-R and FTD-FRS, and PCA component scores. All predictor variables were mean-centred.

5.3 Results

5.3.1 Region of interest volume

5.3.1.1 Group differences

Linear model regression analysis showed group differences in the caudate and amygdala volume (Table 16). Figure 26 illustrates the differences in regional volume reduction for each region-of-interest for MND patients compared to controls.

Table 16: *A priori* region of interest estimated mean volume (ml) and group differences.

Region of interest	MND (*N*=30)	Control (*N*=20)	T statistic	R^2	Group difference
Frontal-striatal					
Caudate	6.44	7.15	*t*=-2.57	0.48	*p*=0.041
Nucleus accumbens	0.91	1.01	*t*=-1.54	0.35	ns
Orbitofrontal	22.88	24.22	*t*=-1.91	0.56	ns
Limbic					
Amygdala	2.89	3.46	*t*=-2.86	0.49	*p*=0.037
Cerebellum	100.46	105.11	*t*=-1.31	0.68	ns

p uncorrected by unpaired *t*-test. No significance survived FDR correction.

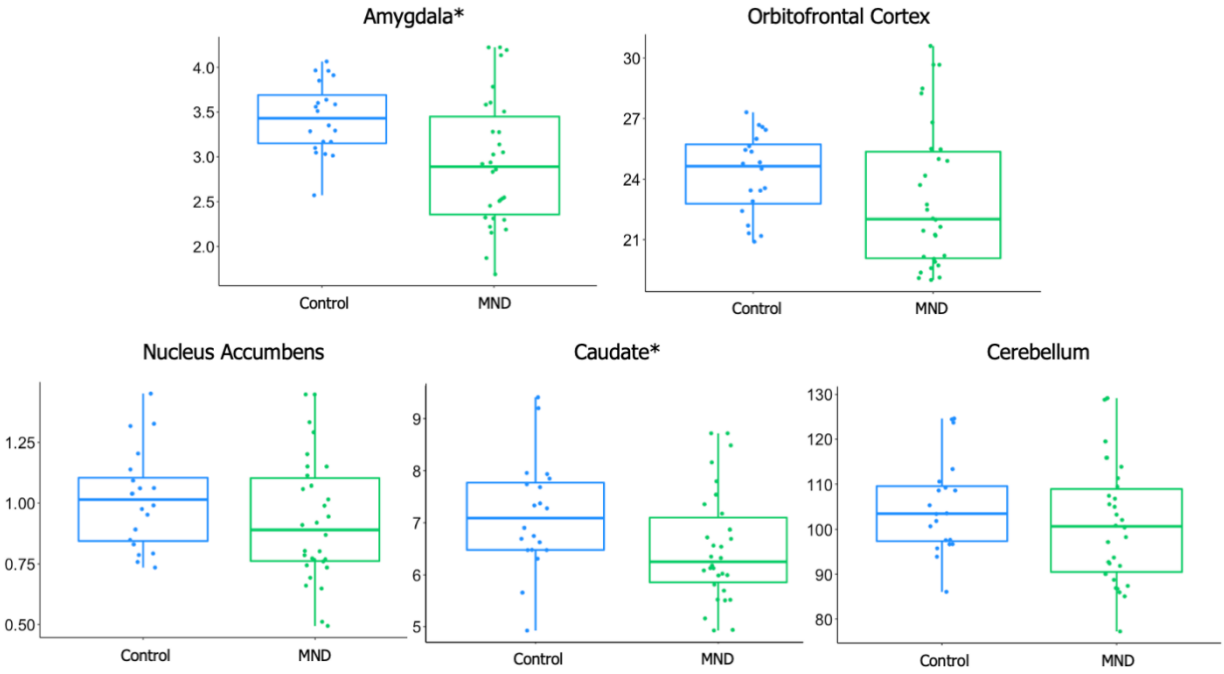

Figure 26: Region-of-interest volume differences between control and MND groups. Y-axes indicate raw regional volume in ml. **p*<0.05, unc.

5.3.1.2 Within-group volumetric correlations with disease severity and age

Figure 27 illustrates partial correlations for the MND group between disease severity, age and region-of-interest volume, controlling for TIV. Correlation analyses revealed positive moderate correlations between FTD-FRS and volume of the amygdala and nucleus accumbens, and negative moderate correlations between all regions-of-interest volume and age. There were no significant within-group correlations between absolute disease severity as measured by the ALS-FRS-R and region-of-interest volume (all $p>0.05$).

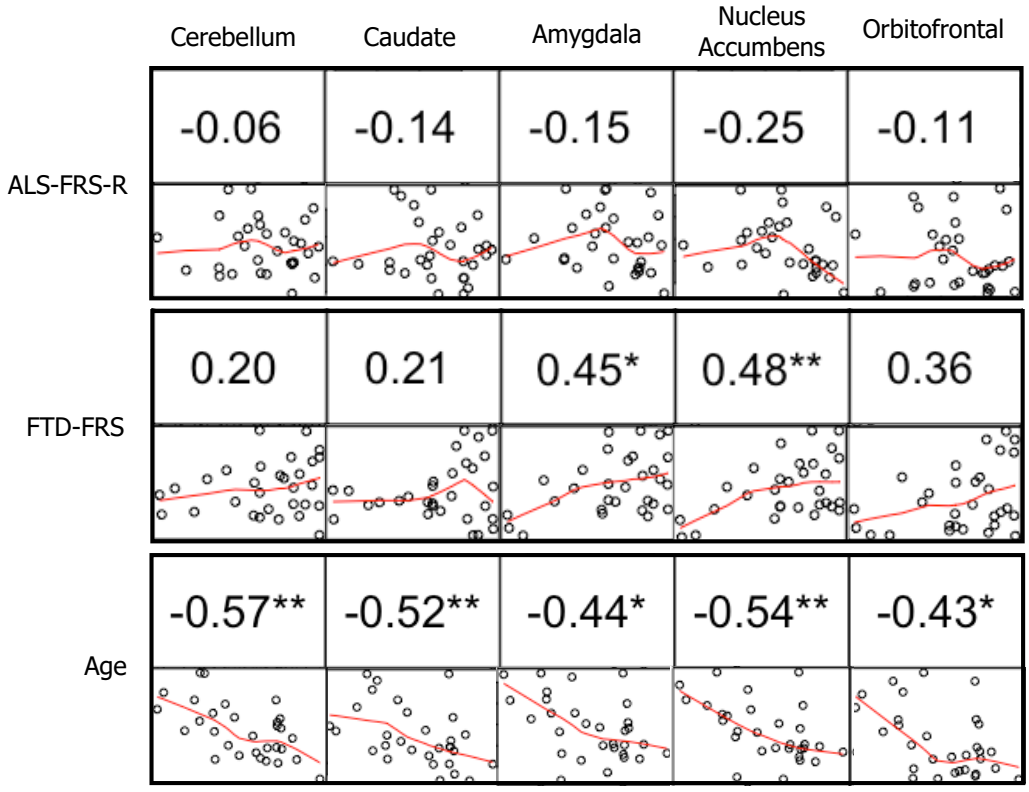

Figure 27: Within group Pearson's *r* partial correlations with scatterplots between MND disease severity scores (ALS-FRS-R and FTD-FRS), age, and region-of-interest volumes. ALS-FRS-F=Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised, FTD-FRS=Frontotemporal Dementia Functional Rating Scale. *$p<0.05$, **$p<0.01$.

5.3.1.3 Region correlations with psychiatric status and cognitive performance

Linear mixed model regression analysis controlling for age and TIV was performed on region-of-interest volumes and the arcsine psychosis index scores (CBI-R psychosis and NPI psychosis), the decision-making outcome variables and the PCA components (within-groups only).

Figure 28 demonstrates the interaction between group and CBI-R psychosis index score on volume of the caudate ($F(1,44)=1.27$, $p=0.050$) and amygdala ($F(1,44)=3.98$, $p=0.043$), however there are some clear outliers (denoted by red arrows). When the group comparison was re-run after removal of the outliers, the significance did not survive for both regions ($p>0.05$) (Figure 28). Group comparison results indicated no other significant interactions between CBI-R or NPI psychosis index scores and the remaining region-of-interest volumes ($p>0.05$).

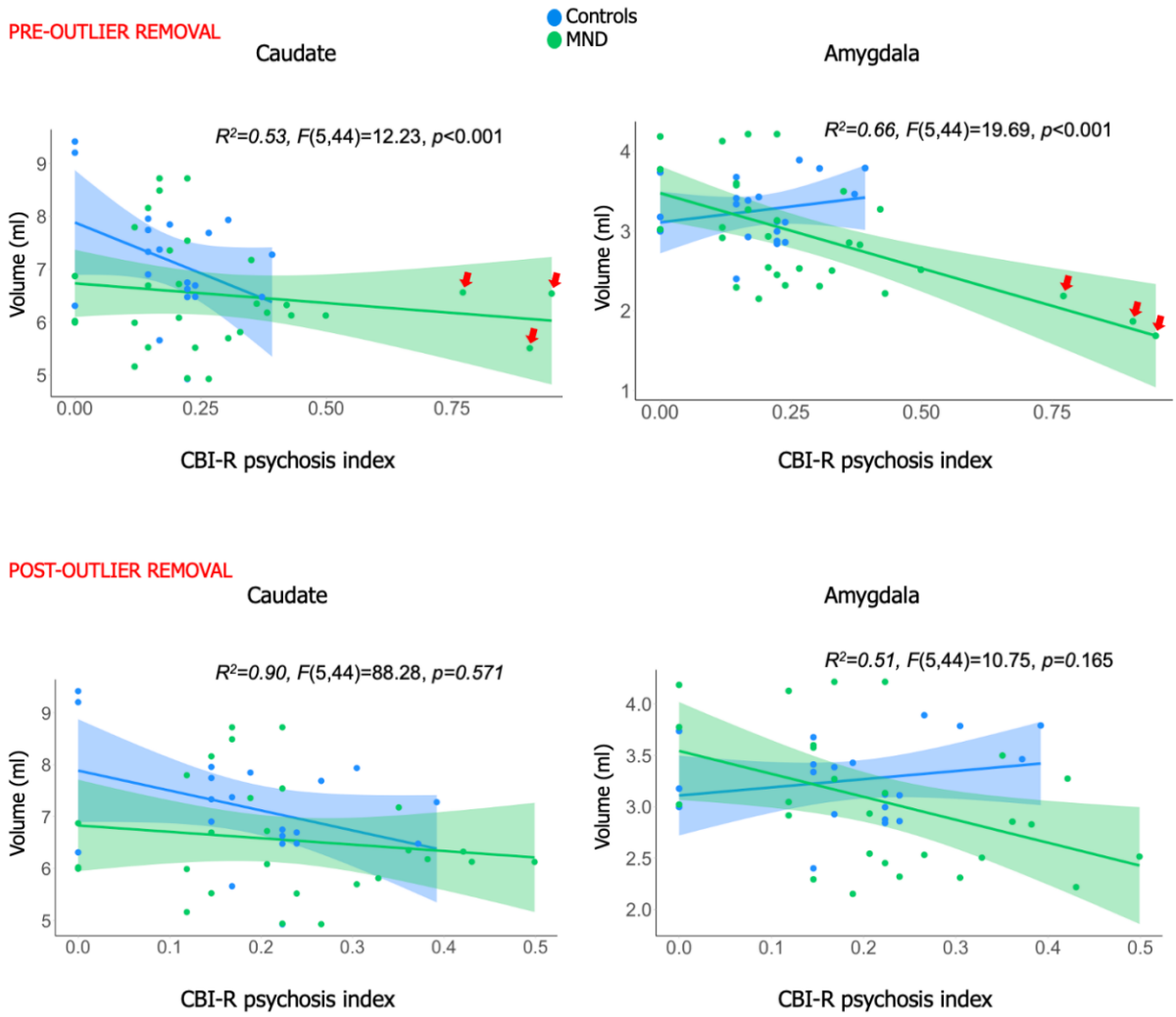

Figure 28: Interaction pre-outlier (denoted by red arrows) and post-outlier removal between group and score on CBI-R psychosis index on regional volume of caudate (left) and amygdala (right). R^2=adjusted R^2 for age and TIV. *F*-statistic=overall model. *p*-value unc. The interaction was non-significant after outlier removal.

Group comparison results indicated an interaction between group and the cost sensitivity score for cerebellar volume ($F(1,44)= 5.18$, $p=0.028$) (Figure 29). No significant interactions were shown between the JTC or increasing cost sensitivity scores and any region-of-interest volume ($p>0.05$).

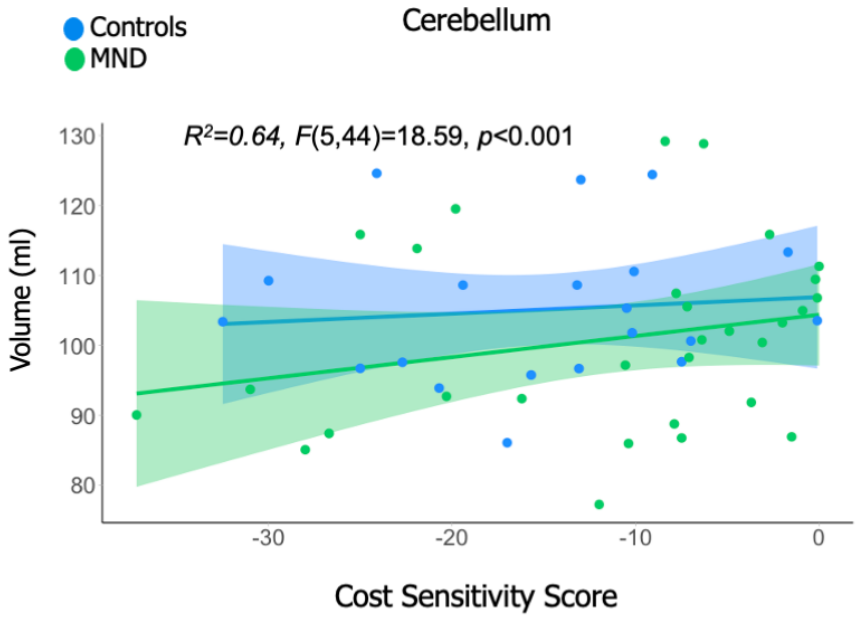

Figure 29: Interaction between group and cost sensitivity score on regional volume of the cerebellum. R^2=adjusted R^2 for age and TIV. *F*-statistic=overall model. *p*-value unc. The figure shows volume change for both MND and controls with respect to how participants responded to the introduction of a cost to sampling information but average volume reduction was lower in the MND group.

5.3.1.4 Within-group volumetric correlations with PCA components

Within MND group partial correlations between the two PCA components and the region-of-interest volumes, controlling for age and TIV, revealed no significant associations for component 1 (Patient-rated Mood and Behaviour) or component 2 (Carer-rated Behaviour) (p>0.05).

5.3.2 Exploratory region volume

5.3.2.1 Group differences

Following the region-of-interest analyses, exploratory investigation extended to broader brain regions including frontal, temporal, parietal, occipital, insula, cingulate, hippocampus, thalamus and putamen. Group comparisons between MND patients and controls revealed the characteristic patterns of extra-motor region volume reduction in the frontal, temporal, occipital and hippocampal regions (Table 17). No significant group differences were shown in the insula, cingulate, parietal lobe, putamen and thalamus (Table 17).

Table 17: Exploratory region estimated mean volume (ml) and group differences.

Region	MND (*N*=30)	Control (*N*=20)	T statistic	R^2	Group difference
Frontal Lobe	152.80	159.97	*t*=-2.10	0.42	*p*=0.042
Temporal Lobe	102.01	109.26	*t*=-2.11	0.54	*p*=0.031
Occipital Lobe	46.16	49.72	*t*=-2.17	0.58	*p*=0.035
Parietal Lobe	104.37	107.53	*t*=-1.18	0.60	ns
Hippocampus	7.05	8.63	*t*=-2.78	0.50	*p*=0.007
Cingulate	15.74	16.94	*t*=-1.27	0.54	ns
Insula	12.02	13.10	*t*=-1.56	0.44	ns
Thalamus	12.98	13.15	*t*=0.11	0.55	ns
Putamen	5.85	9.05	*t*=-1.09	0.43	ns

p-values uncorrected by unpaired *t*-test. No significance survived FDR correction.

5.3.2.2 Region correlations with psychiatric status and cognitive performance

Linear mixed model regression analysis controlling for age and TIV was performed on the exploratory brain region volumes to examine the effect of group and the psychosis index scores (CBI-R psychosis and NPI psychosis), the decision-making outcome variables and the two PCA components (within-groups only).

Group comparison results indicated interactions between group and the CBI-R psychosis index on cingulate volume ($F(1,44)=6.74$, $p=0.013$) and hippocampus volume ($F(1,44)=1.06$, $p=0.002$) (Figure 30). No significant interactions were shown between the NPI psychosis index and any exploratory regional volume ($p>0.05$).

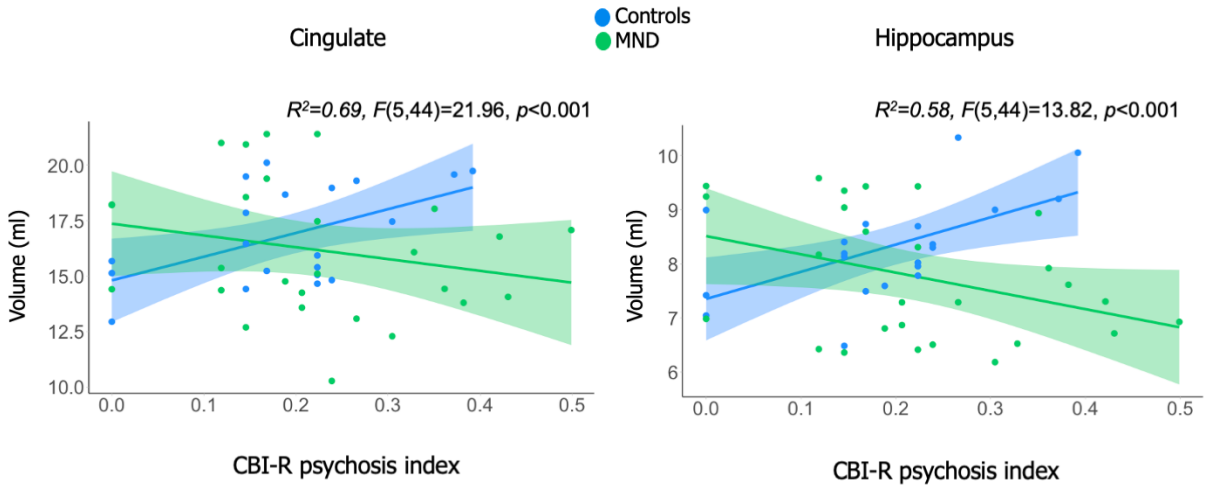

Figure 30: Interaction between group and score on CBI-R psychosis index on regional volume of cingulate (left) and hippocampus (right) for the MND group. R^2=adjusted R^2 for age and TIV. *F*-statistic=overall model. *p*-value unc. The figure shows increased rating on the psychosis index score (higher endorsement of psychosis symptoms) was related to lower regional volume compared to controls.

Group comparison results indicated an interaction between group and the cost sensitivity score on cingulate volume ($F(1,44)=4.74$, $p=0.034$) (Figure 31). No significant interactions were revealed between the JTC or increasing cost sensitivity scores and any exploratory regional volume ($p>0.05$)

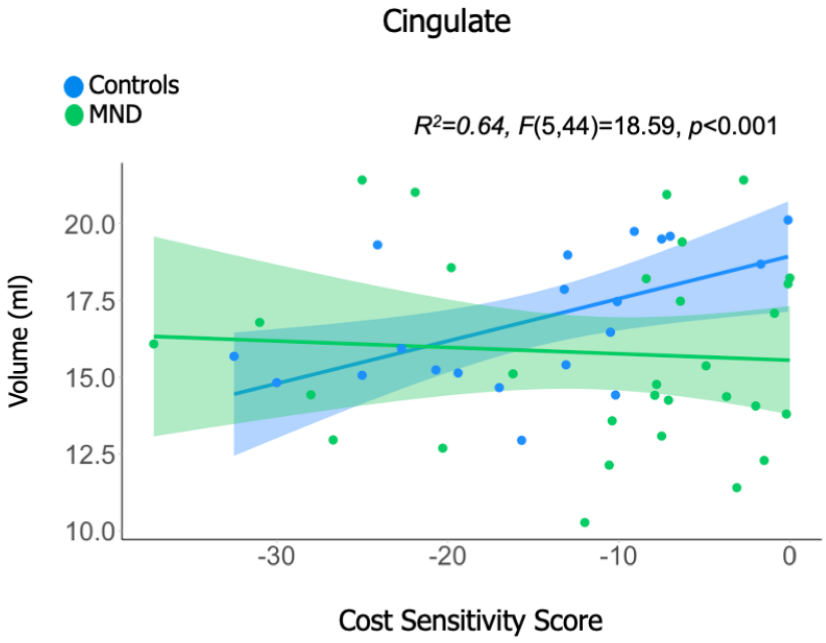

Figure 31: Interaction between group and the cost sensitivity score on regional volume of cingulate for the MND group. R^2=adjusted R^2 for age and TIV. *F*-statistic=overall model. *p*-value unc. This figure shows lower cingulate volume in the MND group related to insensitivity to the cost of sampling information compared to controls.

5.3.2.3 Within-group correlation with PCA components

Within MND group partial correlations between the PCA components and the exploratory region volumes, controlling for age and TIV, revealed no significant associations for component 1 (Patient-rated Mood and Behaviour) or component 2 (Carer-rated Behaviour) ($p>0.05$).

5.4 Discussion

This chapter explored the patterns of brain regional atrophy associated with behaviours and cognitive processes which may promote psychosis in MND. These imaging results from 30 MND and 20 healthy controls demonstrate the involvement of a distinct set of cortical and subcortical brain regions relating to psychosis symptoms and aberrant decision-making processes from the previous chapters in the current MND cohort.

The prediction that changes in *a priori* regions of interest will be related to aberrant cognitive processes known to inform the emergence of psychosis is partly supported but further informed by the involvement of key exploratory regions in association with psychosis behaviour (chapter 3) and poor behavioural adaptation (chapter 4). These are new and key findings that inform previous work examining the neural correlates of overt psychosis in FTD and FTD-MND (Devenney et al., 2017; Sellami et al., 2018) and converge with findings from early psychosis groups. The power of the current study is not based on the small number of people with MND showing overt psychosis symptoms, and analyses were not planned to compare psychotic MND with non-psychotic MND. Rather, correlations are driven by the variation in behaviours suggestive of psychosis, including the cognitive abnormalities hypothesised as cognitive mechanisms that put patients at risk of developing psychosis. By Tier 3 the MND group demonstrating this variation is still small but the variability is sufficient to reveal structure-function associations. These provide insight to key regions involved in psychosis and related cognitive mechanisms that may elucidate their emergence in MND. The anatomical regions associated with the psychosis index score shown here suggest the involvement of frontal-striatal, temporal and cerebellar networks for reward-punishment based decision-making and behavioural adaptation, of which are considered to be compromised in the current MND cohort evident by an insensitivity to negative feedback. These results indicate a speculative relationship between psychosis behavioural symptoms

and suboptimal decision-making with reduced regional volume that may contribute to the vulnerability of emerging psychosis symptoms in the current MND cohort.

Consistent with a large-scale previous study employing similar FreeSurfer methods of volume parcellation in MND (van der Burgh et al., 2020), the current patients showed distinct extra-motor atrophy patterns in frontotemporal structures, namely the amygdala, hippocampus, caudate, and frontal lobe, which correspond to established networks for executive cognition and behaviour commonly reported in MND patients.

The current atrophy patterns are also consistent with other studies using different FSL volume parcellation methods, such as FAST4 (Menke et al., 2018; Menke et al., 2014a) and with studies using FSL methods that extracted grey matter cortical thinning or density parameters (Agosta et al., 2016; Branco et al., 2018; Consonni et al., 2018) who reported similar frontotemporal grey matter alterations in MND compared to controls. Similar studies to the current study have interestingly not found any grey matter volume reductions in MND compared to controls (Bede et al., 2018; Rajagopalan & Pioro, 2014), which could be due to the biased inclusion of MND patients without cognitive or behavioural symptoms. When studies have stratified patients based on their cognitive and behavioural involvement, it has been shown that MND patients with such symptoms show increased grey matter alterations compared to MND without cognitive and behavioural symptoms (Agosta et al., 2016; Bede et al., 2018; Chang et al., 2005; Omer et al., 2017).

Despite the inconsistencies in the literature, it is reasonable to assume that the current volume reductions in MND compared to controls could be driven by the variable involvement of cognitive symptoms in the Tier 3 MND sample. Had I stratified the current MND sample by behavioural symptoms, statistical power would have been significantly compromised. Additionally, some studies may be biased with the known inclusion of C9*orf*72 MND patients (Consonni et al., 2018). The current cohort was not genotyped; however, gene status was

not a primary focus, instead it was to address the gap in the literature by including sporadic MND patients when investigating psychosis along the FTD-MND continuum. Reports on patterns of cortical involvement in C9*orf*72 positive MND patients are mixed. Some describe non-specific and even similar atrophy to C9*orf*72 negative MND patients (Westeneng et al., 2016), whereas others have reported distinct regional atrophy in C9*orf*72 positive compared to negative MND patients (Agosta et al., 2017; Bede et al., 2013; Byrne et al., 2012), especially C9*orf*72 and the early involvement of the thalamus (Bocchetta et al., 2018; Floeter et al., 2016; Schönecker et al., 2018), which was not a region that showed significant volume reduction compared to controls in the current MND cohort.

Contrary to previous MND volumetric reports, no significant patterns of atrophy were identified in the orbitofrontal cortex, nucleus accumbens, cerebellum, thalamus, cingulate, insula or parietal lobe. It is likely that the high variability in disease severity and global cognition, together with decreasing number of participants in the final imaging tier contributed to the lack of volume difference with controls in these regions. Relating to schizophrenia research, the current regional atrophy in the amygdala, hippocampus and frontal lobes in MND is consistent with previous research, using the same FreeSurfer volume parcellation methods, identifying the involvement of frontal-temporal structures affected in schizophrenia patients when compared to controls (Koshiyama et al., 2018; Padmanabhan et al., 2015). Contrary to other functional and structural MRI and neuropathological studies identifying cerebellar volume reduction in MND (Bede et al., 2015; Gellersen et al., 2017; Prell & Grosskreutz, 2013), no cerebellar atrophy compared to controls was identified in the current MND group.

Despite the lack of significant atrophy in some regions of interest and exploratory regions in the current MND group compared to controls, regional volume reductions were found in association with symptoms suggestive of psychosis and decision-making processes; these resembled changes evident in early psychosis groups (Benetti et al., 2013; Borgwardt et al.,

2011; Pantelis et al., 2003; Smieskova et al., 2010) and schizophrenia (Shepherd et al., 2012). This evidence suggests volume change in key cortical and subcortical regions that have been shown in early and chronic psychosis may maintain a constant relation to psychosis symptoms once they emerge. The following section considers the grey matter associations with psychosis behaviour and aberrant decision-making processes found in the current MND group, drawing comparisons with the primary psychosis literature.

5.4.1 Grey matter correlates of psychosis and cost sensitivity

5.4.1.1 Correlations with psychosis

Given the low frequency of overt psychosis in the Tier 3 MND group and large variability of abnormal behaviours suggestive of psychosis captured by the CBI-R psychosis index, the following results are interpreted with caution. Distinct frontotemporal cortical areas relating to symptoms suggestive of psychosis were identified in the current MND group: the hippocampus and cingulate. These regions were included in the exploratory analyses and were not part of the hypothesised regions of interest. No region of interest correlated with the psychosis index scores. The provisional association between behaviours relating to psychosis as rated by the CBI-R, and atrophy in the hippocampus and cingulate could indicate particular importance as these regions are especially vulnerable in prodromal psychosis groups in the acute transition to overt psychosis (Benetti et al., 2013; Borgwardt et al., 2011; Borgwardt et al., 2007; Pantelis et al., 2003; Smieskova et al., 2010).

Neuroanatomical abnormalities in the medial temporal lobe and cingulate that predate the first episode of overt psychosis have been identified in at-risk individuals with prodromal symptoms (Pantelis et al., 2003). Longitudinally, changes in these regions in at-risk individuals who did not subsequently develop psychosis have not been identified (Pantelis et

al., 2003), indicating the medial temporal lobe and cingulate have a strong association with the development of psychosis. Additionally, these regions may play a role in the maintenance of psychosis symptoms as patients with established schizophrenia show qualitatively similar volume abnormalities in the hippocampus and cingulate (Torres et al., 2016; Velakoulis et al., 2006). Evidence from functional connectivity studies have demonstrated functional abnormalities in the medial temporal lobe in schizophrenia patients (Heckers, 2001; Kraguljac et al., 2016; Meyer-Lindenberg et al., 2005) and in at-risk groups (Colibazzi et al., 2017), which corroborate findings that dysfunction in functional circuitry involving this region plays an important role in the pathogenesis of psychosis.

The cingulate is involved in complex and adaptive behaviours, and is strongly connected within the salience network, the main function of which is to detect, analyse and integrate internal stimuli and external emotional stimuli. The current findings are consistent with previous results of cingulate involvement in symptom generation in behavioural and psychiatric symptoms of psychosis illnesses, including schizophrenia as well as FTD (Peters et al., 2016; Seeley et al., 2007; Zhou & Seeley, 2014). Noteworthy, volumetric studies of other neurodegenerative conditions that exhibit psychosis symptoms, as rated and defined by a clinician and/or carer, have identified similar frontotemporal atrophy associations with psychosis. For example, in Parkinson's disease Lenka et al. (2018) observed hippocampal atrophy in Parkinson's patients with psychosis; Sanchez-Castaneda et al (2010) observed an association between visual hallucinations and orbitofrontal cortex volume; and in Alzheimer's disease (Lee et al., 2016; Serra et al., 2010) correlations with delusions and the hippocampus. Evidence from other imaging modalities have demonstrated a loss of neuronal integrity in the anterior cingulate is correlated with visual hallucinations using MR spectroscopy in Parkinson's patients (Lewis et al., 2012), and PET imaging in Lewy body dementia (Nagahama et al., 2010) identified a dysfunction of the frontal cortex (including the cingulate) in relation to delusions.

In MND, the hippocampus and cingulate have consistently been implicated in neuroimaging (Bede et al., 2013; Kato et al., 1993), neuropsychology (Abdulla et al., 2014; Consonni et al., 2019; Machts et al., 2015; Phukan et al., 2012; Takeda et al., 2007) and neuropathological studies (Brettschneider et al., 2012; Takeda et al., 2007, 2009), in relation to typical FTD-like cognitive and behavioural symptoms, and now with a specific relation to psychosis symptoms. Along the FTD-MND continuum, volume changes in these regions have also been related to psychosis in bvFTD, and C9*orf72* FTD-MND patients (Devenney et al., 2017a) as well as implicated in broader bvFTD personality and behavioural changes, such as apathy and disinhibition (Consonni et al., 2019). Therefore, the current results of an association of symptoms suggestive of psychosis in MND and their relation to changes in key cortical structures of the hippocampus and cingulate are consistent with and extend previous work on the investigation of psychosis symptoms that have mainly focused on bvFTD and FTD-MND along the FTD-MND continuum.

5.4.1.2 Correlations with cost sensitivity

The investigation from chapter 4's probabilistic decision-making task revealed in the MND group an insensitivity to the introduction of an explicit cost when sampling information to make a decision (page 175). Insensitivity to feedback is an impaired process that, via compromised representation of value and integrating feedback to update future behaviour, leads to suboptimal decision-making (Gold et al., 2008; Howes & Murray, 2014; Strauss et al., 2014). Such a disruption may inform vulnerability to psychosis, for example the formation, elaboration and potentially fixation of delusional ideas. Lower sensitivity to negative feedback has been observed in patients with schizophrenia (Alain et al., 2002; Bates et al., 2002; Farreny et al., 2016).

In the current chapter, cost sensitivity in the experimental decision-making task showed an interaction with cingulate and cerebellar changes. The cerebellum was an *a priori* region of interest in the current study as it is similarly affected in some patients with MND (Bae et al., 2016; Bede et al., 2015; Gellersen et al., 2017) and various psychosis groups (Kim et al., 2018; Pantelis et al., 2003; Segarra et al., 2008). In addition to its classic role in movement coordination, the cerebellum plays a prominent role in cognition due to its strong cortical and subcortical connectivity (Buckner, 2013; Heyder et al., 2004; Schmahmann, 2019). Despite the lack of general cerebellar volume reduction in the MND group compared to controls, patients' insensitivity to the cost of information showed an interaction with cerebellar volume compared to controls (Figure 29). Cerebellar connections to prefrontal regions, such as the anterior cingulate, and via the basal ganglia, place this region in a network that sub-serves the cognitive processes involved in decision-making and reward-punishment-related processing, as well as the networks that recruit regions for a motor response during performance monitoring. Important to the current results, the cerebellum is thought to be involved in adaptive modification of behaviour and error-based learning (Bostan et al., 2013; Doya, 2000; Peterburs & Desmond, 2016). Adapting behaviour and performance monitoring are generally thought to recruit extensive frontal-striatal networks due to the use of dopamine-dependent coding of response outcome (Ullsperger et al., 2014). However, findings from primate and healthy human functional MRI studies additionally implicate the cerebellum in performance monitoring (Peterburs & Desmond, 2016). In schizophrenia groups, functional MRI has also identified diminished responses to errors in the cerebellum (Becerril et al., 2011), leading to a failure to update rules and adapt behaviour accordingly. Thus, any disruption, such as the degenerative process in MND, causing volume reduction in key regions, including the cerebellum, involved in the decision-making network may have a cascading impact on the multi-dimensional decision-making processes and behavioural adaptation. This may contribute to the abnormalities in the current MND sample in processing cost of information to inform future decisions, emphasised by regional volume

reductions in parts of the striatum and limbic system (Figure 26), with cerebellar changes showing a specifically prominent association with insensitivity to cost of information and adapting behaviour.

In analyses with exploratory brain regions, reduced cingulate volume was shown to be implicated in cost sensitivity in the MND group. Under the assumption that the cerebellum is connected to prefrontal regions, the parallel involvement of the cingulate volume with reduced ability to process cost of information here is unsurprising, not to mention the central role the cingulate plays in reward-based learning (Rolls, 2019). Despite intact positive feedback processing in the current MND sample and reward and punishment having opposite emotional value, they are both processed by the cingulate cortex (Magno et al., 2009; Rushworth & Behrens, 2008). Functional MRI studies have identified that the neural networks responsible for the processing of reward and punishment largely involve separate subregions of the cingulate cortex (Fujiwara et al., 2009; Rogers et al., 2004).

While the current results are not specific to a subregion of the cingulate cortex and only to its averaged regional volume, it is noteworthy to highlight the specific role of the anterior cingulate cortex. The anterior cingulate has been implicated in a distributed network of regions involved in the processing of affective, motivational and cognitive components of negative outcomes in order to improve performance (Devinsky et al., 1995; Kim & Anderson, 2020; Walton et al., 2007), including the prefrontal cortex, ventral striatum and nucleus accumbens. In schizophrenia groups, decreased error-related activation has been identified in parts of the anterior cingulate cortex (Carter et al., 2001; Laurens et al., 2003; Polli et al., 2008), implicating poor behavioural adjustment post error processing.

The decision-making task from chapter 4 involved the introduction of a static and then escalating cost of sampling each item of information, and feedback after a decision was made of either varying positive points or negative points. In this context, a proportion of

feedback was positive and a proportion negative, both to varying salient and valuable degrees. This then requires the necessary ability to balance the weight of these positive and negative outcomes in order to integrate each representation and adjust decisions to maintain maximum reward. The anterior cingulate is extensively connected to the ventral striatum, including the nucleus accumbens, in which activation occurs and neurons discharge in relation to reward processing and positive reinforcement (Magno et al., 2009; Rogers et al., 2004; Schultz, 2016). However, changes in neuronal responsivity to such environmental cues as a cost or negative feedback and the accompanying affective dimensions of negative information processing may be guided more by the anterior cingulate cortex (Devinsky et al., 1995) and be unaffected by positive feedback considerations.

Functional MRI studies (Knutson et al., 2001; Spicer et al., 2007) have detailed differential patterns of activation across reward and punishment conditions and demonstrated the specific involvement of the anterior cingulate cortex together with the ventral striatum in self-initiated behavioural adjustment and not solely in punishment detection or prediction. This suggests that the anterior cingulate cortex does not itself directly regulate or modify behaviour, rather signals to interconnected regions, such as the cerebellum, the need to modify behaviour. The current results indicating reduced volume in the cingulate cortex may contribute to the inefficient detection of or value attribution to the cost of information and most interestingly to the inability to appropriately adjust behaviour by way of future decision-making.

5.4.2 Limitations

To maintain statistical power and retain the variability in psychosis symptoms, the current study did not split the MND cohort by phenotype, psychosis status or other cognitive or behavioural criteria. As defined by the ECAS psychosis carer-rating, the frequency of overt

psychosis in Tier 3 was low (6%). However, the variation of abnormal behaviour suggestive of from the CBI-R was greater. The majority of the current MND cohort did not show such behaviours, thus it is clear that the small number of affected patients may likely have driven the correlation with regional volume. Results are therefore interpreted with caution. The generalizability of future studies will be more valuable if larger numbers of patients experiencing psychosis symptoms are obtained. Additionally, the heterogeneity within this continuous MND cohort is largely acknowledged, as is the evidence in the literature that points to distinct differences in cortical volume between limb versus bulbar phenotypes (van der Burgh et al., 2020), between those categorised by cognitive status (Christidi et al., 2018; Consonni et al., 2018; Rajagopalan & Pioro, 2014) and gene status (Bede et al., 2013; Omer et al., 2017). However, comparatively, other cross-sectional imaging studies have similarly considered abnormal cognition and behaviour as one continuous group (Agosta et al., 2016; Rajagopalan & Pioro, 2014).

A common limitation of imaging studies in MND, including the current study, pertain to selection bias whereby a cohort of able patients are recruited to undergo MRI scanning. This applies to patients in the current study who completed all 3 tiers. Limb onset predominated (86.67%) and the lack of representation from bulbar onset perhaps contributed to the low incidence of psychosis symptoms, as it has been documented that bulbar onset patients tend to have more cognitive and behavioural involvement (Abrahams et al., 1997b; Leigh et al., 2003). All attempts were made to collect the minimal MRI sequences on patients willing, able and safely able to enter the MRI scanner, even if this required the use of a hoist system and a shorter scanning time.

FreeSurfer parcellated volumes were the only regional metric investigated in the current grey matter analyses, however FreeSurfer allows for calculation of surface area, curvature and cortical thickness, the latter commonly reported in the MND literature (Agosta et al., 2016;

Bede,et al., 2013; Consonni et al., 2019; Schuster et al., 2014; van der Burgh et al., 2020) and would be complimentary to use in conjunction with volume.

Parcellating the frontal lobe into its subregions is important not only for detecting volume differences but also for examining the association between reduction in subregion volume and behavioural, cognitive and clinical deficits, given the striking importance of distinct frontal structures in cognition and behaviour. In the current study, the volume reductions in the orbitofrontal subregion may not have been sensitive enough to detect associations with the behavioural components from the psychosis indices, PCA, and cognitive measures, subtleties that may become more obvious with disease progression.

5.5 Conclusion

The grey matter alterations identified in the current MND group, together with their association with features suggestive of psychosis were qualitatively similar to volumetric abnormalities observed in other psychosis groups (at-risk/prodromal stage to chronic schizophrenia). The hippocampus and cingulate were strongly associated with features suggestive o psychosis emphasising the particular vulnerability of these regions to psychosis. The volumetric analyses here also identified cerebellar and prefrontal neural correlates for aberrant decision-making processes, specifically an inability to integrate negative feedback and effectively adapt behaviour. Future studies may be able to focus their interrogation of these regions when exploring the cognitive mechanisms involved in the emergence of psychosis symptoms across the FTD-MND continuum.

Chapter 6 Tier 3B: imaging – white matter

In the previous chapter I presented the structural grey matter changes associated with carer-rated behaviour suggestive of and the cognitive mechanism hypothesised to put patients at risk of psychosis. This chapter is primarily concerned with the investigation of white matter connecting the significant grey matter regions in MND using diffusion-weighted data and diffusion tensor imaging (DTI), specifically Tract-based Spatial Statistics (TBSS). Specifically, in this corollary analysis, the aim is to examine the white matter neural correlates of the psychosis index measures and the two components extracted from the PCA (patient and carer perspective) from chapter 3, and the decision-making task outcome measures from chapter 4. It is expected that the white matter pathways connecting the grey matter regions I identified in chapter 5 will be significant.

The primary aim was to identify distinct white matter correlates in MND participants that will differentially underlie carer-rated psychosis behaviour and aberrant decision-making processes, from chapters 3 and 4 respectively.

6.1 Introduction

Diffuse structural change in white matter tracts is recognised as a pathological characteristic of MND (Agosta et al., 2018; Müller et al., 2016) and primary psychosis conditions (Ellison-Wright & Bullmore, 2009; Kubicki et al., 2007). Consistent patterns or grey and white matter pathology are reported but white matter pathology often extends beyond regions of grey matter atrophy in both MND (Christidi, et al., 2018) and psychosis conditions such as schizophrenia (Kelly et al., 2018). In various prodromal, subthreshold and chronic psychosis groups, associations between white matter alterations and psychosis symptoms (Lener et

al., 2015; Skelly et al., 2008) and related aberrant cognitive processes have been identified (Faria et al., 2019; Pérez-Iglesias et al., 2010; Seitz et al., 2016) but not yet in MND. The following sections will first outline the major white matter involvement in MND; second, detail white matter correlates with specific psychosis symptoms, such as delusions and hallucinations; third, provide evidence for white matter correlates of decision-making processes from primary psychosis conditions. The introduction will finish with an outline of the DTI method used to interrogate white matter pathways in the current study.

6.1.1 White matter correlates in MND

As I have shown in the previous chapter, atrophy in key frontal, temporal and striatal regions were identified in the current MND group, thus it is expected that the white matter pathways connecting these regions will be abnormal. Hallmark white matter pathology in MND include the degeneration of the corticospinal tracts and corpus callosum (Agosta et al., 2007; Chapman et al., 2014; Christidi et al., 2018; Ciccarelli et al., 2009; Filippini et al., 2010; Gabel et al., 2020; Kasper et al., 2014; Kassubek et al., 2005; Sage et al., 2009; Thivard et al., 2007). The application of DTI has proven to be a highly sensitive instrument in detecting white matter alterations in extra-motor pathways, for example in bilateral superior and inferior longitudinal fasciculi, bilateral uncinate fasciculi (Agosta et al., 2007; Sarro et al., 2011) and the cingulum (Sarro et al., 2011).

Evidence from DTI studies has provided valuable insight into the role of frontotemporal white matter networks in the development of cognition and behaviour deficits in MND (Abe et al., 2004; Agosta et al., 2016; Pettit et al., 2013). Similar to grey matter involvement in MND, the white matter pathway involvement also depends on the behavioural and cognitive phenotype. For example, MND patients with executive dysfunction show white matter disruptions in frontal-striatal regions, including between the caudate and the medial

prefrontal cortex and lateral orbitofrontal cortex (Masuda et al., 2016). These frontal-striatal connections play an important role in associative learning and decision-making (Dalton et al., 2013; Krain et al., 2006; Masuda et al., 2016), both of which were impaired in the current MND sample as shown in chapter 4. Behaviourally, significant diffusion properties in the uncincate fasciculus have even been shown to be a predictor of broad neuropsychiatric behavioural involvement in MND (Agosta et al., 2016). The connections to the limbic system and terminations in the anterior temporal lobe and orbitofrontal regions (Catani & Thiebaut de Schotten, 2008) suggest the uncinate fasciculus may be particularly vulnerable in the development of neuropsychiatric symptoms, including psychosis, in some patients with MND.

Additionally, Von Der Heide et al. (2013) proposed that the bidirectional interaction of the uncinate fasciculus between the orbitofrontal and anterior temporal lobes may be instrumental in reward-punishment processing, such that the uncinate fasciculus allows reward-punishment based information to modulate temporal-based value representations. This may be relevant to the specific decision-making process that was abnormal in the current MND sample in chapter 4, which showed an insensitivity to negative feedback. Importantly, white matter damage to frontotemporal pathways in MND has been demonstrated in the absence of significant grey matter atrophy (Abrahams et al., 2005). As such, the early and progressive breakdown of white matter tracts that connect key cortical and subcortical areas in MND may likely be a critical factor in the specific decision-making impairments, and aberrant behaviours related to psychosis observed in the current MND group.

Unlike the hallmark features observed in MND, white matter alterations along the psychosis continuum are more widespread and varied. Overlapping with MND, frequent white matter abnormalities are outlined in section 1.6. That white matter alterations become more significant with increasing clinical evidence of discrete phases of psychosis illness may

provide insight into whether specific pathways are implicated in specific psychosis symptoms and cognitive mechanism underlying psychosis emergence. The next two sections review white matter associations of psychosis symptoms and to the hypothesised cognitive mechanism identified in chapter 4.

6.1.2 White matter correlates with psychosis symptoms

Hallucination and delusion severity are commonly correlated with reduced DTI properties in tracts connecting the frontal and temporal lobes (Lener et al., 2015; Skelly et al., 2008). For example suspiciousness and ideas of reference have been related to reduced DTI properties in the uncinate fasciculus (Nakamura et al., 2005). In high risk groups, DTI alterations in the white matter of the medial and superior temporal lobe is shown to be significantly related to severity of positive (hallucinations and delusions) and negative psychosis symptoms (Bloemen et al., 2010; Krakauer et al., 2017). This is consistent with previous association of grey matter atrophy of the medial temporal lobe with positive psychosis symptoms in at-risk psychosis groups (Allen et al., 2019).

Similarly, reductions in DTI properties in frontal lobe white matter, anterior cingulum and anterior corona radiata have been shown to negatively correlate with positive symptom severity in high risk and first episode psychosis groups (Parnanzone et al., 2017). The frontal regions involving the cingulum and corona radiata are a known area of conjunction for three long-range association fibre tracts that converge through this region: the anterior-thalamic radiation, inferior frontal-occipital and uncincate fasciculi (Catani et al., 2002). It is therefore expected that reduced white matter integrity in this conjunction will significantly impact projections to the frontal lobes from subcortical and temporal lobes which ultimately may underlie aberrant information processing and emerging psychosis symptoms.

6.1.3 White matter correlates of decision-making processes

Evidence that frontotemporal and frontal-striatal dysconnectivity play a crucial role in cognitive deficits involving executive functions in primary psychosis conditions has more commonly stemmed from structural or functional MRI approaches rather than diffusion-based analyses. However, a number of DTI studies have shown correlations with DTI properties in select white matter pathways connecting key regions involved in cognition and most relevantly in decision-making processes. For example poor performance monitoring has been correlated with DTI alterations in the uncinate fasciculus (Nakamura et al., 2005), anterior commissure (Choi et al., 2011) and frontal-striatal pathways connecting inferior frontal gyrus and striatum (Quan et al., 2013). The aforementioned pathways are implicated in the reward system (Haber & Behrens, 2014), the grey matter of which is known to be affected in schizophrenia (see reviews (Ellison-Wright & Bullmore, 2009; Levitt et al., 2010), and the white matter of which has been related to delusions and hallucinations (Bracht et al., 2014). Forming context-appropriate associations by appropriately responding to positive and negative feedback to then guide learning and update future decisions is heavily reliant on the efficient coordination and communication throughout the reward system. A breakdown in any of the reward circuitry connections is argued to underly fixed and false associations (delusions) (Kapur, 2003).

In summary, previous DTI evidence illustrates that even in individuals with subthreshold psychosis symptoms, alterations in white matter integrity have functional and cognitive implications and may underlie emergence or transition to overt psychosis. Together, there is evidence of altered frontal, limbic, striatal and cerebellar white matter structure and connectivity in individuals experiencing similar subthreshold psychosis symptoms to those observed in MND. Given the scope of frontal, limbic, striatal and cerebellar regions and connecting pathways are implicated in early psychosis and conversion to overt psychosis (Allen et al., 2019), it is difficult to attribute emergent subthreshold psychosis symptoms to

any specific region or pathway. However, most notably, evidence has strongly implicated changes in the white matter pathways of frontotemporal and frontal-striatal regions, that have been directly related to psychosis symptoms and action-outcome learning. In view of this literature reporting white matter changes in MND that have been informed by similar tracts implicated across the psychosis continuum, I tested the hypothesis that psychosis behaviour and aberrant decision-making processes will reflect degeneration of white matter tracts in the neural systems underlying psychosis symptoms and supporting decision-making.

6.1.4 Diffusion tensor imaging

The insights gained into the degeneration of multiple white matter motor and extra-motor neural networks in MND has largely been achieved by using diffusion tensor imaging (DTI). In contrast to techniques investigating the volumetric estimates, such as the one described in chapter 5, DTI allows for the non-invasive investigation of the integrity and organisation of white matter structures. DTI analysis is based on the concept that the displacement of water molecules (diffusion) within white matter differs depending on the type, integrity, architecture and the presence of barriers along the tissues (Soares et al., 2013). The diffusion of water within the tissues is altered by pathological changes such as demyelination, axonal damage, inflammation, oedema and ischemia. This displacement behaviour is then mathematically described with a diffusion tensor model to provide microstructural information about the orientation and quantitative anisotropy of the water molecules. White matter is considered to be directionally dependent or anisotropic, with preference for diffusion along tracts, while grey matter is less anisotropic and cerebral spinal fluid is unrestricted or isotropic (Jbabdi et al., 2015; Johansen-Berg & Rushworth, 2009). The diffusion tensor is typically summarized by properties such as fractional anisotropy (FA) mean diffusivity (MD), axial and radial

diffusivity, of which only FA and MD were processed and will be reported in the current chapter in line with previous DTI literature in neurodegenerative conditions also only reporting these metrics (Atkinson-clement et al., 2017; Brueggen et al., 2017; Lansdall et al., 2017; Lillo et al., 2012; Sage et al., 2009). FA refers to the directionality of the molecular diffusion within the tissue and is a composite derived from axial and radial diffusivity, and MD refers to the molecular diffusion rate. Intact white matter will restrict diffusion parallel to the main fibre direction, which leads to higher FA and lower MD, whereas damage to white matter will cause diffusivity to be less restricted, which leads to lower FA and higher MD (Basser et al., 1994).

6.2 Methods

6.2.1 Tier 3 participants

Table 3 (chapter 3, page 113) outlines the demographic and disease characteristics for the subset of MND (*N*=30) and healthy control (*N*=20) participants included in Tier 3. Summarised details on demographics, disease characteristics, psychiatric behaviour and cognition are provided in chapter 5 (section 5.2.1 Tier 3 Participants, page 205).

6.2.2 Diffusion data processing

Diffusion data processing used automated scripts that called on FMRIB Software Library (FSL) diffusion toolbox (version 5.0.9; www.fmrib.ox.ac.uk/fsl) outlined in chapter 2 (page 98).

6.2.3 Diffusion data analysis – tract-based spatial statistics

The analysis employed a voxel-wise general linear group comparison, specifically Tract-based spatial statistics (TBSS) (Smith et al., 2006) of fractional anisotropy and mean diffusivity to identify white matter correlates of psychosis and specific cognitive outcome measures of decision-making and cost insensitivity. Correlations between the mean skeleton DTI tracts and psychosis and cognitive measures of decision-making and cost insensitivity were assessed by nonparametric permutation analysis using the standard FSL TBSS *randomise_parallel* script. As it is not feasible to evaluate every possible permutation, the current study applied 10,000 permutations, deemed a large enough number to reduce the margin-of-error to below 10% of the nominal alpha (CI 0.0500 ± 0.0044). The suggested defaults in the standard FSL *tbss_4_prestats* for *randomise_parallel* were used, including 2D optimisation. Results were reported with the significance threshold of $p<0.05$ after correction for multiple comparisons with the Family Wise Error (FWE) correction, using the threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009) for consistency with most related literature.

The 4D skeletonised FA and MD volumes were statistically tested via voxel-wise general linear model design matrices. The statistical design matrices contained a constant term to model the intercept (of group) with age and disease severity (FTD-FRS) as covariates of no interest. FTD-FRS, rather than ALS-FRS-R, was included due to significant correlations with the behavioural and cognitive measures (chapter 3 and 4) and to control for the generic cognitive and behavioural aspects of the disease continuum, therefore rendering more focused results. For completeness, appendices D and F show the results with ALS-FRS-R and CBI-R psychosis and increased cost sensitivity respectively. For the matrix and contrast involving the PCA components, I decided to include the ALS-FRS-R to control for disease severity. It was deemed more appropriate than the FTD-FRS in this instance due to the substantial overlap of general cognitive and behaviour aspects captured in the FTD-FRS and

the questionnaires imputed into the PCA (chapter 3 page 135). I wanted to capture the white matter associations with broader psychiatric behaviour, rather than cancel them out.

Continuing with covariates of no interest, where total intracranial volume is often considered to contribute to statistical variance, it did not have an effect on the models and so was not included as a covariate in the final models. Separate matrices and contrasts were formulated for disease severity, the two psychosis indices, the two PCA components (within-group analysis only) and the decision-making computer task outcome measures (JTC, cost sensitivity and increasing cost sensitivity) splitting the covariates to investigate group interactions. Within-group analyses did not split the covariates. Covariates of interest in the models were mean-centred across the whole sample (i.e. not within groups) to control for any variation in the model that could be explained by these covariates. If, for example, age was mean-centred within each group, then each group's set of ages would have been centred around the same value of 0, which may have led to a risk of detecting group differences that were merely attributable to age. White matter was labelled using the JHU (John Hopkins University) white matter tractography atlas. Significant skeleton voxels were overlaid onto the MNI152 T1 template to allow anatomical localisation by visual inspection.

Whole-brain voxel-based TBSS was applied instead of a region of interest approach, first because this method makes it possible to study multiple brain regions at the same time. Second, TBSS addresses issues of smoothing and realignment in group analyses (Smith et al., 2006), which increases statistical power by reducing the number of voxels tested. Third, TBSS is far less likely than a region of interest approach to result in Type II errors (false negatives).

6.3 Results

Tract-based spatial statistics identified significant changes in white matter integrity (FA and MD maps) in relation to the CBI-R psychosis index score and the outcome measures of the decision-making task but not the PCA components. No FA increases or MD decreases were identified in the MND group compared to controls.

6.3.1 MND versus controls on FA and MD

Initial voxel-wise group comparisons that included age as a covariate of no interest, revealed a group interaction for two clusters in mean FA for the contrast MND FA < control FA. Significant clusters involved typically affected tracts in MND, including bilateral corticospinal tracts, corpus callosum and internal capsule. Cluster 1 contained 11,828 voxels with the highest intensity voxel located in the corticospinal tract (bilaterally) extending from the precentral gyrus to superior of the corona radiata (t=4.39, TFCE p<0.05) (Figure 32). A second cluster contained 33 voxels and is included in appendix B. There were no significant between-group clusters for the MD maps.

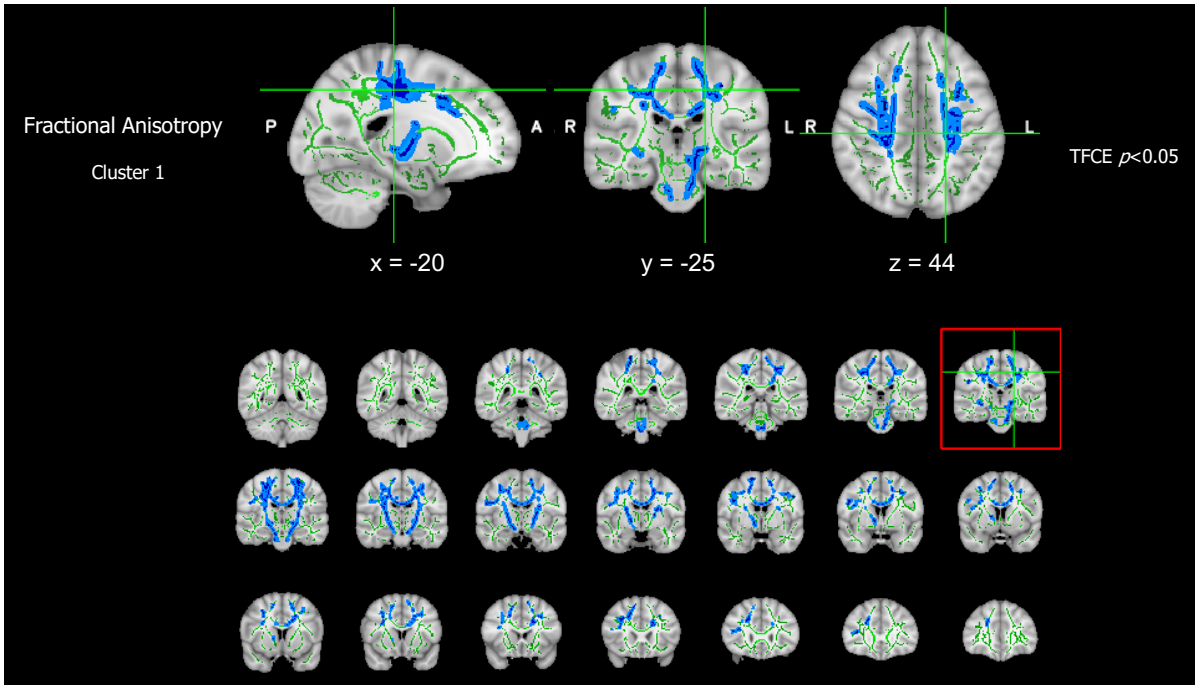

Figure 32: White matter correlates of disease in MND. Decrease in fractional anisotropy (FA, "fattened" skeleton results for MND compared to controls (in light blue with corrected *p*-value in dark blue, TFCE *p*<0.05). Crosshairs indicate highest intensity voxel and anatomical location given in MNI coordinates. Results overlaid on the mean FA skeleton (green) and MNI152 T1 template (grey). P=posterior, A=anterior, R=right, L=left.

6.3.2 MND versus controls on FA and MD with psychosis indices

Voxel-wise group comparison that included the two psychosis index scores (CBI-R psychosis and NPI psychosis) as covariates of interest in separate matrices revealed an increase in MD for CBI-R psychosis index in the MND group along specific tracts. This was a within-group contrast. Three clusters in MD contained between 41 and 2,551 voxels with TFCE $p<0.05$. All three clusters showed the highest intensity along the inferior longitudinal fasciculi and uncinate fasciculi of the bilateral anterior temporal cortex and temporal pole (cluster 1: 2,551 voxels, $t=7.29$, TFCE $p<0.05$; cluster 2: 114 voxels, $t=9.56$, TFCE $p<0.05$; cluster 3: 41 voxels, $t=6.98$, TFCE $p<0.05$) (Figure 33). See appendix C for axial multi-slice images for each of the three significant MD clusters with CBI-R psychosis index score

presented in Figure 33. No significant interactions with the control group were revealed. No significant decreases in FA were revealed. No significant clusters associated with the NPI psychosis index were revealed for the FA or MD maps.

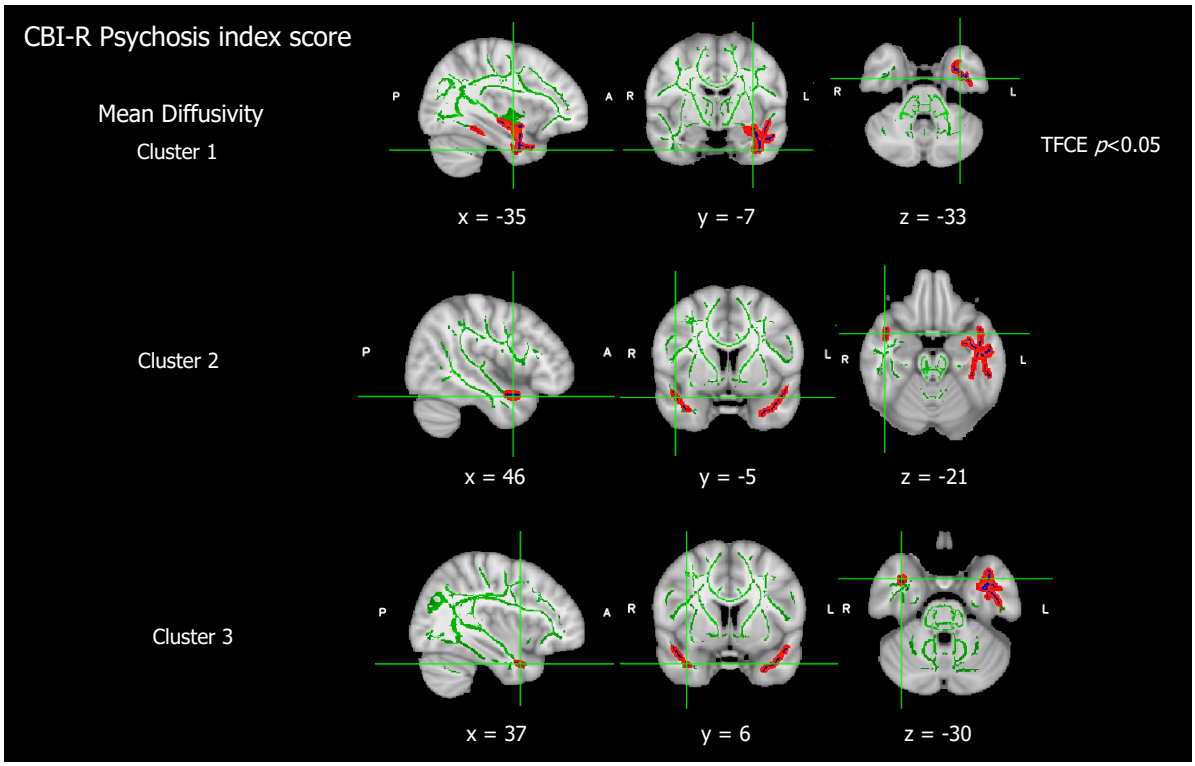

Figure 33: White matter correlates of psychosis in MND. Increase in mean diffusivity in 3 clusters with CBI-R psychosis index score ("fattened" skeleton results for MND but not controls in red with corrected *p*-value in dark blue, TFCE *p*<0.05). Crosshairs indicate highest intensity voxel and anatomical location given in MNI coordinates. Results overlaid on the mean FA skeleton (green) and MNI152 T1 template (grey). P=posterior, A=anterior, R=right, L=left.

6.3.3 MND versus controls on FA and MD with decision-making outcomes

Given the interactions of group x draws to decision and cost sensitivity scores from Tier 2 analyses of the decision-making task (refer to chapter 4, Figure 20, page 175), it was hypothesised that this would be reflected in differences in white matter changes between

MND patients and controls. Two separate models were devised: one with JTC, the other with both overall cost sensitivity and increasing cost sensitivity scores.

In the cost sensitivity matrix, there was a main effect of task, which indicated widespread reduced FA with performance during the increased cost manipulation of the task for both MND and controls in two large clusters. There was no difference between these groups. Within-group contrasts for MND and controls revealed the same significant correlation. Cluster 1 revealed a clear frontal, frontal-striatal emphasis (16,183 voxels, t=3.11, TFCE p<0.05) involving the white matter tracts deep to the cingulate, orbitofrontal cortex and extending into the striatum, including the forceps minor and uncinate fasciculi (Figure 34). Cluster 2 was more inferior (2,271 voxels, t=5.22, TFCE p<0.05) and included frontal and subcortical regions, extending on the right side to the tracts deep to the temporal-parietal junction (Figure 34). See appendix E for axial multi-slice images for the two significant FA clusters with increasing cost sensitivity score presented in Figure 34. There were no significant clusters in the MD maps with overall cost sensitivity scores, and no significant clusters in FA or MD with the JTC score.

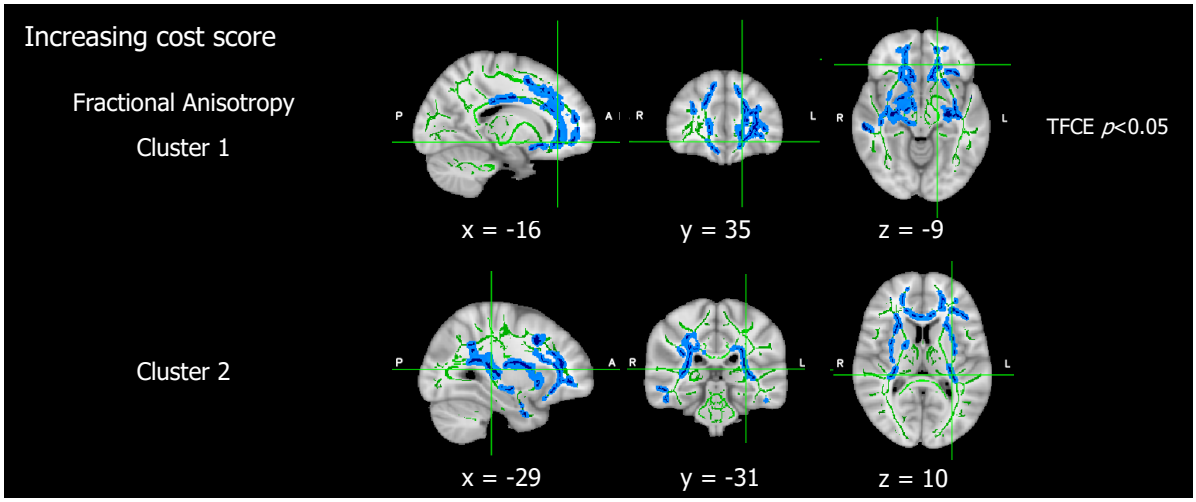

Figure 34: White matter correlates of cost sensitivity in MND. Decrease in fractional anisotropy for MND and controls (in light blue with corrected p-value in dark blue, TFCE p<0.05). Crosshairs indicate highest intensity voxel and anatomical location given in MNI coordinates. Results overlaid on the mean FA skeleton (green) and MNI152 T1 template (grey). P=posterior, A=anterior, R=right, L=left.

6.4 Discussion

In this chapter, carer-rated psychosis symptoms and cognitive alterations that inform the emergence of psychosis symptoms were investigated to determine their relationship with white matter microstructural integrity as measured by DTI properties using TBSS. The whole brain analyses extend previous work by providing evidence of distinct structural network changes in white matter *associated with psychosis symptoms* and *vulnerability to psychosis* by way of poor decision-making processes in MND. The significant white matter changes relating to psychosis and aberrant decision-making processes corroborate the significant frontotemporal grey matter atrophy identified in chapter 5, in terms of changes in FA or MD in pathways underlying the grey matter atrophy.

The current analyses are largely confirmatory with previous DTI studies in MND applying TBSS (Agosta et al., 2016; Kasper et al., 2014; Lillo et al., 2012; Menke et al., 2016; Sarro et al., 2011; Trojsi et al., 2015). These have shown MND-related white matter changes in the corticospinal tracts, bilaterally. Specifically, a decrease in FA was identified in a region where the corticospinal tract and corona radiata overlap, near the precentral gyrus. The current results demonstrated significant differences in MND from healthy controls in global cognition as well as cognitive sub-domains on the ECAS, however, abnormalities in the corticospinal tracts in MND groups without cognitive impairment have also been demonstrated (Kasper et al., 2014). Thus, reflecting the hypothesis that corticospinal tracts alone likely play an important role in subserving cognitive and behavioural alterations in MND in addition to impacting motor abilities.

Additionally, analyses did not reveal any significant correlations between DTI properties and disease severity as measured by the ALS-FRS-R total score or FTD-FRS logit-percentage conversion score, a result consistent with similar studies (Ciccarelli et al., 2009; Iwata et al., 2008; Menke et al., 2014b) yet contrasting with other DTI studies that have noted a positive

correlation between FA and total ALS-FRS-R (Sage et al., 2009; Trojsi et al., 2015). Regarding the primary psychosis literature, positive and negative symptom severity is not consistently related to reductions in FA in established schizophrenia (Kelly et al., 2018) or early psychosis (Samartzis et al., 2014) although negative relationships have been observed in the corpus callosum, internal capsule and thalamic radiation (Kelly et al., 2018; Rosenberger et al., 2012; Whitford et al., 2010). The inconsistent reports on the correlation of DTI parameters with disease severity in MND reflect such explanations as different methodologies and approaches used to evaluate correlations but also the heterogeneity of MND groups on disease characteristics such as functional severity (e.g. Verstraete et al., 2015). The individuals with MND who were well enough to participate in Tier 3 of the current study did not show large variation in their disease severity (Table 3, chapter 3), potentially reflecting a selection bias that is not uncommon in multi-investigation studies involving extended brain scanning and subsequent smaller sample sizes. Now to the results relating to psychosis symptoms and informative decision-making alterations.

6.4.1 White matter correlates of psychosis and cost sensitivity

6.4.1.1 Correlations with psychosis

Abnormalities in white matter tracts have not specifically been related to psychosis in MND before, although this approach has been taken to other psychiatric symptoms such as apathy (e.g. Femiano et al., 2018; Tsujimoto et al., 2011). Similarly, no studies including DTI analyses in bvFTD or FTD-MND have specifically investigated associations with psychosis symptoms, which is surprising given the prevalence of such symptoms especially at the behavioural variant end of the FTD-MND continuum. In the current results, white matter correlates of the CBI-R psychosis index were shown in white matter tracts connecting the occipital-temporal and frontotemporal regions of the brain. Specifically, increased MD in the

white matter connecting the temporal pole, including along the inferior longitudinal and uncinate fasciculi bilaterally, both of which are key association pathways that extend beyond the motor tracts, connecting intra-hemispheric frontotemporal and frontoparietal regions. The inferior longitudinal fasciculus is a ventral bundle with long and short fibres connecting the occipital and temporal lobes. The uncinate fasciculus is also a ventral bundle that connect parts of the limbic system with parts of the frontal lobe (medial and lateral orbitofrontal cortex) (Catani et al., 2002).

The highest voxel intensity was located in the temporal pole, in which the amygdala and hippocampus are strongly connected to the frontal lobe, and to sensory perceptual systems (Catani & Thiebaut de Schotten, 2008). Compromised integrity along these tracts is unsurprising given the frontal, temporal and occipital grey matter reductions from chapter 5, thus it is reasonable to assume that abnormalities in these cortical-cortical association pathways may contribute to the behaviour symptoms in MND. While regional atrophy was not identified in the orbitofrontal cortex or anterior temporal lobe in the current MND sample, changes in white matter pathways have been shown to be present in the absence of corresponding grey matter involvement, using other methods, such as PET combined with structural MRI, for example Abrahams et al. (2005) showed abnormalities in commissural and association fibres despite insignificant grey matter volume reduction.

The abnormalities of white matter tracts associated with features suggestive of psychosis (CBI-R psychosis index) in the current MND group (Figure 33, page 239), are consistent with previous DTI studies that have identified decreased FA and/or increased MD in both the inferior longitudinal and uncincate fasciculi in early psychosis and at-risk individuals (Alvarado-Alanis et al., 2015; Carletti et al., 2012; Von Hohenberg et al., 2014; Cooper et al., 2018; Hatton et al., 2014; Luck et al., 2011; Vijayakumar et al., 2016) and in schizophrenia (Lener et al., 2015; Liu et al., 2013; Phillips et al., 2009; Seitz et al., 2016; Tønnesen et al., 2018). The presence of compromised white matter structure at various stages along the

psychosis continuum emphasises that these changes are apparent in the prodromal and early stages of psychosis emergence and likely increase with disease chronicity. Tract-based deficits in these two association pathways have also been strongly correlated with positive and negative symptom severity in at-risk psychosis groups and primary psychosis conditions. For example, reduced FA in the uncinate fasciculus with positive (Bopp et al., 2017; Nakamura et al., 2005) and negative (Luck et al., 2011) symptom severity, and in the inferior longitudinal fasciculus with disordered thought (Phillips et al., 2009; Schmidt et al., 2015).

In line with the hypothesis that schizophrenia is characterised by disconnection (Friston & Frith, 1995), there are reports of focal white matter lesions in relation to psychosis symptoms and increasing evidence of diffuse white matter involvement. Early reports, emphasise white matter hyperintensities in the frontal cortex in late life psychosis and schizophrenia (Miller et al., 1989; Persaud et al., 1997), whereas other reports do not (Sachdev & Brodaty, 1999), and later, reports of diffuse white matter disease that present with psychosis, such as leukodystrophies, demyelinating and inflammatory diseases, illustrate disrupted frontotemporal white matter connections (Walterfang et al., 2005). This diffuse evidence strongly supports the potential contribution of disruptions to white matter connecting key frontotemporal regions in the pathogenesis of psychosis symptoms. The current results are consistent with white matter involvement most strongly related to psychosis symptoms in the temporal regions more than the frontal regions, however the frontal regions may indirectly be compromised due to affected association tracts in which increased MD have been observed in the current MND sample.

Consistent with the lack of grey matter correlates with neither the patients' nor carers' perspective of patient neuropsychiatric behaviour (PCA components 1 and 2), no white matter tract abnormalities were identified in association with these two perspectives. The divergent perspectives on patient behaviour reflects different insight, however in the absence

of a neural correlate with both perspectives there are a number of possible explanations for this. First, patient and carer ratings may reflect heterogenous, multifocal changes in grey and white matter, which prevent the identification of any consistently localised atrophy or tract correlate. Second, volume analysis and DTI assess fundamentally distinct neural changes (tissue volumetric loss versus the diffusional integrity of white matter connections, respectively), neither of which may be sufficiently sensitive to detect broad behaviour categories but are for specific behaviours. The potential limitations to tract-based methods and interpretation of DTI are discussed below.

6.4.1.2 Correlations with cost sensitivity

White matter correlates with cost sensitivity represented a distinct frontal-striatal pattern, extending to temporal and temporal-parietal junction, identified in both MND and controls. The association found in controls is unclear but may reflect the converging draws to decision between MND and controls in the later stages of the task. Alternatively, following the introduction of increasing cost to sampling information, the steeper adjustment in behaviour may be interpreted as cognitively more effortful. With increasing effort to adjust behaviour in response to negative feedback, there is greater reliance on integrity and coordination of frontal-subcortical pathways. These structures and pathways may already be vulnerable due to degeneration consistent with natural ageing and the association may be more detectible in white matter rather than grey matter in health and disease.

In chapter 5 atrophy in the cingulate was strongly associated with insensitivity to cost of information sampling prior to making a decision in the MND group but not in controls (Figure 31, page 215), which suitably compliments the current white matter association with cost sensitivity in the MND group. That the current tract-based statistics indicated white matter abnormalities in pathways that traverse the anterior cingulate in association with the cost

sensitivity score, suggests not only a direct break down of the cingulate (as indicated in chapter 5) but of its interconnected circuits, particularly in the anterior portion (as indicated in the current chapter). As discussed in chapter 5, functional MRI studies in healthy adults (Kerns, 2006; Kerns et al., 2004; Rogers et al., 2004) have detailed differential patterns of cingulate activation across positive and negative conditions on various cognitive tasks, including trial-by-trial tasks not unlike the current task. These previous studies have demonstrated the specific involvement of the anterior cingulate cortex together with prefrontal cortex in self-initiated and aversive-response behavioural adjustment rather than its unique involvement in negative stimulus detection or prediction. This suggests that the anterior cingulate cortex does not itself directly regulate or modify behaviour, rather signals to interconnected regions, such as the prefrontal cortex, the need to adjust behaviour and improve performance.

Lesion studies in humans (Di Pellegrino et al., 2007; Sheth et al., 2012) and primates (Mansouri et al., 2007) have demonstrated that appropriate behavioural adjustment disappears after precise removal of anterior cingulate (in humans) and dorsal lateral prefrontal cortex (in primates) impeding the necessary signal to other regions. White matter pathways connecting the anterior cingulate region to other key regions involved in behaviour modification primarily include the cingulum in which the short fibres connect the medial frontal gyrus, fusiform gyrus, and parietal lobe (Catani et al., 2002) and ventromedial and dorsolateral frontal-striatal pathways. Compromised integrity in such association pathways between key cortical and subcortical regions that modulate behaviour regulation and performance monitoring may be reflected to some extent in the current association of reduced FA with poor behaviour adaptation to cost of information in the MND group, however it is acknowledged that the result was also significant for the current control group. The current results are consistent with compromised cingulate white matter integrity and associated frontal-striatal white matter tract degeneration previously identified along the

FTD-MND continuum (Christidi et al., 2018; Lillo et al., 2012; Masuda et al., 2016; Rabinovici et al., 2008; Seeley et al., 2008) and are qualitatively similar to findings in schizophrenia.

Specific behaviours and cognitive impairments in patients with MND have been studied regionally in relation to DTI metrics, linking challenging behaviours, attention and executive dysfunction to the white matter association tracts showing associations with FA and MD metrics, including the cingulum, uncinate fasciculus, inferior longitudinal, inferior frontal-occipital, and the corticospinal tract (Sarro et al., 2011). The current results implicating these pathways are broadly consistent with volumetric studies of MND that suggest a breakdown of key circuits for aspects of decision-making (Menke et al., 2014a) and neuropsychiatric behaviours (e.g. Cerami et al., 2014; Consonni et al., 2019; Mioshi et al., 2013). The distinct frontotemporal and frontal-striatal nature of the white matter involvement supports the concept of network-based disruption in MND (Douaud et al., 2011; Kato et al., 1993; Turner et al., 2012) a concept also characteristic in psychosis (Friston & Frith, 1995). Future research with larger samples of MND patients with psychosis symptoms may distinguish patients from controls in identifying disruption to neural circuits for sensory integration and for negative feedback processing, and account for their clinical existence in MND.

6.4.2 Limitations

There are several limitations to the imaging method applied in the current chapter, caveats of behavioural methods are discussed in chapter 4's discussion. DTI is limited in its indirect measurement of the physical properties of white matter connections, for example axon density, calibre and myelination (Jbabdi et al., 2015). The voxel-based whole brain methodology used in the current study does not allow for the direct identification of fibre tracts and so the implication of the tracts in the current results remains tentative. Despite

this, DTI provides *in vivo*, semi-quantitative measures that provide anatomical insights into the human brain in health and disease, which are commonly cross-validated in pre-clinical animal models. For example, preclinical studies have linked FA to myelination, membrane permeability and fibre density in white matter (Beaulieu, 2002; Song et al., 2002, 2003). Ultimately, post-mortem MRI and histopathology studies comparing diffusion and other structural imaging properties may shed more light on the pathological mechanisms of the various observed imaging changes. Linking DTI properties to specific motor neuropathies is challenging despite evidence of different DTI properties reflecting distinct processes (for example demyelination, neurodegeneration, gliosis, calcification and axonal degeneration, all of which are involved in the degeneration of motor neurons).

MRI data acquisition is noisy. Careful consideration of artefacts from motion and registration errors should be evaluated, given multiple directional measurements are obtained at each voxel, which introduces false-positive differences especially if movement differs by phenotype (Pardoe et al., 2016).

In a white matter predominant condition in combination with extensive motor and extra-motor grey matter involvement, such as MND, registration also creates significant challenges for analysing a disease group that may have highly atrophic brains in many cases, obscuring some tracts. Errors resulting from registration have cause to affect the absolute diffusivities or eigenvalues, mimicking the effects of pathology (Zhang et al., 2013). Estimated change in FA may reflect differences in the relative amount of tissue type rather than change in white matter (Smith et al., 2006), especially since TBSS restricts analyses to the central part of the white matter tracts (the “skeleton”), therefore if white matter abnormalities have occurred in areas with extensive grey matter change or peripheral areas these changes might be overlooked.

6.5 Conclusion

White matter tracts are abnormal in MND. Diffusion tensor imaging is highly sensitive to the microstructural white matter changes associated with psychosis symptoms and suboptimal aspects of decision-making. This suggests that white matter tract degeneration may underlie aberrant cognitive processes and behaviour that reflect a risk state of vulnerability to psychosis. Reflective of the concept that psychosis disorders are syndromes of disconnection (Friston & Frith, 1995), the current DTI results support that features suggestive of psychosis in MND may be due to compromised integrity and disconnection in key frontotemporal and frontal-striatal pathways.

Chapter 7 General Discussion

This thesis provides insight into the cognitive and neural mechanisms related to carer-reported symptoms suggestive of psychosis in MND. Previous work had predominantly focused on the FTD end of the FTD-MND continuum and psychosis in those with comorbid FTD-MND, including C9*orf*72 carriers.

The results inform the understanding of behaviours suggestive of psychosis and abnormalities in cognitive mechanisms associated with structural change that accord with my hypothesis about the emergence of psychosis. Even though clinically overt psychosis was rare in the current MND group, many showed pre-psychosis features, which includes symptomatology and behaviour that fall short of clinical criteria for a primary psychosis condition, or cognitive mechanisms which have been associate with the emergence of psychosis. To know whether the identified cognitive and neural mechanisms predict psychosis in MND would require further longitudinal studies.

The breadth and depth of neuropsychiatric symptoms in MND and its phenotypes is broad. This is reflected in the 2017 revision of the Strong 2009 criteria for the diagnosis of frontotemporal dysfunction in MND (Strong et al., 2009, 2017), in which psychosis symptoms (together with abnormal behaviours) maintain a prominent criteria. The 2009 criteria were revised to recognise the presence of neuropsychiatric manifestations in MND. Yet, the presence of psychosis symptoms in patients with MND, has been under reported. In the current MND cohort, the presence of carer-reported psychosis symptoms is lower at 10% than patients further towards FTD in the FTD-MND continuum and especially with C9*orf*72. However, their presence warrants attention beyond describing the nature of delusions and hallucinations. More thorough investigation of psychosis and mechanisms related to psychosis should be applied in FTD and FTD-MND.

This thesis has adopted a new approach to investigate the mechanisms that may contribute to the emergence of psychosis in MND, based on cognitive paradigms and neuroimaging. These structural changes are only part of the story. The analyses used in the current thesis have not sought to identify the neurochemical or genetic factors relating to psychosis and underlying cognitive mechanisms. This perspective could similarly be applied to patients with FTD and FTD-MND. I do not assume homology of psychosis in MND and in primary psychosis disorders. However, to interpret the results from MND, I do draw on findings from other psychosis studies whereby some have resolution of psychosis symptoms and some experience persistent subclinical non-psychosis conditions. Findings from these groups have provided valuable insight, drawn from the primary psychosis literature, pertaining to the development of psychosis symptoms, thus comparisons with the current findings have allowed for cognitive and neural mechanisms not otherwise explored in MND from this perspective.

The cognitive and neural correlates of symptoms and abnormal behaviours suggestive of psychosis in MND reported in this thesis extend the current literature. The psychosis *symptoms* are similar in MND, behavioural variant FTD and FTD-MND literature albeit with different *prevalence*. The grey matter correlates of psychosis symptoms and related abnormal behaviours demonstrate focused frontotemporal regional involvement compared to non-specific and widespread involvement found in a similar previous study comparing FTD-MND C9*orf*72 carriers versus non-carriers (Devenney et al., 2017). Overall, the current neural correlates are new findings to MND and largely extend the behaviour variant FTD and FTD-MND literature. Finally, the current cognitive and neural correlates related to psychosis are largely concordant with the early psychosis literature.

This thesis reports four critical findings specific to MND, in relation to the initial hypotheses:

1) The presence of overt psychosis symptoms was not a common feature, but broader neuropsychiatric symptoms were common and were predictive of psychosis status.

2) Decision-making processes that underly the emergence of psychosis were impaired in MND and related to features suggestive of psychosis, whereas the cognitive mechanisms of attentional control and perceptual inference remained intact.

3) Symptoms and behaviours suggestive of psychosis reflected regionally specific changes in cerebral grey and white matter.

4) Pre-psychosis cognitive mechanisms (insensitivity to negative feedback) reflected changes in cerebral grey and white matter.

7.1 Commonality of psychosis symptoms in MND

In chapter 3 my aim was to provide insight into the physical, demographic, psychiatric, behavioural and cognitive profile of the current MND cohort, and to establish the prevalence of overt and sub-threshold psychosis symptoms. Previous investigations of psychosis across the FTD-MND continuum have lacked the inclusion of sporadic MND participants.

There is variability in the FTD-MND literature on reported psychosis symptoms and the current commonality reported in this thesis is similar. The frequency of carer-reported psychosis symptoms (Tier 2 = 10.7%, Tier 3 = 5.3%) in the current main testing sample of apparently sporadic MND patients was slightly higher than rates described in similar previous cross-sectional studies (<2 – 5%) (Abrahams et al., 2014; Crockford et al., 2018; Lillo et al., 2011) and population-based studies (<2%) (McHutchison et al., 2019). In comparison to studies of FTD-MND patients, current psychosis frequency was consistent

with some studies based on FTD-MND and/or C9*orf*72 patients (Sha et al., 2012), whereas other FTD-MND cohorts showed rates unsurprisingly above the current MND cohort ranging from 14 – 38% (Chiò et al., 2012; Devenney et al., 2017a, 2019; Saxon et al., 2017; Snowden et al., 2012; Takada & Sha, 2012), likely due to the overlapping diagnosis of FTD. Conversely, some FTD-MND studies report a far lower incidence of less than 5% (Mahoney et al., 2012; Simón-Sánchez et al., 2012), further highlighting the variability in reported psychosis symptoms throughout the FTD-MND literature. These rates will become more focused and consistent if future research includes psychosis symptoms when reporting neuropsychiatric behaviours.

High variability of psychosis symptoms was evident in the current MND group and likely due first to the difference in measures used to identify such features, for example gold standard neuropsychiatric inventories and interviews versus carer reports. Second, the subjective nature of psychosis symptoms means they are especially prone to high inter-individual variability. The extrapolation of such complex symptoms is heavily reliant on carer reports. The component representing carer's perspective of patient behaviour from the PCA correctly predicted patients' psychosis status. This indicated consistency in carers' appraisals of behaviours and accuracy in their insight and ability to identify features suggestive of psychosis behaviour, emphasising the clinical importance of obtaining corroborative descriptions from someone who knows the patient well. The observation that overt psychosis symptoms are present at the MND end of the FTD-MND continuum has clinical and research implications. Clinically, the presence of such symptoms warrants attention and should not be overlooked, despite their lower frequency, given their impact on patient decisional autonomy, adherence to treatment and carer stress. Indeed, some MND patients may be showing additional FTD features and/or be C9*orf*72 positive. With this in mind, clinical studies attempting to treat problematic behaviour change may benefit from stratifying groups based on the presence and severity of psychosis symptoms, rather than the

diagnostic labels across the FTD-MND continuum. Documenting and assessing psychosis symptoms only in disease groups where such symptoms are prevalent, will contribute to similar emergences in MND being overlooked. Additionally, further attention should be paid to descriptions of the psychosis experience from the patient as well as carer-reported presence of psychosis behaviour.

7.2 Suboptimal decision-making processes correlate with psychosis in MND

Chapter 4 set out to build on the identification of psychosis symptoms from chapter 3 to establish underlying pre-psychosis cognitive processes based on evidence from early psychosis groups who exhibit similar subthreshold symptoms to the current MND cohort. Three neurocognitive paradigms that have previously detected and informed the emergence of psychosis symptoms in early primary psychosis conditions were applied: 1. decision-making (jumping to conclusions and adaptive behaviour), 2. attentional control, and 3. perceptual inference (top-down, bottom-up information processing imbalance). Impairment in any one of these three cognitive processes would have informed the development of specific psychosis symptoms, such as delusions and visual perceptual inference, or reflect a higher order attentional complexity, as observed in prodromal psychosis and chronic schizophrenia. This cognitive perspective advances previous investigations of psychosis symptoms in FTD-MND by including novel methods to explore the cognitive underpinnings of psychosis emergence, rather than documenting their frequency and severity.

Of the three neurocognitive processes, suboptimal decision-making processes were identified in MND. First, MND participants were more willing to make a decision based on inadequate information and this was related to psychosis-specific behaviour and broader neuropsychiatric behaviour. The association of this decision-making style with reported

symptoms and behaviours related to psychosis, supported the hypothesis that aberrant cognitive mechanisms may underlie a proneness to psychosis inference. Second, patients demonstrated a striking insensitivity to the cost of information sampling compared to controls. These results are similar to early psychosis groups who also display abnormalities in reasoning and are related to psychosis symptoms (Broome et al., 2007; Ermakova et al., 2019; Fine et al., 2007; Langdon et al., 2014). The inferential impulsive decision-making style together with an insensitivity to negative feedback identified in MND has clinical implications. The coexistence of such a combination of aberrant behaviours and cognitive vulnerabilities may exacerbate patients' proneness to developing delusional ideation. Consequently, compromising their judgements and ability to integrate feedback to make appropriate decisions not only about their care but also their quality of life and dying with dignity. Early assessment of behavioural and cognitive change with a focus on decisional processes and aberrant behaviours beyond a psychological response to the diagnosis will support and ensure patient autonomy.

7.3 Grey and white matter correlates of psychosis and vulnerable cognitive state

In chapters 5 and 6, the grey and white matter neural correlates of the established cognitive mechanism and identification of overt psychosis and broader neuropsychiatric behaviour were explored with key regions of interest followed by exploratory regions. Previous investigations of psychosis symptoms in FTD-MND and relating to C9*orf*72 (Devenney et al., 2017b; Sellami et al., 2018) have identified widespread regional involvement relating to psychosis symptoms. I took a focused *a priori* region of interest approach, drawing on circumscribed functional anatomy of the hypothesised cognitive mechanisms, together with abnormal behaviour suggestive of psychosis overlapping in MND and primary psychosis

phenotypes. Symptoms and behaviours suggestive of psychosis reflected atrophic changes in distinct frontotemporal structures (hippocampus and cingulate) and white matter changes in pathways connecting the temporal lobe to frontal and occipital regions (uncinate and inferior longitudinal fasciculi), discussed in the relevant chapters. The neural correlates were broadly concordant with the primary psychosis literature reporting the neurobiology of psychosis symptoms, discussed in chapters 5 and 6, which emphasise the importance of cortical-subcortical networks, including frontal-striatal loops and their grey matter targets and white matter connections. The lack of grey and white matter correlates of carer and patient perspectives of patient neuropsychiatric behaviour may be due to the heterogeneous array of neuropsychiatric behaviours these components captured. Alternatively, neural correlates of such behaviours may be multi-focal and currently undetectable at this stage of illness progression or with the volume parcellation and DTI methods used. The objective cognitive task correlated with more focal, task-specific brain regions on both volume parcellation and DTI, together reflecting frontal-striatal, frontotemporal and cerebellar decision-making regions involved in negative feedback processing and adaptive behaviour. A key validation for the methods adopted in this study was the observation that my similarly calculated psychosis index score to Devenney et al. (2017) correlated with atrophy in the cingulate and hippocampus, which is consistent with their findings in the cingulate and the middle temporal lobe of FTD-MND patients.

7.4 Treatment of psychosis and supporting psychiatric wellbeing

This thesis has focused on delineating the cognitive and neural mechanisms by which psychosis symptoms may emerge in MND in order to better understand the wider at-risk population and support patients' psychiatric well-being. Few studies have recommended the

use of anti-psychotic medication in MND, whether to treat challenging behaviour or for limited effects on neuromuscular junctions (e.g. Patten et al., 2017).

Is this appropriate in a neurodegenerative disorder where psychosis is not a defining clinical feature? Where anti-psychotic medication has been administered in FTD and FTD-MND, it has shown little consistency in effect (Young et al., 2018). Similar drugs are used too for symptoms such as agitation or disinhibition, with little evidence of benefit (Burrell et al., 2016; Manoochehri & Huey, 2012; Young et al., 2018). Therefore, the clinical utility of prescribing anti-psychotics has not yet been proven valuable. Adverse effects additionally limit the use of antipsychotics, such as the increased susceptibility of extra-pyramidal symptoms identified in patients with FTD (Pijnenburg et al., 2003; Tsai & Boxer, 2014).

The experience of psychosis for many may not be related to disability or the need for additional individualised care above the existing overriding physical disability of MND. However, the presence of psychosis symptoms, even if subtle and including disordered cognition, may exacerbate the challenges of MND, contribute to carer stress and complicate care.

Even subtle changes in character and behaviour should be recognised: careful neuropsychological and neuropsychiatric assessments are required to do so, considering patient experience and carer reports together. Rather than emphasising a disorder, I propose that an emphasis on symptomology, with/or without dysfunction, should be maintained. Through awareness and understanding, the risk of stigmatization can be reduced, and patients and their carers can be reassured that such behaviours as psychosis are a part of the disease and not a product of relational dysfunction. Symptomatic treatments remain the cornerstone of management for patients and this includes behaviour and cognition (Leigh et al., 2003). Further longitudinal research is needed to determine whether there is a specific link between psychosis symptoms, poor outcomes and reduced

survival. This would determine whether psychosis symptoms are correlative or causative of rapid cognitive and functional decline to death and thus affirm the treatment of psychosis.

7.5 Clinical implications

The presence of psychosis symptoms in apparently sporadic MND patients can be as detectable as those observed in behavioural variant FTD and in FTD-MND, yet they often do not receive the same attention. They may even be masked by other aspects of the disability arising from MND.

The clinical appearance of psychosis symptoms may be subtler in MND and intra-individual variance is high (shown in this thesis). As such, in a clinic setting, both overt and milder psychosis symptoms may be overlooked, especially in the context of overriding concern for physical impairment. It is acknowledged that subtle psychosis symptoms are difficult to identify and measure objectively, in the absence of objective measures of psychosis.

Psychosis symptoms can also be difficult to interpret, which raises the important issue as to whether behaviours represent 'traits' or states' (Masellis et al., 2010): are reported behaviours in keeping with previous life experiences and emerge only as pathology progresses or do they represent a state caused by MND pathology itself? In the absence of more sensitive measures of psychosis symptoms it is difficult to determine the relationship between psychosis symptoms, medically unexplained symptoms and perceptual changes. The use of many rating scales and questionnaires that incorporate the multidimensionality of delusions and hallucinations, allow for good delineation of symptoms but these are limited by self-report or clinician-rated, which assume intact patient or carer insight. While screening tests, such as the ECAS carer interview, are useful for the detection of obvious psychosis

symptoms, more in-depth neuropsychological investigation is validated for accurate patient classification.

Beyond the challenges of identifying and delineating psychosis symptoms and related aberrant behaviours in MND, refining the full range of the phenotype from a clinical, neuropsychology and neuroimaging standpoint is an objective which should be applied to as many patients who are initially identified as showing features suggestive of psychosis. For example, genetic screening for C9*orf*72, establishing a complete family history relating to neurodegenerative *and* psychiatric conditions, interrogating key cognitive processes, multimodal neuroimaging and eventually correlating with pathological information.

7.6 Study limitations

Specific limitations are discussed in each chapter but in this section, a few general limitations to the study are highlighted here.

7.6.1 Study sample

The inclusive approach to this study, considering the MND group as one continuous group, resulted in a clinically, cognitive and behaviourally heterogeneous group. Sub-dividing by cognition or psychosis status would have compromised the statistical power, reduced the variability of psychosis symptom frequency and severity, and increased the error in the imaging signal. Replication with larger sample sizes may justify performing additional analyses on sub-groups. For example, sub-dividing and analysing by specific psychosis symptoms separately, such as delusions and hallucinations, will add value as different psychosis symptoms may have different neural circuitry.

The current findings may have been impacted by the presence (or absence) of C9*orf*72 repeat expansion, which unfortunately was unable to be established for all participants due to long and ongoing Covid-19-related delays in the laboratory of our collaborators. Obtaining C9*orf*72 status would be of interest as psychosis symptoms are the most clinically distinguishing feature of positive versus negative cases (Snowden et al., 2012). Positive cases have been anatomically distinguished by specific atrophic patterns involving the left-side fusiform, supramarginal, superior temporal gyrus, orbitofrontal cortex, lateral occipital cortex and posterior cingulate regions (Bede et al., 2013), areas related to psychosis symptoms (Devenney et al., 2017), and which were implicated in the current results.

Recruitment biases included patients who were more motivated and physically able to complete all investigations across the three tiers, thus representation of bulbar patients was lacking. Additionally, the thesis recruited overwhelmingly "WEIRD" participants (representing Western, Educated, and from Industrialised, Rich and Democratic populations). This is an issue that international multi-site collaborations and small single-site studies must address for recruiting diverse and representative populations.

7.6.2 Methods

The assessment battery sought to capture overt psychosis symptoms, abnormal behaviours relating to psychosis, broader neuropsychiatric behaviours and distinct cognitive processes while considering the ability and frailty of MND patients. The battery was necessarily selective, attempting to assess recognisable and milder psychosis symptoms through available questionnaires and interviews, and substantiating them with experimental neurocognitive paradigms. Results are therefore only applicable to general psychosis and distinct cognitive processes. Studies using additional measures may identify specific

psychosis symptoms, such as delusions and hallucinations, and measure additional discrete cognitive processes relating to psychosis emergence.

It is possible that the presence of apathy may have impacted on task engagement or was not accurately captured due to an inability to perform on certain questionnaires/tasks. Self-rated questionnaires rely on reflection and insight, while behavioural tasks are heavily dependent on motor function, all of which may be limited in MND patients. These confounds are inherent in studies of neurodegenerative populations. The inclusion of carer reports provided further insight into neuropsychiatric behavioural change in the current patients, although personal distress of carers cannot be discounted when considering the catastrophic changes their loved ones are experiencing. Additionally, the discrepancy between patient and carer ratings of patient behaviour suggests they differ in their opinion of disturbing disease features. Use of large datasets, and examination of varying degrees of psychosis symptom severity and behavioural components, rather than individual assessments, may minimise the impact of these confounds.

Since the current study, there have been no new validated measures of psychosis across the FTD-MND continuum or in neurodegenerative conditions. Investigations continue to apply "gold standard" psychiatric tools that have often been validated in young adult primary psychosis populations, such as the Positive and Negative Symptom Scale (Kay et al., 1987). Such psychiatric tools are useful but may not be optimal in MND and old-age cohorts. Less obvious symptoms, such as stereotypical thinking or bizarre ideas in psychiatry are classed as part of a formal thought disorder (Hart & Lewine, 2017), a major recognisable psychosis symptom, whereas in neurology they may be labelled as behavioural features or "frontal behaviours" (Witgert et al., 2010). There may be a need for the development of a psychosis-specific questionnaire. The carer report on the ECAS and standard neuropsychiatric behaviour inventories (e.g. CBI-R and NPI) identify overt and subtle psychosis symptoms but could be complemented by better primary psychiatric tools to assess psychosis behaviour.

Best practice for neurologists should be unbound by primary psychosis diagnostic labels and focus on awareness of overt and sub-threshold psychosis symptoms, as well as broader neuropsychiatric behaviour change, often masked by predominant motor change in MND.

Limitations pertaining to imaging methods, including FreeSurfer volume parcellation and subcortical segmentation (chapter 5) and diffusion-weighted imaging (chapter 6) have been discussed in their relevant chapters. In general, MRI is unique in being able to assess simultaneous brain structure and function *in vivo* and is highly sensitive to cerebral pathology. However, the sequences used in the current thesis were not optimised to MND pathology due to streamlining MRI protocols for overlapping projects within the research group. Among the unused sequences are resting state functional MRI. This imaging method is useful to examine functional network connectivity to confirm if dysfunction within large scale brain networks, such as cortico-striatal networks, are responsible for psychosis risk in MND and FTD-MND. Application of fMRI would inform the DTI white matter connecting pathways, as DTI is limited in its indirect measurement of the physical properties of white matter connections, for example axon density, calibre and myelination (Jbabdi et al., 2015). The voxel-based whole brain methodology (TBSS) used in the current study does not allow for the direct identification of fibre tracts and so the implication of the tracts in the current results remains tentative yet could be complimented by fMRI investigations. Ultimately, post-mortem MRI and histopathology studies comparing diffusion and other structural imaging properties may shed more light on the pathological mechanisms of the various observed imaging changes, which would require longitudinal designs and follow-up until death.

7.7 Future research

Replication of findings is critical to scientific research; however, it is strongly encouraged that future research across the FTD-MND continuum encompass all phenotypes between and including the two extremes: behavioural variant FTD to apparently pure MND. Without such a comprehensive representation, assumptions and conclusions cannot be translated to all groups. With larger cohorts spanning the entire FTD-MND continuum, it will be beneficial to stratify patients based on the presence of psychosis symptoms, rather than diagnosis to provide a basis for examining their underlying neural correlates and identify targets for psychosis symptomatic treatment. Considering FTD-MND phenotypes together remains sensitive to the heterogeneity both within and across groups. For example, although MND patients meet different diagnostic criteria to behavioural variant FTD, patients often develop similar behavioural changes, such as psychosis.

In the current study the experience of hallucinations and delusions in addition to bizarre behaviours that fall into neither of these categories, were combined under two index scores (from the CBI-R and NPI). The rate of these symptoms was relatively low. Yet in the context of findings that the rate of delusions and not hallucinations was different from controls (Devenney et al., 2014) in an FTD-MND cohort, it may be that the cognitive and neural mechanisms involved in the formation and generation of delusions and hallucinations may differ and warrant careful consideration in future studies. Studies that combine multiple imaging techniques to evaluate multiple measures of grey and white matter integrity will be more likely to capture not only the full spectrum of network degeneration in MND but specific networks relating to specific symptom profiles and the full spectrum of psychiatric manifestations. Although the neuroimaging findings in the current thesis are novel to MND, they are preliminary and further neuroimaging projects should include methods of analysing functional connectivity to confirm whether dysfunction in large-scale brain networks are responsible for psychosis in MND and FTD-MND.

To progress understanding of the nature of psychosis symptoms in MND and how they relate to cognitive and neural mechanisms, it will be necessary to identify candidate mechanisms for how psychosis symptoms may emerge based on a growing understanding of relevant cognitive and neural systems. A priority in terms of experimental work, such as the neurocognitive tasks included in the current thesis, could be to test emerging candidate mechanisms in disease control populations, rather than solely alongside healthy control subjects. These comparison groups may include those that resemble milder psychosis symptoms such as at-risk, prodromal or first episode psychosis groups, or other neurodegenerative conditions such as Alzheimer's disease and dementia with Lewy bodies.

7.8 Conclusion

This thesis has provided insight into the prevalence and cognitive and neural mechanisms relating to psychosis in MND. It applied a unique cognitive perspective together with multimodal imaging techniques to investigate psychosis in MND. The findings of suboptimal decision-making processes relating to psychosis symptoms and neural corelates are new in MND research and specifically add to the limited research investigating psychosis further along the FTD-MND continuum. Psychosis symptoms in MND can be as overt as those seen in behavioural variant FTD and FTD-MND but are more commonly much subtler with large intra-individual variability. Screening tools are necessary to detect overt psychosis symptoms with more detailed neuropsychological investigation to delineate dimensions and interrogate specific cognitive processes, such as decision-making. Suboptimal decision-making, characterised by an inferential impulsive decision-making style and an insensitivity to negative feedback, were related to behaviours and symptoms suggestive of psychosis and may represent a cognitive and behavioural vulnerability to the development of psychosis in MND. Despite sporadic findings in the FTD-MND literature, including those in the current

thesis, the full spectrum of psychiatric manifestations, and specifically the precise incidence of psychosis symptoms, remain to be established in MND and FTD-MND.

The current imaging results suggest that psychosis and related cognitive processes are not due to the impairment of any one brain region, but a state of more widespread network disruption. This results from multifocal atrophy and compromised integrity of white matter association tracts. The grey and white matter correlates identified in the current thesis may reveal a vulnerability to psychosis that may not otherwise have become apparent without a break down in frontotemporal-frontal-striatal and cerebellar white matter connections or regional volume. Multimodal neuroimaging may have particular value as an objective measure in characterising specific behavioural symptom profiles in MND, especially under the framework that natural degeneration of biological systems drives clinical symptoms to become evident at a relatively advanced stage of pathology (Menke et al., 2017).

My work suggests a high degree to which psychosis phenomena and brain network degeneration are shared between primary psychosis disorders and psychosis within a neurodegenerative condition. I propose that these homologies can be exploited to improve both diagnosis and treatment options across the FTD-MND continuum.

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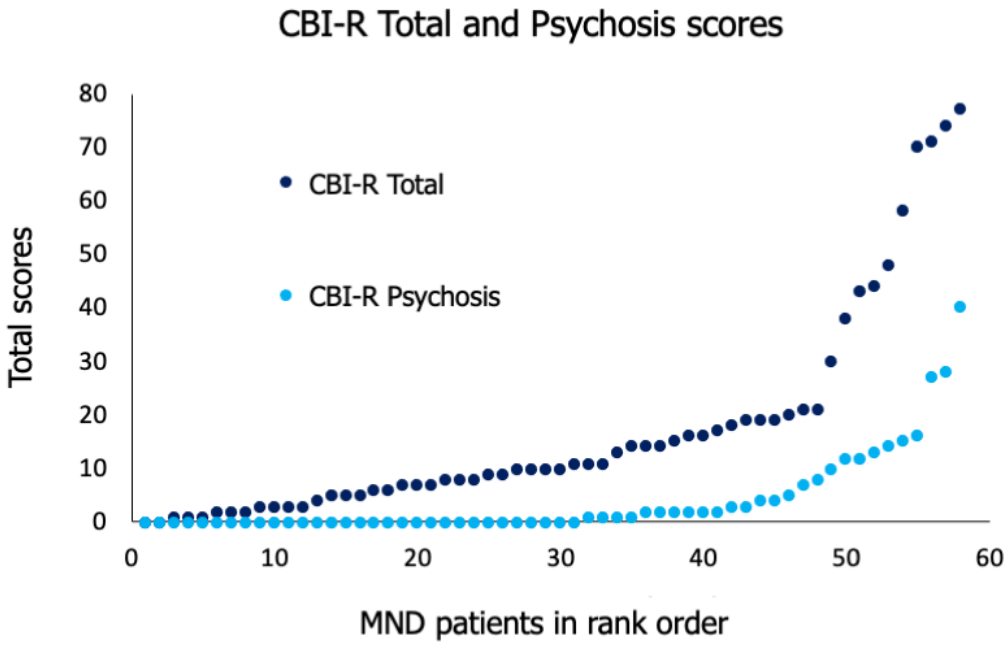
Appendices

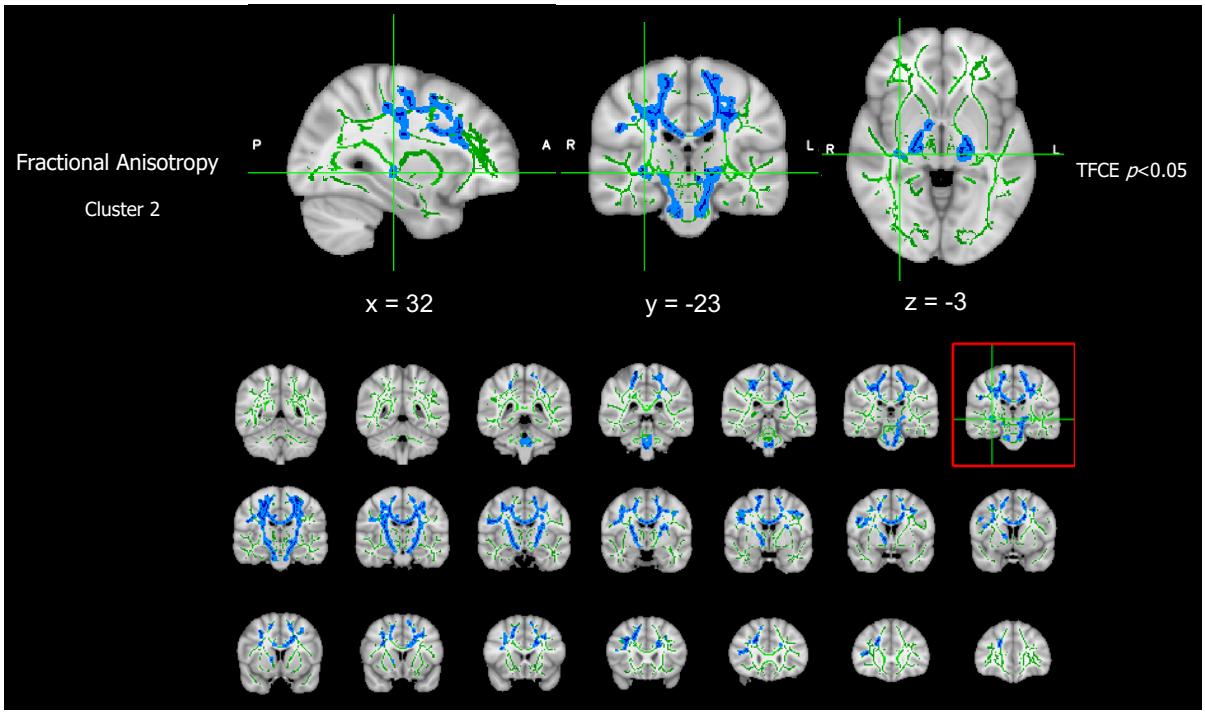
Appendix A

Pilot data collected as part of the clinical work-up with CBI-R on MND patients attending MND Care Centre prior to main study recruitment. Graph illustrates *N*=58 patients in rank order on their CBI-R total frequency score (x-axis). CBI-R psychosis score is a sub-set of the sections aimed at detecting features suggestive of psychosis: *Abnormal Behaviour*, *Beliefs*, and *Motor and Stereotypical Behaviours*. A score above 10 (y-axis) indicates behaviours occur at least a few times per week.



Appendix B

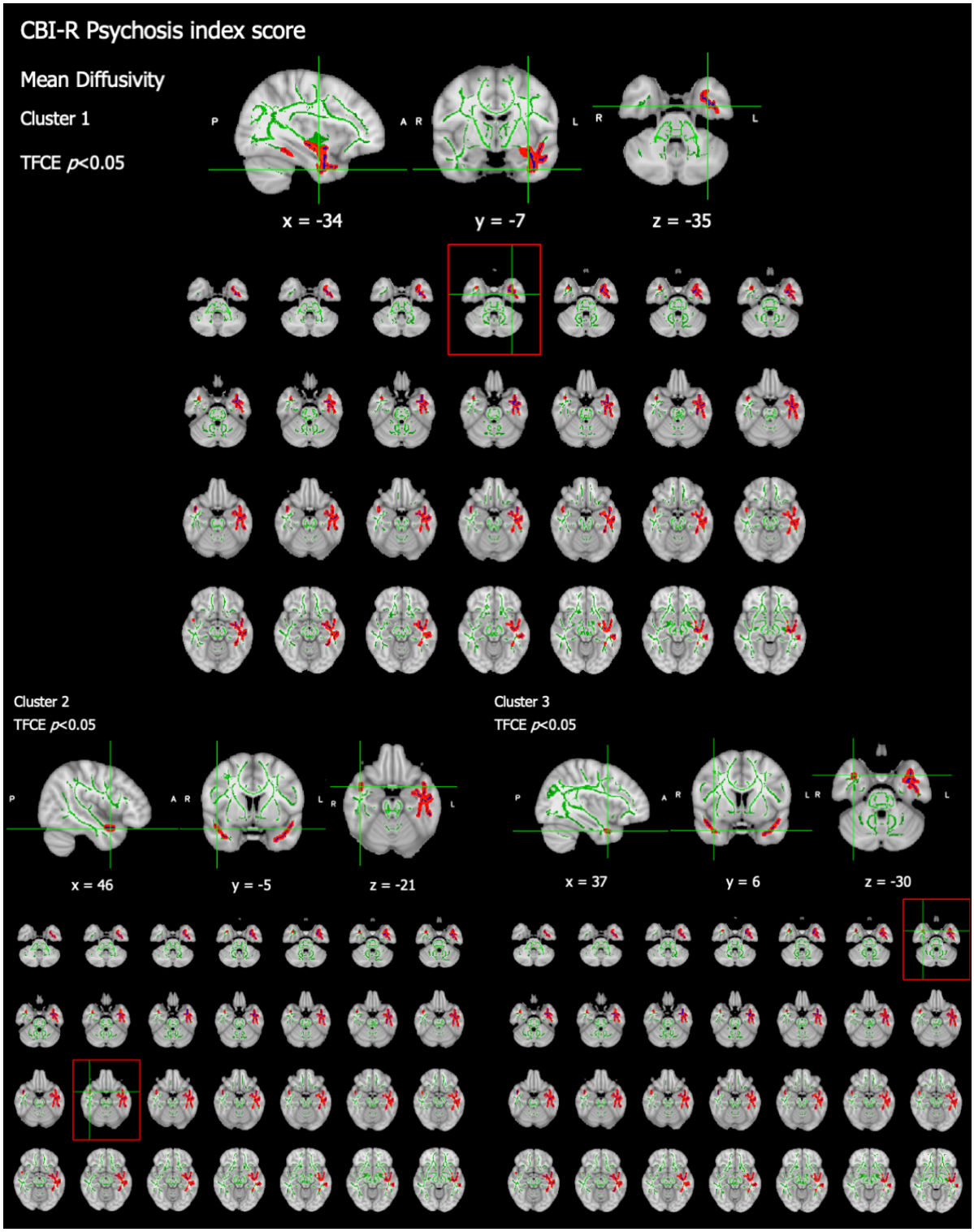
Coronal multi-slice images from initial group analysis illustrating decrease in fractional anisotropy in cluster 2 (33 voxels) in MND compared to controls. The highest intensity located in the right inferior frontal-occipital fasciculus region, superior to the parahippocampal gyrus (*t*=3.47, TFCE *p*<0.05).



Crosshairs indicate highest intensity voxel and anatomical location given in MNI coordinates (x,y,z). Results overlaid on the mean FA skeleton (green) and MNI152 T1 template (grey). P=posterior, A=anterior, R=right, L=left.

Appendix C

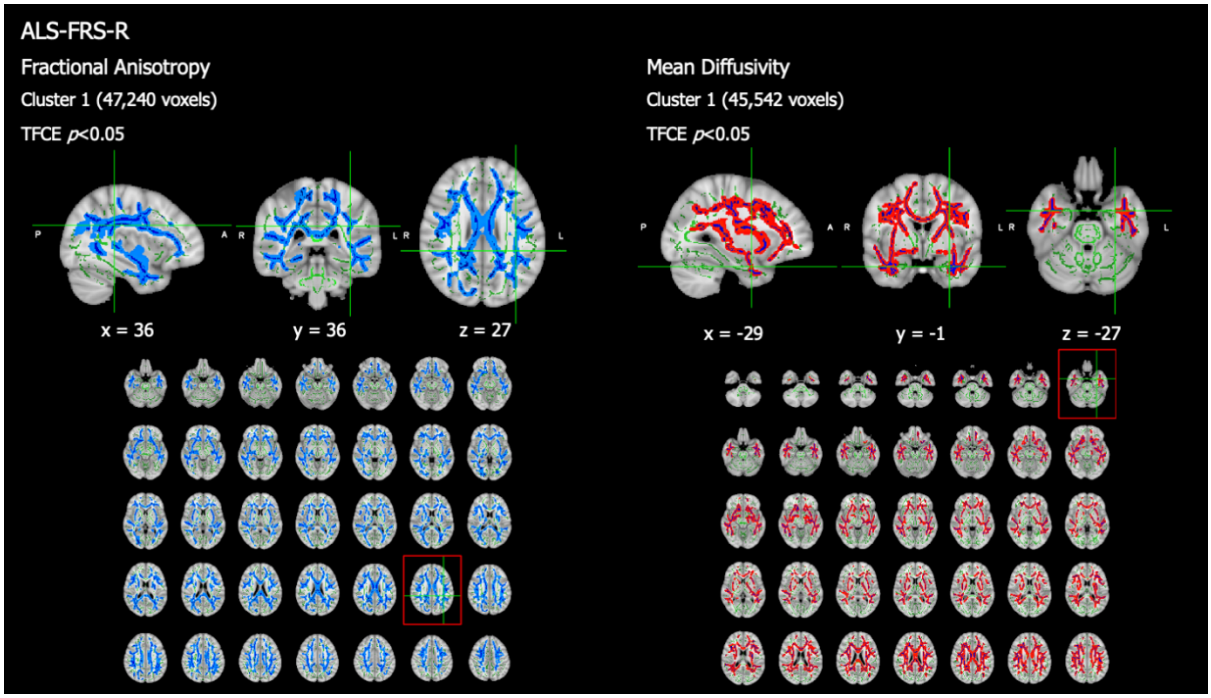
Axial multi-slice images illustrating increase in mean diffusivity with CBI-R psychosis index score in clusters 1 (2,551 voxels), 2 (114 voxels) and 3 (41 voxels) in MND compared to controls.



Crosshairs indicate highest intensity voxel and anatomical location given in MNI coordinates (x,y,z). Results overlaid on the mean FA skeleton (green) and MNI152 T1 template (grey). P=posterior, A=anterior, R=right, L=left.

Appendix D

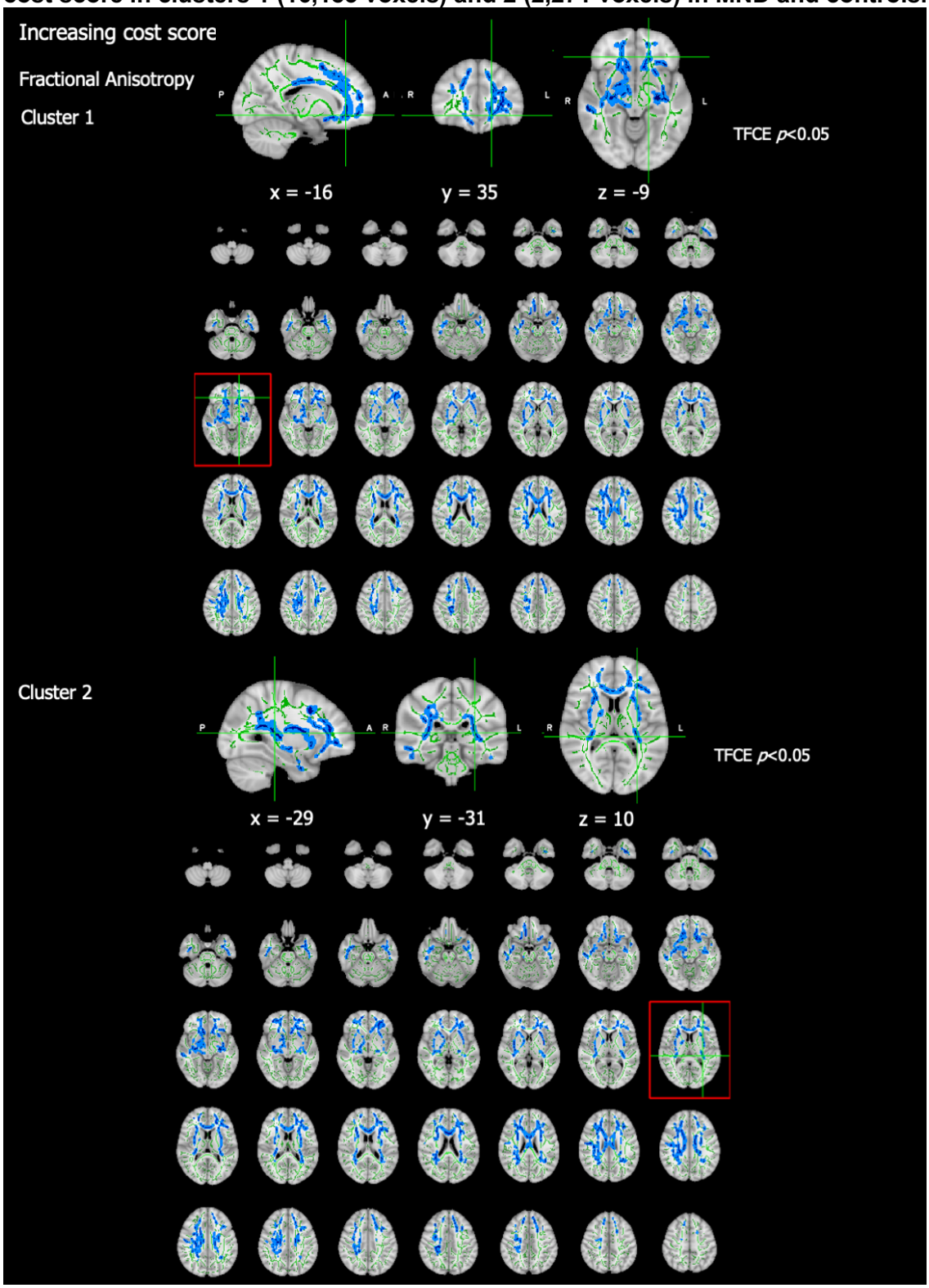
Axial multi-slice images illustrating 1 cluster each of a decrease in fractional anisotropy (left) and increase in mean diffusivity (right) with CBI-R psychosis index and ALS-FRS-R as a covariate of no interest in MND compared to controls.



Crosshairs indicate highest intensity voxel and anatomical location given in MNI coordinates (x,y,z). Results overlaid on the mean FA skeleton (green) and MNI152 T1 template (grey). P=posterior, A=anterior, R=right, L=left.

Appendix E

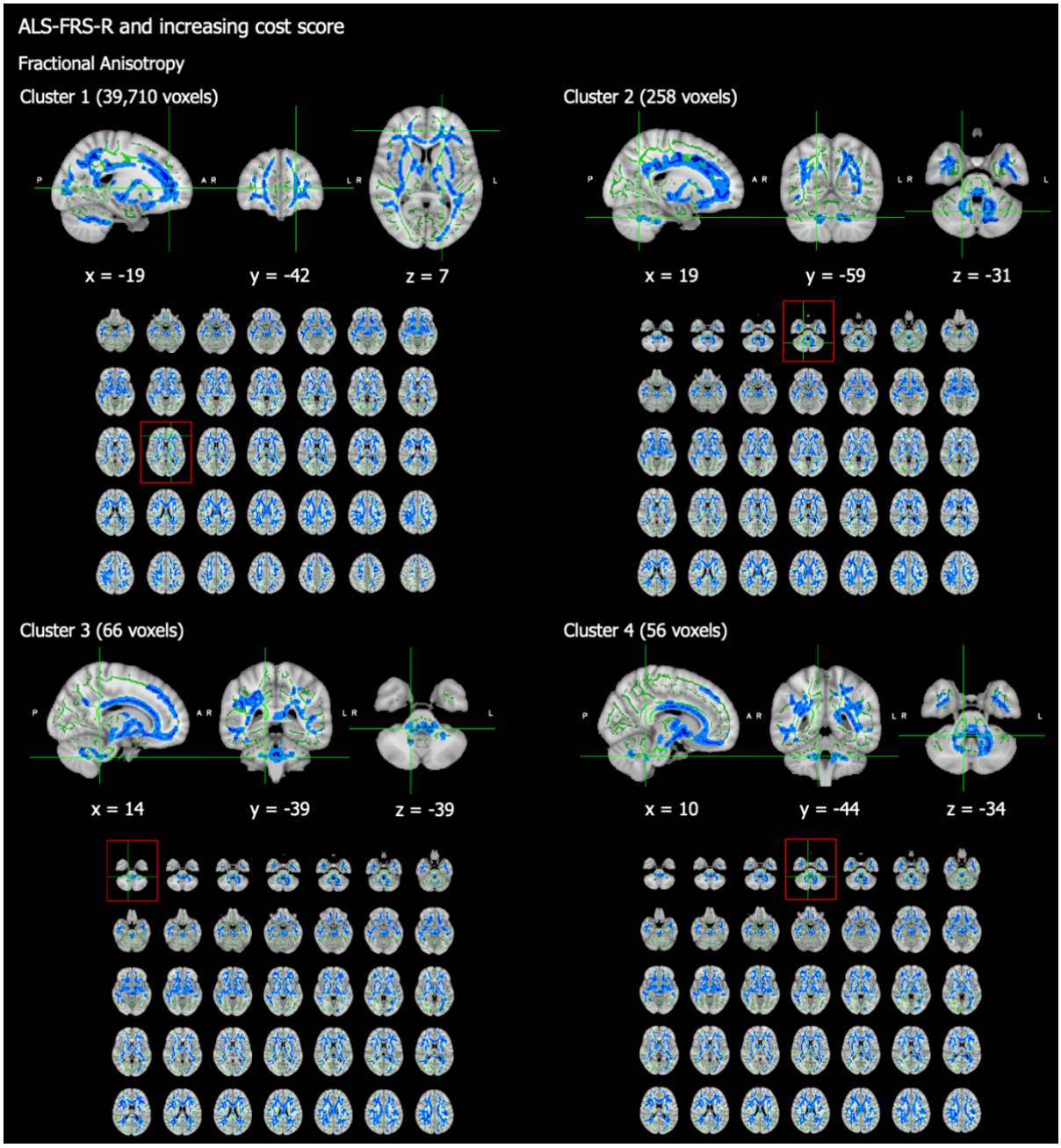
Axial multi-slice images illustrating decrease in fractional anisotropy with increasing cost score in clusters 1 (16,183 voxels) and 2 (2,271 voxels) in MND and controls.



Crosshairs indicate highest intensity voxel and anatomical location given in MNI coordinates (x,y,z). Results overlaid on the mean FA skeleton (green) and MNI152 T1 template (grey). P=posterior, A=anterior, R=right, L=left.

Appendix F

Axial multi-slice images illustrating 4 clusters of a decrease in fractional anisotropy with increasing cost score and ALS-FRS-R as a covariate of no interest in MND and controls.



Crosshairs indicate highest intensity voxel and anatomical location given in MNI coordinates (x,y,z). Results overlaid on the mean FA skeleton (green) and MNI152 T1 template (grey). P=posterior, A=anterior, R=right, L=left.