Mood instability: its cognitive and neural correlates and the effects of L-type calcium channel antagonism.

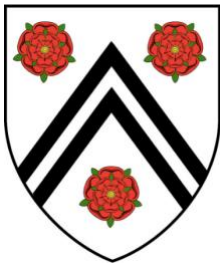
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DPhil Thesis, Hilary Term 2020





Mood instability: its cognitive and neural correlates and the effects of L-type calcium channel antagonism.

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Submitted for the degree of DPhil in Psychiatry, Hilary Term 2020

Abstract

Mood instability is commonly experienced in the general population. It is associated with risk for subsequent diagnosis of bipolar disorder (BD) and is a prominent feature of several other psychiatric disorders. Despite the significance of mood instability in psychopathology, there is little research examining its potential underlying mechanisms. In a study measuring mood, cognitive function and resting-state magnetoencephalography (MEG) over 10-weeks, the first part of this thesis aimed to characterise mood instability and explore its cognitive and neural correlates in healthy individuals at low and high risk of BD as indicated on the Mood Disorder Questionnaire (MDQ). Findings demonstrated that instability in negative mood was significantly different between individuals scoring low and high on the MDQ. Individuals with high MDQ scores demonstrated deficits in learning context-based regularities across days, and higher levels of negative mood instability in this group were also associated with changes in neural activity such as reduced switching between brain states, and reduced time spent in a fronto-limbic state thought to be necessary for mood regulation.

The second part of this thesis aimed to explore the candidacy of L-type calcium channel (LTCC) antagonism as a potential treatment for mood instability. Healthy individuals with high MDQ scores participated in a double-blind, placebo-controlled, experimental medicine study. For two weeks in the absence of any intervention, measures of mood and neural activity were assessed. This was followed by a 2-week randomisation phase to either nicardipine SR or placebo, during which all measures were repeated. Compared to placebo, LTCC antagonism was not found to reduce mood instability or significantly affect resting-state MEG measures of spectral power, alpha peak frequency, or characteristics of fast transient brain states.

Overall, these findings provide insights into the potential mechanisms that might underlie mood instability, highlighting areas for future investigation. While the candidacy of LTCC antagonism in mood instability was not confirmed, this work demonstrates the feasibility of multimodal, high-intensity studies to investigate transdiagnostic constructs and the potential of new treatments.

Acknowledgments

There are a lot of individuals I am privileged to have worked with during my DPhil. Firstly, I would like to express my deep gratitude to my supervisors Paul Harrison and Kia Nobre. They provided unfaltering support, encouraged me to push myself and importantly had confidence in my abilities, even at times when I did not believe in myself. Secondly, thank you to everyone in the Brain and Cognition Lab. I will always appreciate how lucky I have been to learn from and work amongst so many remarkable students and post-docs, many of whom are now close friends. Two post-docs in particular made this thesis possible. Andrew Quinn introduced me to the world of MEG. He is a great beer brewer, and incredible teacher. It is due to his patience and careful guidance that I developed the skills to analyse the MEG data included in this thesis. Nahid Zokaei helped me in the early days of this thesis, kindly dedicating many hours rescuing me from failing Matlab scripts and providing much valued advice for cognitive data analyses. She is a great scientist that I look up to very much.

I am grateful to have been part of truly collaborative research efforts. I would like to thank fellow DPhil students Priyanka Panchal and Lucy Potter who were involved in data collection for the COMET and OxCaMS studies, respectively. Kate Saunders, an amazing academic psychiatrist, was highly involved in both studies and spent many hours in the lab with me creating matching placebo and drug capsules. Finally, none of this research would have been possible without clinical staff at the Clinical Research Facility, imaging staff at the Oxford Centre for Human Brain Activity, and of course all of the participants who dedicated their time to this research.

My thanks also extend to Amy Bilderbeck and Andrea Cipriani who were not directly involved with my DPhil, but who both provided me with countless opportunities to develop my research career early on and enthusiastically supported my decision to undertake this DPhil.

Lastly, it is hard to put into words just how appreciative I am of the encouragement provided from my parents Shirley and Martin, my brother James, my partner Marcus and my close friends, particularly Izzie. They have all been there to celebrate my small successes along the way, get me back on track when things were tough, and have continually expressed how proud they are of me. The thought of the pride on their faces at the end is what has really determined me to finish. The last 4 years have been challenging but with their enduring support I never lost my way for long.

Declarations

Some parts of the introduction, methods and discussion sections of Chapter 6 and 7 have been published:

Atkinson LZ, Colbourne L, Smith A, Harmer CH, Nobre AC, Rendell J, Jones H, Hinds C, Mould A, Tunbridge EM. (2019). The Oxford study of Calcium channel Antagonism, Cognition, Mood instability and Sleep (OxCaMS): study protocol for a randomised controlled, experimental medicine study. *Trials* 20(1):120. doi:10.1186/s13063-019-3175-0.

In accordance with the guidelines, the body of this thesis does not exceed 50,000 words (excluding references, appendices, figures and tables) and contains less than 150 figures.

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List of abbreviations

ACC	Anterior Cingulate Cortex
ACS	Affective Control Scale
ADHD	Attention Deficit Hyperactivity Disorder
AE-HMM	Amplitude Envelope Hidden Markov Model
AIM	Affect Intensity Measure
ALS	Affect Lability Scale
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
APMS	Adult Psychiatric Morbidity Survey
APSCL	Assessment of Psychological Symptoms Checklist
ASL	Arterial Spin Labelling
ASRM	Altman Self Rating Mania Scale
AUDIT	Alcohol Use Disorders Identification Test
BBB	Blood Brain Barrier
BD	Bipolar Disorder
BDI	Bipolar Disorder type I
BDII	Bipolar Disorder type II
BDNOS	Bipolar Disorder Not Otherwise Specified
BI	Blinding Index
BIS	Barratt Impulsiveness Scale
BOLD	Blood Oxygen Level Dependant
BPD	Borderline Personality Disorder
CI	Confidence Interval
CLN	Corticolimbic Network
CMF	Clinical Monitoring Form
COMET	COgnition and Mood Evolution across Time
COPE	Contrast of Parameter Estimate
CRF	Clinical Research Facility
DAN	Dorsal Attention Network
DERS	Difficulties in Emotion Regulation Scale
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DSM-IV	The Diagnostic and Statistical Manual, 4th edition
ECG	Electrocardiogram
EEG	Electroencephalography
EOG	Electrooculogram
FC	Functional Connectivity
FMRI	Functional Magnetic Resonance Imaging
FO	Fractional Occupancy
FoV	Field of View
FPN	Frontoparietal Network
FSN	Frontostriatal Network
GLM	General Linear Model
GWAS	Genome-Wide Association Study
HDRS	Hamilton Depression Rating Scale
HMM	Hidden Markov Model
HPS	Hypomanic Personality Scale
ICA	Independent Component Analysis
ICC	Intra-class Correlation
ICD	International Classification of Disease
IT	Interval Time
ITI	Inter-trial Interval
LT	Life Time
LTCC	L-type Calcium Channel

MDD	Major Depressive Disorder
MDQ	Mood Disorder Questionnaire
MEG	Magnetoencephalography
MF	Median Frequency
MINI	Mini-International Neuropsychiatric Interview
mPFC	Medial Prefrontal Cortex
MSSD	Mean Successive Squared Difference
NART	National Adult Reading Test
NIHR	National Institute for Health Research
NIMH	National Institute of Mental Health
NIMH-LCM	National Institute of Mental Health LifeChart Method
NNMF	Non-negative Matrix Factorisation
OCD	Obsessive-Compulsive Disorder
OCMR	Oxford Centre for Magnetic Resonance imaging
OFC	Orbitofrontal Cortex
OHBA	Oxford Centre for Human Brain Activity
OSL	OHBA Software Library
OxCaMS	Oxford study of Calcium channel antagonism, Mood instability and Sleep
PANAS-SF	Positive And Negative Affect Scale (short-form)
PC	Phase Coupling
PCA	Principle Component Analysis
PDA	Personal Digital Assistant
PFC	Prefrontal Cortex
PSD	Power Spectral Density
PTSD	Post-Traumatic Stress Disorder
QIDS	Quick Inventory of Depressive Symptomatology
RCT	Randomised Controlled Trial
RDoC	Research Domain Criteria
RMSSD	Root Mean Successive Squared Difference
rrMDD	Remitted Major Depressive Disorder
rsFC	Resting-State Functional Connectivity
RSN	Resting-State Network
RT	Reaction Time
SCID	Structured Clinical Interview for DSM-IV
SCNi	Sleep and Circadian Neuroscience Institute
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the Mean
sgACC	Subgenual Anterior Cingulate Cortex
SN	Salience Network
SNP	Single Nucleotide Polymorphism
SR	Switching Rate
SSS	Signal Space Separation
TDE-HMM	Time Delay Embedded Hidden Markov Model
TE	Echo Time
TR	Repetition Time
tRMSSD	time-adjusted Root Mean Successive Squared Difference
TTCC	T-type Calcium Channel
TVA	Theory of Visual Attention
UKMP	UK MEG Partnership
VAS	Visual Analogue Scale
VGCC	Voltage-Gated Calcium Channel
VMPFC	Ventral Medial Prefrontal Cortex
VSTM	Visual Short-Term Memory
WM	Working Memory
YMRS	Young Mania Rating Scale

Chapter 1. Introduction

1.1 Mood instability: terminology

The concept of mood instability is central to this thesis and so it is appropriate to begin with a definition. Mood instability is dynamic in nature and has been proposed to reflect "rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences" (Marwaha et al., 2014). The literature surrounding mood instability, in both the psychiatric and general population, has used many different terms interchangeably to describe this concept, relating to mood, affect and emotion. Such terms include 'mood dysregulation, mood lability, mood swings, affective dysregulation, affective lability, affective instability, emotional dysregulation, emotional lability and emotional instability' (Broome, Saunders, Harrison, & Marwaha, 2015; Marwaha et al., 2014). In addition, descriptions have emphasised different characteristics. Some describe rapid mood changes as triggered by external, environmental events (Siever & Davis, 1991; Trull et al., 2008) or the "marked reactivity of mood" as in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 2000), pertaining to a lack of control. Other descriptions encompass the frequency and intensity of mood changes, though few specify the time periods over which mood changes are expected to occur, for example, over days or weeks. When referring to mood instability in this thesis, the aforementioned definition by Marwaha et al., (2014) is adopted.

1.2 The epidemiology of mood instability

Mood instability is a prominent feature of several psychiatric disorders, such as bipolar disorder (BD), borderline personality disorder (BPD), major depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD), schizophrenia, anxiety disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) (Patel et al., 2015). Using the Assessment of

Psychological Symptoms Checklist (APSCL), 83.8% of patients referred to two community mental-health teams self-reported mood instability (Gilbert et al., 2005). Other self-reported rates of mood instability, this time from the Adult Psychiatric Morbidity Survey (APMS) in response to 'do you have a lot of sudden mood changes?', have been found to be upwards of 49% for those diagnosed with a psychiatric disorder other than BD (Marwaha et al., 2013). In the clinical records of patients attending mental-health care services in the United Kingdom with a psychotic, affective, or personality disorder, mood instability was documented by healthcare professionals in 12.1% of cases (Patel et al., 2015). Mood instability was found to be most common in BD (Patel et al., 2015). Although prevalence rates differ between studies, likely due to differences in psychiatric populations observed as well as in self-report vs. clinician report, it is clear that mood instability is a prominent feature of multiple psychiatric disorders, particularly BD. This might not be surprising given these disorders share symptomatology and are highly comorbid.

A burgeoning literature further suggests that mood instability plays a role in the development and prognosis of psychiatric disorders. Self-reported mood instability has been noted in offspring at high genetic risk of BD (Birmaher, 2013; Duffy et al., 2019) and newly diagnosed patients (Stanislaus et al., 2020). It is a risk factor for the subsequent diagnosis of mood disorders (Hafeman et al., 2016; Howes et al., 2011), and its presence is associated with an earlier age of onset (Henry et al., 2008). In addition, mood instability is found to be present in individuals who have suffered childhood maltreatment, the experience of which increases risk for mood, personality, and anxiety disorders (Teicher et al., 2015). Mood instability is associated with increased symptom severity in depression (Thompson, Berenbaum, & Bredemeier, 2011) and ADHD (Sobanski et al., 2010). It is associated with shorter time to recurrence of mood episodes (Perlis et al., 2006) and predicts poorer long-term functional recovery in BD (Gershon & Eidelman, 2015; Joffe et al., 2004; O'Donnell et al., 2018; Patel et al., 2015; Stange et al., 2016;

Strejilevich et al., 2013). Further, it has a negative impact on quality of life and functional ability (Bauer et al., 2009; Faurholt-Jepsen, Frost, et al., 2019b; Judd et al., 2005; Proudfoot et al., 2014; Simon et al., 2007), and is associated with increased use of healthcare services and antipsychotic and mood stabiliser medications (Patel et al., 2015).

Not only is mood instability present in psychiatric disorders, it is also commonly experienced in the general population (Broome et al., 2015). This is unsurprising given that symptoms of psychiatric disorders overlap with normal psychological states (e.g. low mood) that can range in severity and duration. Using data from 7,403 adults who responded to the APMS in 2007, Marwaha et al., (2013) found that the population prevalence of mood instability in the UK was relatively high at 13.9%. Mood instability was found to be more prevalent in women (17.6%) than men (11.5%), echoing the reported gender prevalence of mood disorders. It was observed across all age groups, but highest in individuals aged 16–24 (26%) and 25-34 (19.5%), gradually decreasing with age (Marwaha et al., 2013). This is also comparable to clinical studies that find greater mood instability in younger patients (McKnight et al., 2017; Patel et al., 2015). Altogether, the high prevalence of mood instability in both the psychiatric and general population, and association with poor outcomes across psychiatric disorders, warrant the further investigation of mood instability.

1.3 The genetic basis of mood instability

Genome wide-association studies (GWAS) are observational studies of the genome that identify genetic variants, usually single nucleotide polymorphisms (SNPs), occurring more frequently in individuals with a particular trait or diagnosis, compared to those without. GWAS undertaken in adult male twins (Coccaro et al., 2012) and in a sample from the UK Biobank (Ward et al., 2017) have shown that mood instability is a moderately heritable trait (~8%) in the general population.

GWAS have further attempted to identify whether mood instability shares any genetic risk for developing a number of psychiatric disorders including BD, MDD, ADHD, schizophrenia, PTSD and anxiety disorders. Ward and colleagues (2017) were the first to identify four genome-wide significant loci specifically associated with mood instability, which were replicated (plus 46 novel loci) in a larger follow-up sample of the UK Biobank (Ward et al., 2019). The presence of mood instability was defined by those who answered 'yes' to a single question - 'does your mood often go up and down?'. A greater proportion of individuals with self-diagnosed BD, recurrent severe MDD, recurrent moderate MDD, and single-episode MDD reported mood instability (74%, 71.4%, 64.2% and 43.7, respectively) compared to controls (35.3%), consistent with previous research. In a subset of the study sample who did not self-report having a psychiatric disorder, the authors found a strong genetic correlation between loci identified to be associated with mood instability and MDD, schizophrenia, and anxiety disorders. However, they did not find any genetic association between mood instability and BD, perhaps due to underpowered GWAS analyses and/or the limited psychiatric information available in UK Biobank (Ward et al., 2017). Interestingly, in the follow-up study, loci associated with mood instability included genes that are expressed and involved in brain development and function, including those associated with synaptic transmission (Ward et al., 2019). Given this, further research would benefit from exploring whether mood instability is associated with alterations in neural activity and function (see Chapter 1, Section 1.8 and Chapter 5).

Overall, the studies by Ward and colleagues (2017, 2019) provide strong biological evidence for a genetic basis to mood instability and for the link between mood instability and psychiatric disorders. Particularly, it confirms that mood instability confers risk to multiple psychiatric disorders. In this way, mood instability is likely similar to neuroticism, which is also a heritable trait in the general population (Okbay et al., 2016; Power & Pluess, 2015) and significantly

associated with risk for psychiatric disorders (Lahey, 2009). This provides the opportunity to investigate mood instability in non-clinical samples, as has been done in this thesis.

1.4 Measuring mood instability

There is no single standardised or validated measure of mood instability. Thus, the investigations described above identified mood instability using a range of methods. Mood instability can be assessed through psychiatric assessment using the Structured Clinical Interview for DSM-IV (SCID), self-report questionnaires such as the Mood Disorder Questionnaire (MDQ), or clinician-administered rating scales. In addition, GWAS and population-based studies, as mentioned above, have typically determined the presence of mood instability based on answers to a single, self-report question. Whilst these are all accepted approaches to measure mood instability, it has been suggested that methodological inconsistencies lead to differences in prevalence estimates, can make results difficult to interpret across studies, and leads to variations in the behaviour being measured (Broome et al., 2015).

A notable limitation is that measures of mood instability are dominated by the use of retrospective questionnaires, either clinician-administered or self-report, relying on recall of symptoms over extended time periods. These methods are subject to inherent biases, such as mood-congruent biases at the time of assessment (Shiffman, Stone, & Hufford, 2008). This is particularly problematic when it is not just mood state to be recalled, but also the frequency and intensity of mood states given the dynamic nature of mood instability (Broome et al., 2015; Harrison et al., 2016). Indeed, in a qualitative study that investigated the psychiatric assessment of mood instability, patients reported struggling to recollect and communicate their experience effectively and be understood by their clinician (Bilderbeck et al., 2014).

The introduction of remote mood monitoring has facilitated progress in measuring mood instability. Patient-based self-report measures are increasingly common in research, and in the clinical management of mood disorders. For example, the National Institute of Mental Health LifeChart Method (NIMH-LCM) (Born et al., 2009) and the Clinical Monitoring Form (CMF) (Sachs, Guille, & McMurrich, 2002) are two paper-based mood charts used to investigate the longitudinal course and treatment outcomes of mood disorder patients, which have been validated against other formal rating scales for depression and mood elevation (Born et al., 2014; Denicoff et al., 2000; Sachs et al., 2002). However, paper-based self-report methods can be inconvenient and unreliably completed with the potential for missed ratings to be retrospectively completed (Lieberman et al., 2010; Stone et al., 2003). Digital technologies, such as the use of personal digital assistants (PDAs) and mobile technologies, have rapidly become popular to facilitate more accurate time-based assessments.

The ubiquity of PDAs, smartphones, and tablets facilitates the remote capture of self-reported mood symptoms, providing numerous benefits over paper-based self-monitoring (Faurholt-Jepsen, Geddes, et al., 2019). These technologies can be used to capture higher frequency information, facilitate prompting of completion, and provide accurate timestamps. They allow for the longitudinal, repeated collection of data in a minimally invasive way. Utilising such methods to report mood over short periods of time, for example daily symptom reporting, helps to alleviate recall bias and provides a more dynamic perspective of mood over time. This helps overcome limitations of conventional retrospective reports and single-time point measures, both in the clinic and in research settings. In addition, it is possible to capture contemporaneous cognitive, physiological (e.g. actigraphy, sleep and heart rate measures), and social measures (e.g. screen on-time and call time), which can be integrated to provide a richer and more nuanced understanding of clinically important phenotypes such as mood instability. Digital phenotyping has become increasingly popular as a research and clinical tool in psychiatry (Insel, 2017, 2018)

and has been used for the collection of mood and cognitive data in this thesis. Different ways to quantitatively characterise mood instability using data from remote mood monitoring are explored and discussed in detail in Chapter 2.

1.5 Longitudinal remote mood monitoring to capture mood instability

The interest in mood instability for this thesis was originally developed from observations of mood instability in BD. BD is typically characterised by episodes of abnormally elevated (hypomania or mania) and low (sad or depressed) mood. Discrete mood episodes are interspersed with periods of euthymia during which time mood returns to normal. The duration of discrete mood episodes and the severity of mood elevation distinguishes between BD subtypes, including BD-type I (BDI), BD-type II (BDII) and cyclothymia. Whilst there has been much focus, both in clinical practice and research, on discrete mood episodes, this is now thought to be overly simplistic as deviations in mood can be observed both outside of, and within such episodes. In BD, mood during euthymia is not as stable as has often been assumed, and persistent mood instability is thought to be of clinical significance (Harrison et al., 2016; Henry et al., 2008).

A number of studies utilising longitudinal, remote mood monitoring for example the MONARCA system (Bardram et al., 2013; Faurholt-Jepsen, Frost, et al., 2019a; Faurholt-Jepsen et al., 2015, 2013), SIMPLe (Hidalgo-Mazzei et al., 2015) and Chrono Record (Bauer et al., 2004) have revealed that chronic mood instability, rather than discrete mood episodes, may be more typical over the course of BD (Judd et al., 2002, 2003; MacQueen et al., 2003). One pioneering remote mood monitoring system developed at the University of Oxford, True Colours, was designed to prompt individuals with BD to complete self-reported measures of (hypo)manic and depressive symptoms via text message or email (Bopp et al., 2010; Goodday et al., 2020). Self-reported observations using the True Colours system have shown that outside of discrete

episodes of elevated or low mood, many individuals with BD continue to experience mood instability during euthymia (Bonsall et al., 2012; Bonsall et al., 2015; McKnight et al., 2017; Moore et al., 2014; Tsanas et al., 2016). In particular, Tsanas et al., (2016) revealed differences in the weekly and daily dynamics of mood instability between those with BD and BPD in self-reported symptoms of low mood and irritability. Additionally, levels of mood instability in diagnostic groups were significantly higher than in healthy control participants, confirming and extending previous findings from studies that used one-off ratings scales (Aminoff et al., 2012).

Longitudinal self-monitoring studies in MDD have also highlighted greater daily variation in negative mood symptoms and to a lesser extent, positive symptoms in depressed individuals compared to healthy controls (Crowe et al., 2019; Peeters et al., 2006; Thompson et al., 2011). A recent meta-analysis of studies assessing mood over time found associations between lower psychological well-being and higher instability in negative mood symptoms in MDD patients (Houben, Van Den Noortgate, & Kuppens, 2015). Longitudinal self-monitoring has also been implemented in BPD (Ebner-Priemer, Santangelo, & Bohus, 2016; Trull et al., 2008; Tsanas et al., 2016) and anxiety (Bowen et al., 2006). Overall, these studies show how digital methods successfully enable the collection of finer grained detail about mood in order to recognise psychiatric experiences such as mood instability that are otherwise hard to capture.

1.6 The relationship between mood instability and cognition

Despite the significance of mood instability in psychopathology, there is little research examining its association with cognitive functions, such as attention, learning and memory, and decision making. Much research has revealed that cognitive impairments are present in diagnostic groups known to experience mood instability, particularly in mood disorders (Cullen et al., 2016; Lima, Peckham, & Johnson, 2018; Marazziti et al., 2010; Martinez-Aran et al., 2004; Martino et al., 2015). A number of meta-analyses have demonstrated impairments across multiple cognitive

domains including working memory (WM), attentional processing, executive function and response inhibition, which importantly persist during euthymia, similarly to mood instability (Bora, Yucel, & Pantelis, 2009; Bortolato et al., 2015; Bourne et al., 2013; Robinson et al., 2006; Torres, Boudreau, & Yatham, 2007). It would be of great value to understand the extent to which mood instability is associated with dysfunctional cognitive and neuronal processing. This has been explored in Chapters 3, 4, and 5.

A number of longitudinal studies have suggested that cognitive deficits in euthymic BD patients tend to be stable over time (Budde & Schulze, 2014; Chaves et al., 2011; Samamé, Martino, & Strejilevich, 2014; Santos et al., 2014). Most recently, Martino et al., (2018) found that deficits in measures of attention, verbal WM, and executive function in BD participants compared to healthy controls were stable between baseline and follow-up assessments and were not associated with a measure of mood instability obtained over the study period of at least 48 months. Mood instability used was calculated as a ratio between the number of weekly mood changes on the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS) and number of weeks of follow-up (Strejilevich et al., 2013). The study would suggest that cognitive performance is not affected by the presence of underlying mood instability. However, cognitive performance was only measured twice, at baseline and end of follow-up, at least 48 months apart. It is unclear whether cognitive performance fluctuated between these two time-points, alongside the frequency of observed mood changes.

In addition, mood instability may not be associated with global measures of attentional performance, memory, and executive function; but instead be associated with more subtle changes in the stability of cognition. Budde & Schulze (2014) identified three studies that showed greater inter-individual variability in cognitive performance over 2-4 repeated assessments in euthymic and clinically stable BD patients compared to controls (Depp et al.,

2008, 2012; Gildengers et al., 2009). It would be of interest to test whether cognition, like mood, can fluctuate over narrow temporal windows. Frequent and simultaneous remote monitoring of mood and cognition should help reveal this relationship (addressed in Chapter 4).

The aforementioned research has focused primarily on measures of non-affective cognition, that is, cognitive processing that does not integrate emotional salience or emotional stimuli. Rather, affective cognition does integrate such stimuli and often elicits an emotional response. Both are key to effective functioning given that internal factors such as mood and emotion dynamically interact during perception, attention, decision-making and memory (Nobre, *in press*). For example, mood and emotion can modulate top-down attentional processing, prioritising or biasing resources toward highly salient stimuli (Pessoa, 2008). Impairments in affective cognition, particularly emotional processing are observed in psychiatric disorders (Kjærstad et al., 2019; Miskowiak et al., 2019; Panchal, Kaltenboeck, & Harmer, 2019). It has been proposed that abnormal emotional processing results from dysfunctional communication between cognitive and affective brain networks that influence the identification and production of emotional states and their regulation on subsequent behaviour (Phillips et al., 2003). It is possible that mood instability results as a consequence of disruption to these mechanisms. The underlying neural processes are discussed in Chapter 1, section 1.7.

A systematic review by Broome and colleagues (2015) synthesised studies assessing mood instability and outcomes from affective and non-affective cognitive studies in psychiatric disorders. From these studies they summarised that the presence of mood instability was associated with greater distractibility to conflicting stimuli in attention demanding tasks, and recognition of facial emotions was impaired, alongside increased attention toward highly salient stimuli (e.g. depicting anger and disgust) in emotion recognition tasks (Broome, He et al., 2015). Adding to the above evidence, a recent study found associations between mood instability and

negative emotional processing biases in euthymic BD (Bilderbeck et al., 2016). Specifically, higher instability in self-reported depressive symptoms correlated with greater accuracy in the classification of negative words relative to positive words and higher instability in self-reported (hypo)manic symptoms was associated with greater negative bias in free recall. Whilst measures of emotional processing biases were assessed only once at baseline in these studies, they nevertheless suggest associations between mood instability and biases in cognitive emotional processing.

Only recently have studies examined associations between cognition and mood instability in healthy populations, rather than as a feature of psychiatric disorders. These studies have focused on affective cognition and the relationship between mood instability and reward. Eldar and Niv (2015) suggested that mood instability can bias the way reward outcomes are perceived, thus affecting how an individual learns about such outcomes in time. In their task, participants learnt, on a trial-by-trial basis, to choose the most rewarding stimulus after which they were presented with a random draw resulting in a large win, or loss in reward. In participants with high mood instability, an unexpected win or loss led to greater positive or negative changes in mood, and biases in perceived reward value during subsequent learning. This feedback loop was not observed in individuals reporting stable mood (Eldar & Niv, 2015). Using a reinforcement-learning model, the authors demonstrated a bidirectional relationship between mood and biases in the perceived outcomes of reward values that might contribute to mood instability. Eldar and colleagues (2016) theorised that, although mood can increase the efficiency of learning about environmental contingencies when the perception of outcomes is appropriate in intensity and duration, biases in mood toward the perception of outcomes can increase responsivity of outcomes, becoming dysfunctional in the case of mood instability (Eldar et al., 2016). Nothing is currently known about whether mood instability is associated with non-affective cognition and learning in the absence of reward. This is investigated in Chapter 4.

1.7 Possible neural correlates of mood instability

It is unclear whether and how dysfunctional neural mechanisms co-exist with the experience of mood instability. Due to the scarcity of research available, neuroimaging of psychiatric disorders more generally is discussed first.

Brain areas communicate both within and between large-scale functional networks. These functional networks can be characterised by distributed brain areas that show correlated neural activity, or patterns of functional connectivity (FC). They have been predominantly investigated by observing temporally coherent changes in blood-oxygen-level-dependant (BOLD) signal in two or more brain areas during functional magnetic resonance imaging (fMRI). Whilst healthy cognitive and affective processing is supported by complex, precisely synchronised communication within and between networks, psychiatric disorders are increasingly thought to arise from altered activity within, and disrupted communication between networked brain areas (Buckholtz & Meyer-Lindenberg, 2012; Drevets, Price, & Furey, 2008; Hamilton, Chen, & Gotlib, 2013; Menon, 2011). No specific network disruptions are attributed to any one psychiatric disorder. Just as symptoms overlap across psychiatric disorders, observed patterns of network dysconnectivity are also transdiagnostic, mainly observed across the frontoparietal network (FPN), frontostriatal network (FSN), corticolimbic network (CLN), and the default mode network (DMN), which are thought to support executive, affective, motivational and self-referential aspects of cognition (Buckholtz & Meyer-Lindenberg, 2012).

Importantly, network dysconnectivity in psychiatric disorders are not only observed during active cognitive and affective processing, but also during rest (Alamian et al., 2017; Woodward & Cascio, 2015), demonstrating the functional and clinical importance of resting-state networks (RSNs). RSNs reflect the temporal coupling of spontaneous neural activity between brain areas.

Consistent RSNs have been demonstrated in healthy individuals (Damoiseaux et al., 2006; Raichle et al., 2001) and are similar to task-related connectivity networks (Smith et al., 2009). These provide a framework to understand dysfunctional resting-state FC (rsFC) in psychiatric disorders (Hamilton et al., 2013) and mood instability. A number of studies support the view that rsFC is altered in psychiatric disorders such as BD and MDD in comparison to healthy controls, both within and between networks, including; the FPN involved in top-down regulation of attention and emotion, the salience network (SN), the dorsal attention network (DAN), and the DMN, particularly the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) involved in regulating emotional experience and emotional salience (Kaiser et al., 2015; Mulders et al., 2015; Strakowski, DelBello, & Adler, 2005; Vargas, López-Jaramillo, & Vieta, 2013). In particular, aberrant rsFC between the PFC, amygdala and cingulate cortex in those with euthymic BD has been hypothesised to be a "neural correlate of subthreshold symptoms" (Syan et al., 2018).

Whilst a number of studies have demonstrated aberrant rsFC in psychiatric disorders, only one has directly assessed whether it is associated with the presence of mood instability. Servaas and colleagues (2017) investigated associations between self-reported mood instability and alterations in FC in remitted MDD patients at high risk of recurrence (rrMDD). Participants provided self-report mood measures ten times a day, six days prior to rsfMRI. They found that rrMDD patients, compared with healthy controls, experienced greater instability in negative affect and that this was related to how information was processed within and between specific subnetworks including the DMN, FPN, and the SN, e.g. striatum. Using graph theory, two measures of network connectivity were calculated for each subnetwork; the local efficiency (a measure of integration among proximal nodes) and the participation coefficient (the extent to which a node is connected to nodes in a different subnetwork). The authors found fewer connections between the DMN and other subnetworks in rrMDD patients when compared to healthy individuals,

which they proposed reflected a more isolated position of the DMN (Servaas et al., 2017). In addition, they found that rrMDD patients who experienced more instability in feeling 'down' had significantly fewer connections between the SN and other subnetworks, and those that experienced more instability in feeling 'irritated' showed higher local efficiency coefficients in the FPN. Overall, this study suggests the possibility of detecting neurobiological correlates of mood instability that exist in a clinical population. However, clearly more research is needed in this area, including across transdiagnostic and non-clinical samples.

Most neuroimaging evidence in psychiatric disorders and mood instability comes from the use of fMRI. However, the BOLD signal is an indirect measure of neuronal activity as mediated through haemodynamic changes as a result of metabolic costs. While the haemodynamic response affords excellent spatial resolution, it lags brain activity by orders of magnitude. Magnetoencephalography (MEG) is an alternative non-invasive brain-imaging technique that provides a direct measure of the underlying neuronal activity, particularly the magnetic fields associated with excitatory post-synaptic potentials of pyramidal cells (Lopes da Silva, 2013; Proudfoot et al., 2014). Periodic variations in neural activity are termed neural oscillations, which can be categorised into distinct frequency bands (Schnitzler & Gross, 2005). Furthermore, the temporal resolution of MEG is much faster than that of fMRI, in the order of milliseconds, providing the potential to reveal important information about fast neuronal dynamics underlying healthy cognitive function.

Importantly, RSNs identified in MEG are comparable to those identified using fMRI (Brookes et al., 2011). Research utilising MEG in psychiatric research is still in its infancy (Uhlhaas, Grent-'T-Jongl, & Gross, 2018; Uhlhaas et al., 2017), but abnormal oscillations have been found in schizophrenia, ADHD, depression and BD compared to healthy controls. These MEG studies will be discussed in more detail in Chapter 5, in which MEG is used to assess whether mood

instability is associated with alterations in global oscillatory activity across frequency bands and altered neuronal dynamics of RSNs.

1.8 Pharmacological treatments for mood instability

Despite important advances in understanding psychiatric disorders and mood instability, current research has not led to advancements in identifying biomarkers or developing new pharmacological targets. A class of drugs called mood stabilisers, including lithium, carbamazepine, lamotrigine, and valproate, are used to treat BD and other disorders that demonstrate mood instability. In particular, lithium is the first-line pharmacological treatment for BD, effective in the long-term management of the disorder (Goodwin et al., 2016) and in the prevention of suicide (Cipriani et al., 2013). However, mood stabilisers, despite their name, are effective in preventing relapse to discrete 'clinical' episodes of (hypo)mania and depression in BD and do not therapeutically target persistent mood instability or result in mood stability (Goodwin et al., 2016).

Assessing the efficacy of interventions to reduce mood instability may prove informative. Indeed, mood instability has been suggested as a more sensitive outcome measure in randomised controlled trials (RCTs), rather than most currently reported outcomes such as time to relapse or recurrence of depressive or (hypo)manic episodes which likely require prolonged follow-up (Bonsall et al., 2012; Bopp et al., 2010; Faurholt-Jepsen et al., 2015; Harrison, Geddes, & Tunbridge, 2018; Saunders et al., 2016).

A recent randomised, placebo-controlled trial has assessed the effects of lithium on measures of mood instability, cognition, and neural markers over 6 weeks (Saunders et al., 2016). Whilst the results of this study are not yet available, Saunders and colleagues hypothesised that if markers of mood instability could be identified, then mood stabilisation in response to short-term lithium

treatment might predict longer term treatment outcomes and reduce the risk of acute mood episodes. This provides an interesting model in which to rapidly identify possible novel treatments. However, lithium has a significant side effect profile and potential harms (lithium toxicity) which require regular monitoring by clinicians (McKnight et al., 2012). This highlights the need to develop more acceptable pharmacological treatments for mood instability. Currently, a promising target is that of voltage-gated calcium channels (VGCCs).

1.9 Calcium signaling in psychiatric disorders and related phenotypes

Calcium is one of the most important signalling molecules in the body. Its entry and exit to and from cells, and how it is stored, is tightly controlled by VGCCs. There are a number of subtypes of VGCC including the pore-forming α_1 subunit and supporting β and $\alpha_2\delta$ subunits. L-type VGCCs (LTCC), named due to their long-lasting activation, belong to the α_1 subunit (Zamponi et al., 2015). There are four proteins of the LTCC family comprising $Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$ and $Ca_v1.4$ (Catterall et al., 2005). The $Ca_v1.2$ and $Ca_v1.3$ proteins are primarily expressed in the brain (Bhat et al., 2012). In excitable cells, influx of calcium via LTCCs controls numerous physiological processes including regulation of gene expression in neurons, neurotransmitter release, action potential generation, and synaptic plasticity (Berridge, 2014; Calin-Jageman & Lee, 2008; Casamassima et al., 2010; Striessnig et al., 2006). Rodent models have demonstrated that inhibiting the function of LTCCs using calcium-channel antagonists is associated with the disruption of drug-associated contextual cue memories in a condition place preference paradigm (Degoulet et al., 2016) as well as antidepressant and anxiolytic effects, such as decreases in immobility time during the forced swim test (Lee et al., 2012; Striessnig et al., 2006). In Striessnig et al., (2006), the effect was not present in mice with mutations in the $Ca_v1.2$ α_1 subunit, suggesting these channels are important for controlling mood behaviours in mice.

In humans, dysregulation of calcium signalling has long been associated with various psychiatric disorders, including BD and related phenotypes such as disrupted circadian activity and impaired cognitive function (Berridge, 2014). Numerous studies have identified elevated levels of intracellular calcium (Ca^{2+}) ion concentration in individuals with BD (Dubovsky et al., 1991; Dubovsky et al., 1994), which is found to be normalised with lithium treatment (Warsh, Andreopoulos, & Li, 2004; Wasserman et al., 2004). Indeed, a recent meta-analysis found that basal cellular Ca^{2+} in platelets and lymphocytes of patients with BD is elevated by an estimated 29% compared to controls (Harrison et al., 2019). The authors found evidence of elevations in both mania and depression, but not in euthymia, and in patients who were medication-free. In addition, studies have demonstrated abnormalities in calcium signalling in stem cells and neurons derived from BD patients compared to healthy controls (Chen et al., 2014; Hahn et al., 2005) of which these abnormalities are reversed in the neurons derived from responders to lithium compared to non-responders (Mertens et al., 2015; Stern et al., 2018). Alterations in the homeostasis of calcium signalling is therefore likely to play an important role in the pathophysiology of multiple psychiatric disorders.

Recent genomic evidence suggests that dysregulation in calcium signalling might, in part, be due to polymorphisms of LTCC genes, particularly the *CACNA1C* gene, which encodes the voltage-gated LTCC $Ca_V1.2$ protein (Bhat et al., 2012; Heyes et al., 2015). GWAS consistently implicate loci within *CACNA1C* with risk for BD (Craddock & Sklar, 2013; Keers, Farmer, & Aitchison, 2009). *CACNA1C* is also a risk loci for major depression and schizophrenia (Green et al., 2010; Liu et al., 2011; Rao et al., 2016; Smoller et al., 2013), indicating it is a shared susceptibility gene. Genetic evidence therefore cuts across psychiatric diagnoses, much like mood instability. Rodent and patient work strongly implicate *CACNA1C* in mood, working memory, learning, reward responsiveness, sleep, and neural plasticity (Heck et al., 2014; Kabir, Lee, & Rajadhyaksha, 2016; Koppe et al., 2017; Lancaster et al., 2014; Moon et al., 2018; Moosmang, 2005; Parsons et al.,

2013), suggesting LTCCs also contribute to cognitive and circadian aspects of psychiatric phenotypes. Although a recent GWAS did not identify associations between mood instability and *CACNA1C,* this study was limited by a single question used to identify mood instability and self-report to identify excluded psychiatric disorders (Ward et al., 2019). Nevertheless, a great body of evidence provides the rationale to think that calcium signalling might play an important role in mood instability. The BD risk variant in *CACNA1C* is likely to increase (rather than decrease) $Ca_v1.2$ channel expression and function (Bigos et al., 2010; Yoshimizu et al., 2015), suggesting antagonism of the channel may be effective in psychiatric disorders. Genomic findings have ignited renewed interest into research of LTCC antagonists as potential treatments for psychiatric disorders (Harrison, Tunbridge, Dolphin, & Hall, 2019; Zamponi et al., 2015), Their clinical use is discussed below.

1.10 Calcium channel antagonists

Existing LTCC antagonists are licensed and currently used in cardiovascular medicine to treat hypertension and angina. They have previously been used in clinical studies as potential pharmacological treatments for BD and mood regulation (Levy & Janicak, 2000; Pazzaglia et al., 1993). A recent systematic review identified 23 studies that assessed calcium-channel antagonists in BD. Six were RCTs and seventeen were observational studies. Six RCTs comparing verapamil, an LTCC antagonist of the phenylalkylamine type, with placebo or lithium, demonstrated no evidence that it was effective during episodes of acute mania (Cipriani et al., 2016). The authors suggested this was possibly due to the poor blood-brain barrier (BBB) permeability of verapamil, compared to other LTCC antagonists. Overall, the lack of controlled studies and absence of studies observing the effect of LTCC antagonists across the course of BD provided no strong evidence for or against their use. It is therefore of interest to investigate LTCC antagonists that permeate the BBB in rigorously controlled studies that can assess their effects on mood and mood instability, as well as cognition and brain activity known to be affected by calcium

signalling (Harrison, Tunbridge, et al., 2019). Chapters 6 and 7 describe a double-blind study assessing the behavioural and neural effects of a LTCC antagonist that does permeate the BBB.

A small number of studies have assessed psychiatric outcomes in individuals using LTCC antagonists for the purpose of cardiovascular health. Data from electronic medical records in Scotland showed higher rates of hospital admission for depression in individuals prescribed LTCC antagonists, compared to other hypertensive medications (Boal et al., 2016). However, this study did not account for confounding by unmeasured covariates, and therefore requires validation. More recently, Hayes and colleagues (2018) used data from Swedish population registers to compare psychiatric outcomes at times when an individual was exposed, and not exposed, to LTCC antagonists. They showed that, in individuals with BD, schizophrenia and non-affective psychosis, exposure to LTCC antagonists during follow-up resulted in 10-20% lower rates of psychiatric hospitalisation and self-harm, but not for non-psychiatric hospitalisation (Hayes et al., 2018). Specific improvement for psychiatric outcomes with exposure to LTCC antagonists led Hayes and colleagues (2018) to conclude that this class of drug would be a potential candidate for repurposing. Interestingly, epidemiological studies not only suggest a possible psychiatric signal of LTCC antagonists, but also for other brain disorders. Meta-analyses show their use is associated with a 20-30% lowered risk of developing Parkinson's Disease (Liss & Striessnig, 2019).

1.11 Aims of the thesis

Mood instability is a psychopathological and transdiagnostic phenotype, also present in a proportion of the general population. It is assumed to be useful in psychiatric research, in line with the Research Domain Criteria (RDoC), a project of the National Institute of Mental Health (NIMH) (Broome, Saunders, et al., 2015; Insel et al., 2010). Through integration of self-reports, neuropsychological and cognitive testing, measurement of brain activity, and genetic profiling,

the RDoC aims to understand functioning and identify treatment targets that span traditional diagnostic boundaries. Importantly, it suggests symptoms should be jointly considered with biological processes relevant to the dysregulation of cognition and emotion (Insel & Cuthbert, 2015). Following this approach, this thesis, and the studies within it, focuses on mood instability rather than on any particular discrete psychiatric diagnoses.

Both mood instability and cognitive deficits exist across psychiatric disorders, but little is known about the relationship between them and the direction of any potential relationship. To redress this gap, the first part of this thesis examines whether mood instability is related to disruption in mechanisms that sustain and balance emotional and cognitive function. The COgnition and Mood Evolution across Time study (COMET), was a 10-week multimodal observational study designed to enable the longitudinal investigation of mood, cognition, physical activity, and neural activity. The COMET study was set-up and actively recruiting at the beginning of this DPhil, and my primary initial role was in the collection of neuroimaging data. Utilising self-reported mood data from COMET, Chapter 2 quantifies the longitudinal course of mood instability and compares it to one-off measures of mood instability. Chapter 3 assesses whether there are any baseline attentional processing deficits in participants with high levels of mood instability compared to those with low levels of mood instability and examines whether emotional stimuli bias attentional processing parameters. Chapter 4 examines longitudinal associative learning data and investigates whether task performance over time is associated with mood instability. In Chapter 5, resting-state MEG data are analysed using two different methods. Firstly, differences in global oscillatory power across different frequency bands are explored between individuals with low and high levels of mood instability. Secondly, a more dynamic analysis approach is applied in order to investigate whether transient brain states and their associated networks demonstrate more unstable activity in individuals with higher levels of mood instability.

The second part of this thesis addresses the putative role of LTCC antagonists as a potential treatment for mood instability and hence associated mood disorders. It examines whether LTCC antagonism stabilises mood instability and/or alters dynamics of neural activity. The Oxford Calcium Channel Antagonism in Cognition, Mood and Sleep Study (OxCaMS) was a 4-week experimental medicine study using a randomised, double-blind, placebo-controlled design. In a within- and between-participant design, participants with mood instability completed mood, cognitive, and neural measures at baseline and longitudinally, both pre- and post-randomisation to a LTCC antagonist or placebo. The study was developed collaboratively during this DPhil, registered on the ISRCTN registry (https://doi.org/10.1186/ISRCTN33631053) and the study protocol published (Atkinson et al., 2019). Chapters 6 and 7 present results from OxCaMS: in Chapter 6, mood instability is compared between drug and placebo groups pre- and post-randomisation to assess whether LTCC antagonism has a stabilising effect on mood. In Chapter 7, using the same analyses as applied to MEG data in Chapter 5, it is explored whether the dynamics of resting-state MEG data are altered by LTCC antagonism. Lastly, in Chapter 8, the findings of this thesis are summarised, their implications discussed, and suggestions for further work are proposed. More specific aims and hypotheses relating to each dataset are further outlined in the relevant chapters.

Part 1 – COMET: Cognitive and Neural markers of Mood Instability

Chapter 2. Characterising mood instability in healthy individuals

2.1 Introduction

A growing body of work has been undertaken to characterise and understand mood instability in psychiatric populations. However, studies have used different measures to capture the dynamic nature of mood instability. In a recent systematic review by Marwaha and colleagues (2014), a total of 24 measures were found to be used across the literature. These included, but were not limited to the Affective Lability Scale (ALS) (Harvey, Greenberg, & Serper, 1989), the Affect Intensity Measure (AIM) (Larsen, Diener, & Emmons, 1986), the Affective Control Scale (ACS) (Williams & Chambless, 1997) and the Difficulties in emotional regulation scale (DERS) (Gratz & Roemer, 2004). However, the authors concluded that one-off measures, used independently, may fail to adequately capture the key features of mood instability (Marwaha et al., 2014).

Both mood intensity and lability are considered to be important facets of mood instability (Henry et al., 2008; Marwaha et al., 2014). Mood intensity refers to the magnitude with which positive or negative affect are experienced, whilst mood lability refers to the frequency of observed mood changes. In many studies, the AIM and ALS are used in combination to assess these features of mood instability in different diagnostic groups, including BDI and BDII, BPD and ADHD (Henry et al., 2001; Koenigsberg et al., 2002; Marshall-Berenz et al., 2011; Marwaha et al., 2018; Reich, Zanarini, & Fitzmaurice, 2012; Richard-Lepouriel et al., 2016; Solhan, Trull, Jahng, & Wood, 2009; Thompson et al., 2011). Some studies suggest that mood lability, rather than mood intensity, more significantly differentiates between diagnostic groups (Henry et al., 2001) and between those with a psychiatric diagnosis and those without (Marwaha et al., 2018; Richard-Lepouriel et al., 2016).

Mood instability can also be captured with quantitative indices obtained from longitudinal, self-reported mood measures. One frequently used validated measure for longitudinal, self-report

mood monitoring is the Positive and Negative Affect Scale (PANAS) which comprises a number of positive and negative affect dimensions (Watson, Clark, & Tellegen, 1988). The negative affect dimension is said to represent feelings of nervousness, hostility and sadness, whilst the positive affect dimension represents feelings of enthusiasm, alertness and energy (Watson & Clark, 1997). Such measures can be assessed at multiple time points to capture changes in mood e.g. 10x daily, daily, and weekly, which allow for a finer grained assessment of the dynamics of positive and negative mood instability. Generally, compliance to such frequent monitoring is found to be high (Saunders et al., 2017; Walsh, Golden, & Priebe, 2016). The COMET study presented in this chapter used both single time-point and longitudinal measures to characterise mood instability.

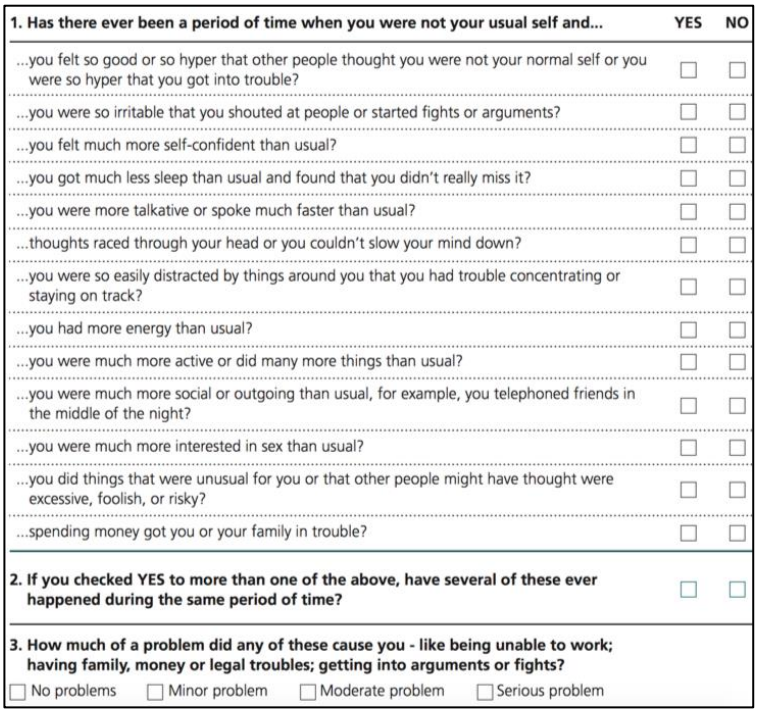
Varying approaches to quantify dynamics in mood from longitudinal data have been used in the literature (Faurholt-Jepsen, Geddes, et al., 2019). Variability captures the extent to which an individual's mood at a given time has diverged from a 'normal', or baseline mood. Most simply, the standard deviation (SD) quantifies the amount of variability, or dispersion, in mood scores across a sampling period, but does not take into account the temporal succession of the data. Instability, on the other hand, captures the degree of change in an individual's mood from one moment to another. Instability is better captured by the mean square of successive differences (MSSD) which summarizes the extent that successive mood scores differ from each other, taking into account both amplitude changes and the temporal dependency between data (Ebner-Priemer & Trull, 2009; Jahng, Wood, & Trull, 2008). The MSSD has previously been used in longitudinal studies to quantify mood instability in patients with BD (Gershon & Eidelman, 2015; Tsanas et al., 2016) and BPD (Carr et al., 2018; Jahng et al., 2008; Nica & Links, 2009; Solhan et al., 2009) and therefore allows comparison across studies. Both measures will be used to quantify variability and instability in healthy individuals with high and low levels of mood instability for the current analyses.

Aside from research examining mood instability in psychiatric populations, further research has assessed mood instability in individuals at risk of mood disorders. No difference in instability was found between offspring at high genetic risk of BD and controls using weekly clinical ratings of anxiety, depression and (hypo)mania and daily 'Mood Zoom' ratings (Duffy et al., 2019). However, using daily PANAS ratings, individuals scoring highly on the Hypomanic Personality Scale (HPS) demonstrated greater instability compared to those who had low scores on the HPS (Hofmann & Meyer, 2006). Using cut-offs on validated questionnaires such as the HPS or the MDQ therefore seems a successful way to identify healthy individuals who experience mood instability. Although differences in the choice of mood measures and temporal assessment may account for some heterogeneous findings, the investigation of mood instability in otherwise healthy individuals is appealing as confounding effects of medication, episodic mood changes and scar effects of repeated mood episodes can be avoided.

The MDQ is the most widely used brief self-report screening tool to identify manic or hypomanic symptoms of BD in research and clinical settings (Hirschfeld et al., 2000) (Figure 2.1). Higher scores on the MDQ are associated with increased probability of detecting a BD diagnosis. In particular, a symptom score of seven or more and the endorsement of psychosocial impairment (e.g. at work, home, in relationships) is found to have high specificity and sensitivity for detecting BD in outpatient populations (Hirschfeld et al., 2000; Twiss, Jones, & Anderson, 2008). However, the MDQ has also been found to identify a number of false positives, including individuals in the community with sub-threshold psychiatric symptoms (Carta et al., 2015) and those with BPD, anxiety, and ADHD (Zimmerman et al., 2011; Zimmerman et al., 2010). Zimmerman and colleagues (2011) postulated that shared symptoms of impulsivity and mood instability between these disorders may account for their false identification by the MDQ. In the general population, the sensitivity of the MDQ is found to be lower, and the specificity higher, suggesting it may be limited in detecting BD (Zimmerman & Galione, 2011), but could be used

to identify a 'bipolar phenotype' (Rock et al., 2013; Rock, Goodwin, & Harmer, 2010). Nevertheless, it has not been tested whether the MDQ can be used as a tool to identify individuals who experience mood instability, regardless of the presence or absence of a psychiatric diagnosis.

The COMET study tested whether the MDQ identified healthy individuals likely to experience high levels of mood instability, a bipolar phenotype, and those likely to exhibit low levels of mood instability. The present analyses firstly aimed to characterise overall instability, variability and mean of daily self-reported scores on the short-form of the Positive and Negative Affect Scale (PANAS-SF) (Thompson, 2007) between groups with high and low MDQ scores. Secondly, it was of interest to compare the dynamics of positive and negative affect scores longitudinally across the study period. Thirdly, as affect intensity and affect lability have been suggested to be two core features of mood instability, it was assessed how these baseline trait measures related to the degree of mood instability experienced by individuals. Given that there is little existing research exploring longitudinal mood instability in otherwise healthy individuals, these analyses were considered to be largely exploratory. It was hypothesised that participants with higher MDQ scores would demonstrate greater instability in both trait and longitudinal measures compared to individuals with lower MDQ scores.



1. Has there ever been a period of time when you were not your usual self and...	YES	NO
...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	☐	☐
...you were so irritable that you shouted at people or started fights or arguments?	☐	☐
...you felt much more self-confident than usual?	☐	☐
...you got much less sleep than usual and found that you didn't really miss it?	☐	☐
...you were more talkative or spoke much faster than usual?	☐	☐
...thoughts raced through your head or you couldn't slow your mind down?	☐	☐
...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	☐	☐
...you had more energy than usual?	☐	☐
...you were much more active or did many more things than usual?	☐	☐
...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	☐	☐
...you were much more interested in sex than usual?	☐	☐
...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	☐	☐
...spending money got you or your family in trouble?	☐	☐
2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?	☐	☐

3. How much of a problem did any of these cause you - like being unable to work; having family, money or legal troubles; getting into arguments or fights?

☐ No problems ☐ Minor problem ☐ Moderate problem ☐ Serious problem

Figure 2.1 The Mood Disorder Questionnaire (MDQ).

2.2 Methods

The study received ethical approval from the Oxfordshire Research Ethics Committee (MSD-IDREC-C2-2014-023). See Appendix 1 for contributions to data collection and data usage for the COMET study.

2.2.1 Participants

Potential participants were recruited through advertisements at the University of Oxford and in the local community. Those that expressed an interest to take part in the study were emailed the study information sheet, and a baseline questionnaire to assess eligibility. In addition, potential participants were also identified from the Sleep and Circadian Neuroscience Institute (SCNi) cohort. The SCNi sends a battery of questionnaires to assess physical and mental well-being to all University of Oxford students (undergraduates and postgraduates) at the beginning of their second academic term. Only students who had consented to take part in further studies, and who met initial eligibility criteria for the COMET study, were contacted to take part.

Participants were healthy volunteers, minimum age of 18, who were identified as having either high or low levels of mood instability as defined by responses to the MDQ. Participants who answered "yes" to experiencing seven or more symptoms in question 1 ("Has there ever been a period of time when you were not your usual self and…") and indicated in question 2 that a combination of these symptoms had occurred during the same period of time were identified as having high mood instability (high MDQ). Participants who answered "yes" to five or fewer items in question 1 were identified as having low mood instability (low MDQ). Endorsement of functional impairment in question 3 was not used as a criterion for either group in this study.

Exclusion criteria included individuals unable to give informed consent; those currently pregnant or breastfeeding; those with contraindications to MRI and MEG scanning; a history of, or current neurological condition (e.g. epilepsy); current use of medications (excluding the contraceptive pill), including use of lithium, antidepressants, antipsychotic, or anticonvulsant medication in the past 6 weeks; and current substance abuse. Additional exclusion criteria for the low MDQ group included history/current axis 1 psychiatric illness and any first degree relative with BD or other mood or personality disorder. Additional exclusion criteria for the high MDQ group included a history/current axis 1 psychiatric illness, excluding BDI, BDII or BDNOS, MDD or anxiety disorder.

Of 81 participants initially recruited to the COMET study (43 high MDQ and 38 low MDQ), two participants failed to meet inclusion criteria during study screening (1 high MDQ and 1 low MDQ) and one participant withdrew consent for any data to be used (1 high MDQ). A total of 78 participants (41 high MDQ and 37 low MDQ) completed the study screening visit (outlined below) and gave continued consent for their data to be used.

2.2.2 Overall study procedure

COMET was a 10-week prospective study. There were two study visits to the National Institute for Health Research (NIHR) Oxford cognitive health Clinical Research Facility (CRF), Warneford Hospital, at baseline (week 0) and at the end of the study (week 10). Baseline screening visit took approximately 3 hours. At this visit, participants provided informed consent and baseline demographic information including age, gender, handedness and education level. Participants were screened using the Structured Clinical Interview for DSM Disorders (SCID) by a trained researcher or clinician to validate inclusion and exclusion criteria for the study.

2.2.3 Baseline assessments

At baseline, eligible participants completed a number of standardised, trait and state questionnaires on an iPad using Qualtrics Software (Qualtrics, Provo, UT). All were short, self-report measures. Trait measures included the AIM (Larsen, 1984) and the short-form Affective Lability Scale (ALS-SF) (Oliver & Simons, 2004). The AIM consists of 40 items which participants rate, on a 6-point Likert scale (1-6, 1 = Never; 6 = Always), the extent to which they experience emotional reactions to typical life events e.g. "when I solve a small personal problem, I feel euphoric". The ALS-SF consists of 18 items for which participants indicate, on a 4-point Likert scale (0-3, 0 = very uncharacteristic of me; 3 = very characteristic of me), whether they experience mood shifts across 5 dimensions including depression, elation, anger, anxiety and euthymia e.g. "one minute I can be feeling okay and then the next minute I'm tense jittery and nervous." Sub-domains of the ALS-SF include those items that capture depression/mania, depression/anxiety, and anger. The ALS-SF has been shown to capture the same construct measured with the longer 54-item version of the scale, with a strong correlation of r=.97 between both measures (Look et al., 2010). Higher average scores on both AIM and ALS-SF measures indicate greater mood intensity or lability.

In addition to questionnaires, participants also completed a baseline cognitive task. The Combi emoTVA task assessed parameters of visual attention and attentional bias. This task is described and analysed in Chapter 3.

2.2.4 Baseline and follow-up brain scans

During the first week of the study (week 0-1) and at study endpoint (weeks 9-10), participants underwent MEG scanning and fMRI. MEG scanning took place at the Oxford Centre for Human Brain Activity (OHBA). During baseline and endpoint MEG testing, each participant underwent a 10-minute, eyes-open resting-state scan. fMRI took place at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). During baseline and endpoint fMRI testing, participants underwent a T1-weighted structural MRI scan. Resting-state MEG and structural MRI data are described further and analysed in Chapter 5.

2.2.5 Longitudinal mood and cognitive assessment

For the 10-week study period following the baseline visit, participants were asked to complete short mood assessments and cognitive tasks 5 days a week. At the baseline visit, participants were provided with an iPad and trained by a researcher in how to complete these tasks on a pre-installed iPad app. On testing days, mood assessment was always completed prior to completing the battery of cognitive tasks. All daily tasks did not take longer than 10 minutes to complete in total. If participants missed too many days in a row e.g. 2 days, they were prompted by the study team to increase compliance. All data were automatically recorded and stored. Longitudinal mood and cognitive assessments are further described below.

2.2.5.1 *Mood monitoring*

To capture real-time frequent changes in daily mood, participants completed the PANAS-SF once a day, 5 days a week. The PANAS-SF is a 10-item validated scale measuring state affect,

with 5 positive affect and 5 negative affect items (Thompson, 2007). These affect items always appeared in a pre-determined order and were as follows: upset, hostile, alert, ashamed, inspired, nervous, determined, attentive, afraid and active. Each item was rated by participants on a 5-point Likert scale (1 = Very slightly/Not at all; 5 = Extremely). Each day, participants were asked to rate items based on how they felt during the current day. Previous work has demonstrated that the PANAS can be implemented with different temporal instructions which show high internal consistency, including when participants are asked to respond daily compared to momentarily, over the past few days and over the past week (Watson & Clark, 1997; Watson et al., 1988). In addition, the underlying two-factor structure of the PANAS, comprising both negative and positive affect dimensions, is reliable and robust across these temporal intervals (Watson & Clark, 1997). Scores for individual affect items were electronically recorded and a total for each positive and negative affect subscale was available for each day.

2.2.5.2 *Cognitive assessment*

Four novel app-based cognitive tasks were developed for the COMET study to assess cognition alongside mood instability. One task is analysed as part of this thesis; 'Whack-a-T', assessing attention-based learning (described in Chapter 4).

2.2.6 Statistical analyses of mood and questionnaire data

Statistical analysis was carried out in Matlab 2016b and SPSS (Version 24, IBM Statistics for Mac). Baseline demographics were compared between groups using independent samples t-tests or Mann-Whitney U tests as appropriate for continuous data, and chi-square tests for categorical data.

2.2.6.1 *Compliance*

The completed testing sessions (both mood questionnaires and tasks) were epoched into 10 weeks based on the number of sessions completed by a participant during a 7-day period in the study (note that participants were asked to complete 5 mood and task sessions per week but would not always achieve this). Within each epoch, the mean number of testing sessions across participants was calculated. A repeated-measures ANOVA was conducted to assess task compliance across weeks. The number of completed sessions each week (10) was the within-subject measure and participant group (low MDQ vs high MDQ) was the between-subject measure. Days for which task data was not submitted were not interpolated.

2.2.6.2 *PANAS-SF Mood Questionnaire*

The overall instability, variability and mean of daily positive and negative affect scores on the PANAS-SF over 10 weeks were calculated. Instability over this time period was quantified using the MSSD. By using the square-root of MSSD scores (referred to here as RMSSD), the inherent positive skew of MSSD data is normalised for parametric analyses. The standard formula for calculating RMSSD is:

$$RMSSD = \sqrt{\frac{1}{N}\sum_{i=1}^{N-1}(x_{i+1} - x_i)^2}$$

Where N is the total number of data points in the timeseries and x_i indicates the i_{th} data point in the timeseries, with i+1 indicating successive data points. However, the RMSSD assumes that successive data points are equally distributed in time, which is not necessarily the case as participants are asked to provide 5 mood and task sessions per week and may have missing data.

The RMSSD was adjusted to account for the elapsed time between submitted data points (referred to as the tRMSSD) with the formula:

$$tRMSSD = \sqrt{\frac{1}{N}\sum_{i=1}^{N-1}\left(\frac{x_{i+1} - x_i}{t_{i+1} - t_i}\right)^2}$$

Where N is the total number of data points in the timeseries, x_i indicates the i_{th} data point in the timeseries, t_i indicates the i_{th} timestamp at which the datapoint was submitted and i+1 and t+1 indicating successive data points and timestamps, respectively. Rather than calculating the average difference between points as in the RMSSD, instead the average squared slope is calculated (Taquet et al., *in prep*). Illustrations of this and resulting low and high tRMSSD values are shown in Figure 2.2A.

There was a strong positive correlation between the RMSSD and tRMSSD for both negative (r=.94, n=74, p<.001) and positive PANAS-SF items (r=.78, n=74, p<.001) (see Figure 2.2B and 2.2C). Not accounting for longer periods of time between data points, e.g. due to missed days, led to an artifactually higher mood instability when using just the RMSSD. The tRMSSD was used to adjust for this artefact, without having to impute the missing data.

Variability was quantified using the SD, a measure of dispersion of data points from the mean. It accounts for changes in the amplitude of data points only, not their temporal dependency.

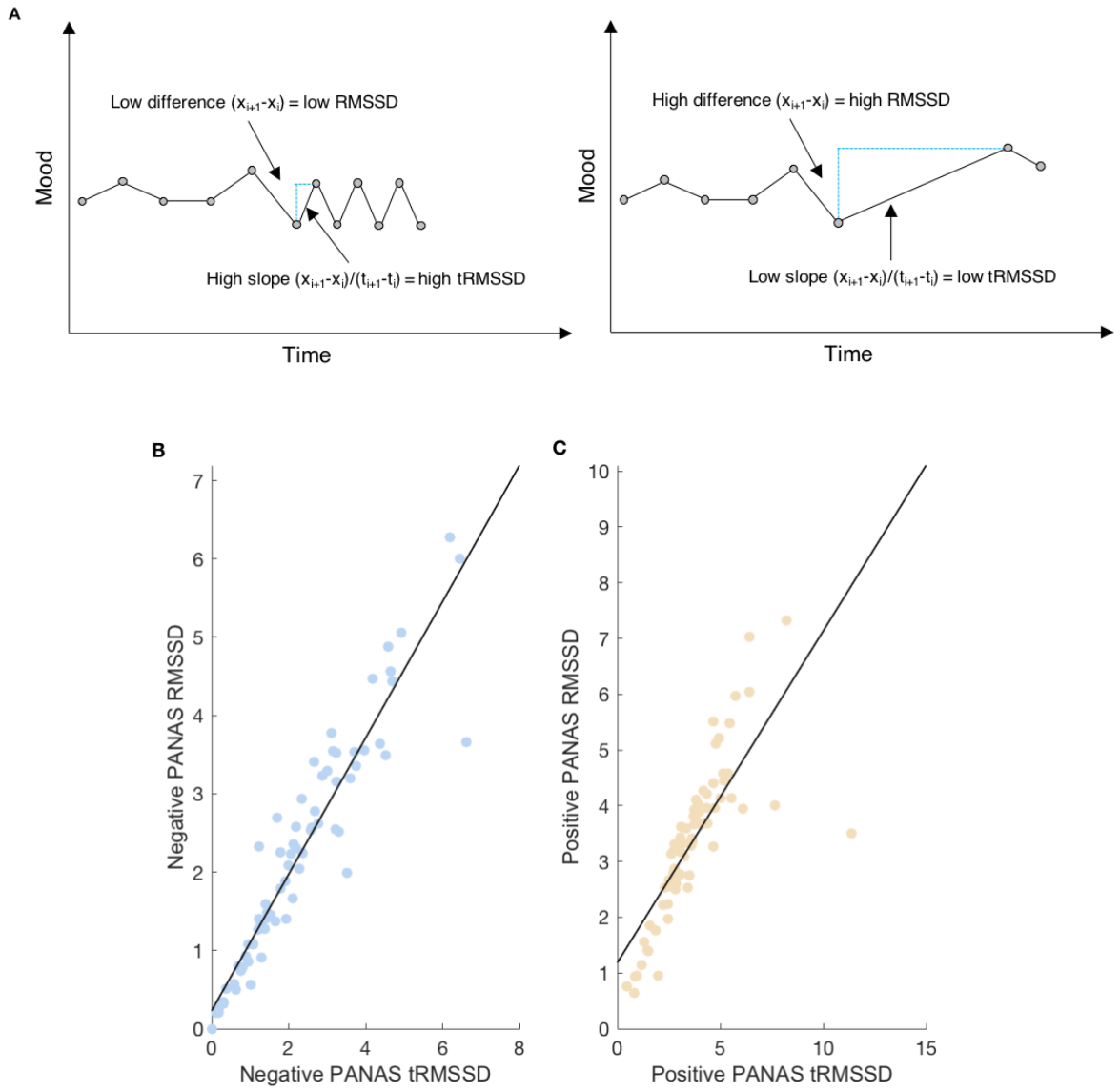


Figure 2.2. A. Illustration of the differences in calculation of RMSSD and tRMSSD for low and high values. **B.** Correlation between RMSSD and tRMSSD calculated using negative item scores on the PANAS-SF. **C.** Correlation between RMSSD and tRMSSD calculated using positive item scores on the PANAS-SF. Fit to all data points shows the least-squares (LS) line.

In addition, daily positive and negative affect subscale scores were epoched into 10 weeks, based on how many responses were submitted by a participant during a 7-day period in the study. Within each epoch, the instability (tRMSSD), variability (SD) and mean and of positive and negative affect scores were calculated to assess changes in mood across weeks. Days in which mood scores were not submitted were not taken into account in the current analysis, and missing

data were not imputed due to uncertainties in the appropriate methods of imputation (Faurholt-Jepsen, Geddes, et al., 2019).

Spearman correlations were used to explore associations between baseline MDQ scores (non-normally distributed) and overall instability in daily mood scores, and associations between mood variables and baseline questionnaire measures that utilised Likert rating scales. Change in PANAS-SF scores over time were analysed using repeated-measure ANOVAs with the between-subject factor of high or low MDQ group, and the within-subject factor of time (weeks 1-10). Where assumptions of sphericity were violated, degrees of freedom and significance values were adjusted with Greenhouse-Geisser correction. Significant differences were explored further using independent samples t-tests with Bonferroni correction.

2.3 Results

2.3.1 Baseline group differences

Of 78 participants (41 high MDQ; 37 low MDQ), one participant in the high MDQ group did not provide any longitudinal mood or cognitive data and three further participants in the high MDQ group completed the mood and cognitive tasks for less than three out of ten weeks (11 days, 14 days and 15 days) and were therefore excluded from further analyses of longitudinal data. For the remaining 74 participants (37 high and 37 low MDQ) there were no differences between groups in age ($t(72)=.22$, $p=.83$), gender ($\chi(1)=.00$, $p=1.00$), or the mean number of days of mood and cognitive task data completed ($U=598.5$, $p=.35$, $r=-.11$). Demographics of analysed participants are shown in Table 2.1.

By design, participant groups differed significantly in their baseline MDQ score, with high MDQ participants having a higher median score (Mdn=9) than low MDQ participants (Mdn=1) ($U=.0$, $p<.001$, $r=-.87$) (Figure 2.4A). The high MDQ group also demonstrated higher median scores

than the low MDQ group on trait affect intensity measured by the AIM (Mdn=145 vs. Mdn=140, U=480.5, p=.03, r=-.26), trait affect lability measured by the ALS-SF (Mdn=41 vs. Mdn=20, U=121.5, p<.001, r=-.71) and all 3 subscales of the ALS-SF (all p<.001) (Table 2.1).

Table 2.1. Baseline demographics of analysed participants	**High MDQ (*n*=37)**	**Low MDQ (*n*=37)**
Age (mean, range)	25 (18-46)	25 (18-49)
Female (n, %)	24 (65%)	24 (65%)
MDQ score (median, range)	9 (7-13)*	1 (0-4)*
Affect Intensity Measure (AIM) (median, range)	145 (87-200)*	140 (55-182)*
Affective Lability Scale (ALS-SF) (median, range)	41 (18-59)***	20 (18-40)***
ALS-SF – depression/mania (median, range)	21 (8-30)***	10 (8-20)***
ALS-SF – anxiety/depression (median, range)	12 (5-18)***	5 (5-10)***
ALS-SF – anger (median, range)	8 (5-17)***	5 (5-10)***
Tasks completed/50 (median, range)	47 (31-50)	48 (35-50)
Lifetime DSM-IV disorders (n, %)****	8 (21.6%)	0 (0%)
BD-Not Otherwise Specified (NOS)	2 (5.4%)	-
BD-II	2 (5.4%)	-
Major Depressive Disorder	6 (16.2%)	-
PTSD	1 (2.7%)	-
Past alcohol dependence	2 (5.4%)	-

SD = standard deviation. *** p<0.001, **p<0.01, * p<0.05

**** 3 participants had received 1 diagnosis of a DSM-IV Axis-1 Disorder, 4 participants had received 2 diagnoses of DSM-IV Axis-1 Disorders and 1 participant had received 3 diagnoses.

2.3.2 Task compliance

There were no group differences in the number of mood questionnaires and cognitive tasks completed each week, (F(1,65)=.36, p=.55, η_{p^2}=.005), or group-by-week interaction (F(6.32, 410.95)=.95, p=.47, η_{p^2}=.014, Greenhouse-Geisser corrected). Participants completed

significantly fewer mood questionnaires and tasks with increasing weeks in the study (F(6.32,410.95)=3.55, p=.002, η_{p^2}=.052, Greenhouse-Geisser corrected). Post-hoc comparisons revealed that, compared to week 1, compliance was significantly lower in weeks 9 (mean difference=-.79, p=.004) and 10 (mean difference=-.87, p=.016) (Figure 2.3).

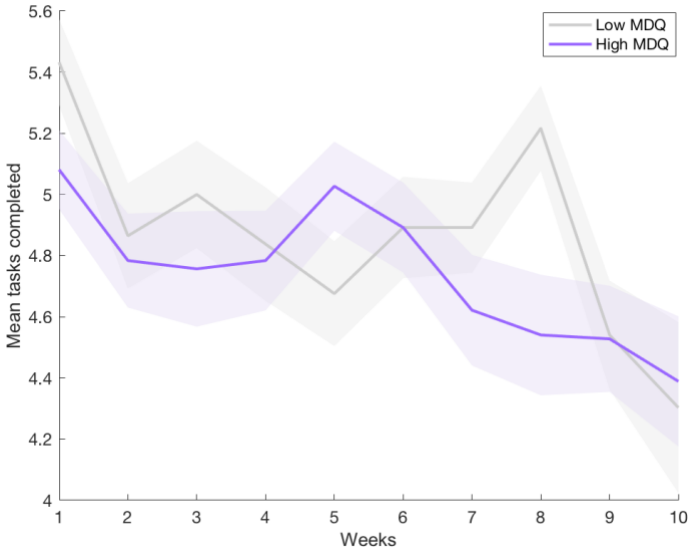


Figure 2.3. Mean number of questionnaires and tasks completed each week (epoched), by low and high MDQ groups. Error patches represent ±SE of mean.

2.3.3 Overall instability, variability and mean of PANAS-SF ratings

The high MDQ group demonstrated greater overall instability in negative affect compared to the low MDQ group, as measured by tRMSSD (2.81 ± 1.51 vs 1.61 ± 1.42, t(72)=-3.52, p=.001) but not greater overall instability in positive affect (3.97 ± 1.53 vs 3.35 ± 1.99, t(72)=-1.5, p=.14) (Figure 2.4B).

High MDQ participants further demonstrated greater overall variability, as measured by SD, in both negative affect (2.26 ± 1.12 vs 1.18 ± .89, t(72)=-4.59, p=<.001) and positive affect (3.15 ± .82 vs 2.48 ± 1.06, t(72)=-3.05, p=.003) compared to low MDQ participants (Figure 2.4C).

The high MDQ group experienced greater mean negative affect scores (7.75 ± 2.20) than the low MDQ group (5.90 ± 1.03) ($t(72)$=-4.62, p=<.001). However, the high and low MDQ groups did not differ in mean positive affect scores (11.74 ± 2.75 vs 11.51±3.79 respectively, $t(72)$=-.30, p=.77, Figure 2.4D). All comparisons are shown in Table 2.2.

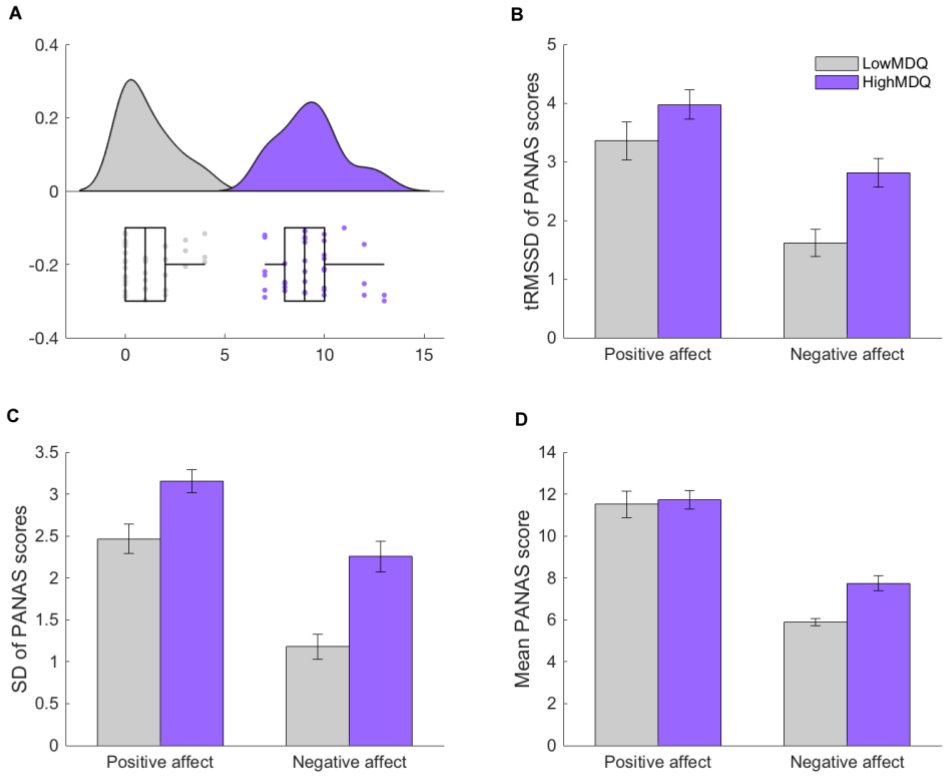


Figure 2.4. **A.** Distribution of MDQ scores in low (grey) and high (purple) MDQ groups. **B.** Group mean instability of negative and positive PANAS-SF scores. Individual participant instability quantified using time adjusted Root Mean Square of Successive Differences (tRMSSD). **C.** Group mean variability of negative and positive PANAS-SF scores. Individual participant variability quantified using SD. **D.** Group mean of negative and positive PANAS-SF scores. Error bars represent ±SE of mean.

Table 2.2. Difference in overall mood instability, mood variability and mean mood on subscales of the PANAS-SF questionnaire (mean, SD)	**High MDQ *n*=37**	**Low MDQ *n*=37**
tRMSSD negative affect	2.81 (1.51)**	1.61 (1.42)**
tRMSSD positive affect	3.97 (1.53)	3.35 (1.99)
SD negative affect	2.26 (1.12)***	1.18 (0.89)***
SD positive affect	3.15 (0.82)**	2.48 (1.06)**
Mean negative affect	7.75 (2.20)***	5.90 (1.03)***
Mean positive affect	11.74 (2.75)	11.51 (3.79)

tRMSSD = time adjusted Root Mean Square of Successive Differences, SD = standard deviation. *** p<.001, **p<.01, * p<.05

2.3.4 Correlations between MDQ scores and mood instability

There was a significant positive association between higher MDQ scores and increased levels of negative mood instability ($r_s(74)$=.38, p=.001). However, the association between higher MDQ scores and positive mood instability did not reach significance ($r_s(74)$=.21, p=.08).

2.3.5 Weekly dynamics of PANAS-SF ratings

Change in PANAS-SF scores over each week of the study were assessed to observe any differences between groups. Firstly, changes in instability were considered (Figure 2.5A). Weekly mean instability (tRMSSD) in *negative* affect scores revealed a significant main effect of group ($F(1,71)$=15.94, p<.001, ηp^2 =.18). High MDQ participants demonstrated consistently higher instability than low MDQ participants in negative affect scores in weeks 1, 3, 5-7, 9 and 10 (all p<.05). There was no main effect of week (F(6.19,439.11)=.92, p=.49, ηp^2 =.01, Greenhouse-Geisser corrected) or group by week interaction ($F(6.19,439.11)$=1.29, p=.26, ηp^2 =.02, Greenhouse-Geisser corrected). Weekly mean instability (tRMSSD) in *positive* affect scores also revealed a significant main effect of group ($F(1,71)$=7.05, p=.01, ηp^2 =.90); high MDQ participants demonstrated higher instability in positive affect scores in week 7 (p=.03) compared

to low MDQ participants. A significant main effect of week was also observed (F(5.71,405.59)=3.98, p=.001, ηp^2 =.05, Greenhouse-Geisser corrected); instability in positive affect at week 1 was significantly higher than instability in positive affect in weeks 5, 7 and 9 (all p<.05). There was no week by group interaction (F(5.71,405.59)=.32, p=.92, ηp^2 =.004, Greenhouse-Geisser corrected).

Secondly, changes in variability, as measured by SD, were considered (Figure 2.5B). Weekly mean variability in *negative* affect revealed a significant main effect of group (F(1,71)=17.90, p<.001, ηp^2 =.20). High MDQ participants demonstrated consistently higher variability than low MDQ participants in negative affect scores in weeks 1-3, 5-7, 9 and 10 (all p<.05). There was no main effect of week (F(7.13,505.87)=1.42, p=.78, ηp^2 =.02) or group by week interaction (F(7.13,505.87)=1.86, p=.07, ηp^2=.03). Weekly mean variability (SD) in *positive* affect scores also revealed a significant main effect of group (F(1,71)=11.16, p=.001, ηp^2 =.14); high MDQ participants demonstrated higher variability in positive affect scores across weeks 1-4, 6, 7 and 9 (all p<.05) compared to low MDQ participants. A significant main effect of week was also observed (F(7.49,531.74)=4.68, p<.001, ηp^2=.06); variability in positive affect at week 1 was significantly higher than variability in positive affect at weeks 4, 7, 9 and 10 (all p<.05). There was no week by group interaction (F(7.49,531.74)=.70, p=.81, ηp^2=.01).

Lastly, changes in mean affect scores were assessed (see Figure 2.5C). Weekly mean *negative* affect scores revealed a main effect of group (F(1,71)=17.90, p<.001, ηp^2 =.20); high MDQ participants showed consistently higher mean negative affect scores than low MDQ participants over all weeks (p<.05). There was no main effect of week (F(7.13,505.87)=1.42, p=.19, ηp^2 =.02, Greenhouse-Geisser corrected), or week by group interaction (F(7.13,505.87)=1.86, p=.07, ηp^2 =.03, Greenhouse-Geisser corrected). Weekly mean *positive* affect scores did not show a main

effect of group ($F(1,71)=.04$, $p=.84$, $\eta_{p^2}=.00$). However, there was a significant main effect of week ($F(4.71,334.69)=2.85$, $p=.02$, $\eta_{p^2}=.04$, Greenhouse-Geisser corrected); mean positive affect scores at week 3 were significantly less than week 1 ($p=.02$). There was no group by week interaction ($F(4.71,334.69)=.87$, $p=.50$, $\eta_{p^2}=.01$).

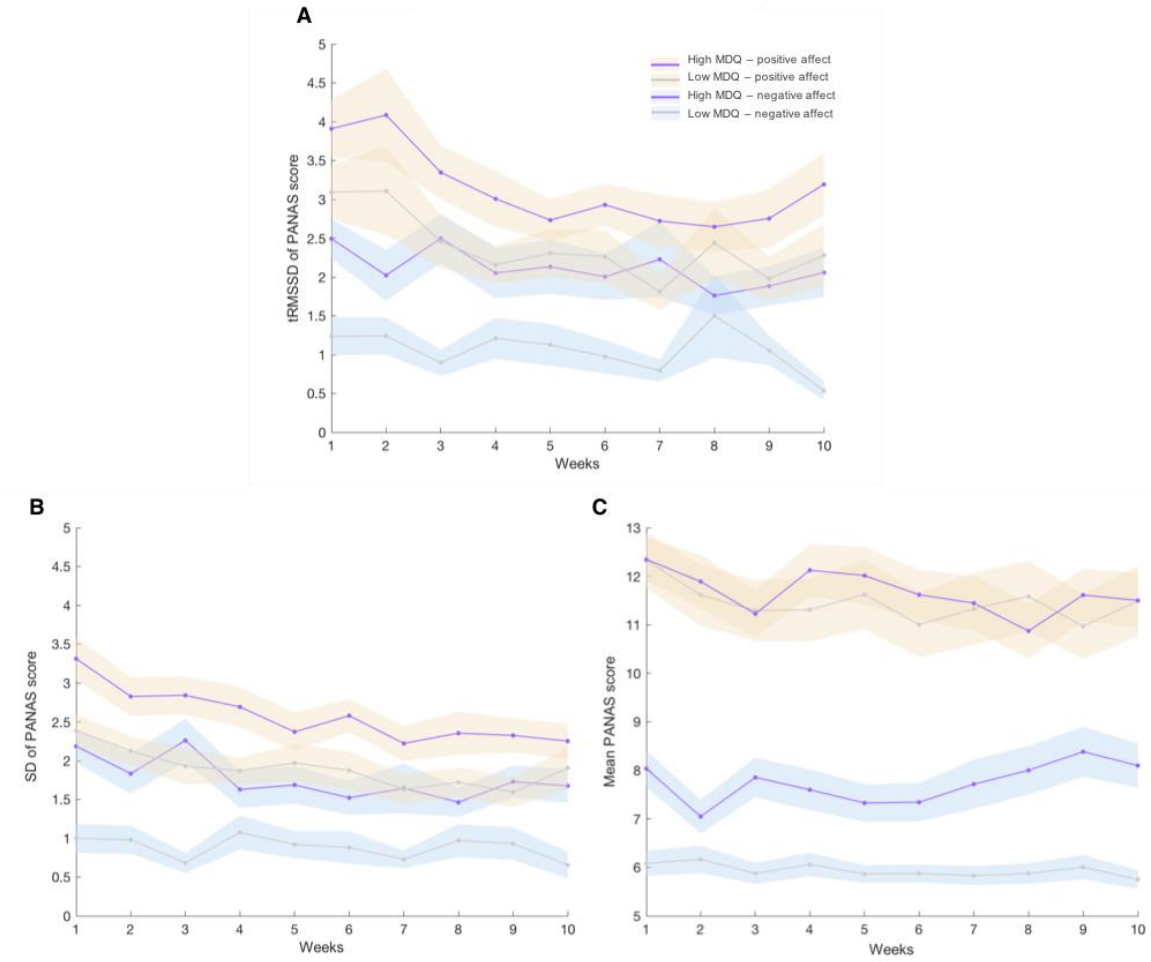


Figure 2.5. **A.** Mean tRMSSD each week (epoched) for positive affect (orange patch) and negative affect (blue patch), by low (grey line) and high (purple line) MDQ groups. **B.** Mean SD each week (epoched) for positive affect (orange patch) and negative affect (blue patch), by low (grey line) and high (purple line) MDQ groups. **C.** Mean mood score each week (epoched) for positive affect (orange patch) and negative affect (blue patch), by low (grey line) and high (purple line) MDQ groups. Error patches represent ±SE of mean.

2.3.6 Correlations between trait and longitudinal measures of mood instability

The relationship between baseline AIM and ALS-SF scores was examined. Spearman's Rho correlations revealed a significant positive relationship between total AIM scores and total scores on the ALS-SF ($r_s(74)=.42$, $p<.001$).

It was further tested whether AIM and ALS-SF baseline scores correlated with instability as quantified by the tRMSSD. Scores of affect intensity, as measured by the AIM, were significantly positively correlated with overall instability in negative affect ($r_s(74)=.31$, $p=.007$) but were not correlated with instability in positive affect ($r_s(74)=.17$, $p=.16$). Scores of affect lability, as measured by the ALS-SF, were significantly positively correlated with overall instability in both negative ($r_s(74)=.56$, $p<.001$), and positive affect ($r_s(74)=.31$, $p=.008$).

2.4 Discussion

This chapter describes a novel, prospective between-subjects experimental comparison of mood and mood instability. The findings show that the MDQ screening tool can be used to recruit individuals that experience differences in mood dynamics, captured through longitudinal remote mood monitoring. It was found that individuals with high MDQ scores experienced heightened instability, variability and mean levels of negative affect when compared to individuals with low MDQ scores. However, low and high MDQ groups can perhaps be less differentiated in their experiences of positive mood instability, variability and mean positive affect, both overall and when assessing weekly dynamics. Further, regardless of participant groups, higher MDQ scores were found to correlate with heightened experiences of negative mood instability. Measures of negative mood instability also correlated with trait measures of affect lability and affect intensity, whilst positive mood instability only correlated with trait measures of affect lability. Overall, this study validates the suitability of low and high MDQ groups for further cognitive and neural comparison.

The COMET study is the first to use the MDQ as a brief, self-report online screening tool to identify healthy individuals from the general population who are likely to demonstrate high and low levels of mood instability. Recruiting two groups of participants with varying levels of mood instability, allowed a comparison of meaningful differences in the dynamics of mood over time. Importantly, whilst the high MDQ group experienced significant mood instability, they were healthy volunteers, not recruited from a patient population. Only a small proportion met criteria for ever having been diagnosed with a psychiatric diagnosis, as indicated by the screening procedure. Four out of 37 participants (11%) met criteria for BDII or BD-NOS and six out of 37 participants (16%) met criteria for MDD, although all were euthymic or stable at the time of the study. It is unknown how many participants exhibiting high levels of mood instability from the COMET study may go on to develop mood disorders, given that mood instability is a risk factor for their development. Due to its success in recruiting this sample of interest, further work in this thesis has also used the MDQ as an online screening tool to identify individuals with high levels of mood instability in the general population (see Chapter 6).

The findings of this study only partly confirm hypotheses. Participants with greater MDQ scores did report higher scores on trait measures of mood intensity and lability at baseline than those with lower MDQ scores. In addition, the high MDQ group demonstrated higher overall instability and variability in negative affect, and higher overall variability in positive affect measured using the PANAS-SF, compared to those with low MDQ scores, which was also apparent across all ten weeks of the COMET study. However, there was no difference between groups in overall instability of positive affect, which had been expected. Other studies using the PANAS have observed greater mood instability in both positive and negative affect in healthy participants at risk of BD, and patients with BD, BPD and MDD known to experience mood instability, compared to healthy controls (Crowe et al., 2019; Hofmann & Meyer, 2006; Tsanas et

al., 2016). Conversely, some studies have reported that only instability in negative affect differentiates between patients and controls (Houben et al., 2015; Peeters et al., 2006; Servaas et al., 2017; Thompson et al., 2012).

Of note, it was observed that instability and variability in positive affect scores decreased over the course of the study (10 weeks) in both groups. It is unclear why this would occur in just one affective dimension of the PANAS-SF. However, it may provide one reason why instability in positive affect does not seem to differentiate well between groups, as discussed above. Importantly, all participants in this study were medication free and therefore any changes in mood instability or variability over time were not due to pharmacological intervention. It is possible that being more aware of mood states by regular monitoring may reduce instability and variability, or one's own perception of them (Bakker & Rickard, 2018). Whilst a qualitative assessment of participant experiences was not carried out in this study, previous work has described that regular monitoring more easily enables the identification of changes in mood states (Saunders et al., 2017). In this way, mood monitoring may unintentionally act as an intervention. This is something to consider when assessing the longitudinal relationship between mood instability and cognition, particularly in positive affect.

Mean negative, but not positive affect, was found to be consistently greater in high MDQ compared to low MDQ participants. This pattern of findings could be in line with evidence that shows depressive symptoms are increased and more frequently observed in psychiatric disorders such as BD, MDD (Judd et al., 2003; Watson, Clark, & Carey, 1988) and populations exhibiting mood instability (Bowen et al., 2013; Thompson et al., 2011). For example, Bowen and colleagues (2013) found modest correlations (ranging from 0.41-0.59) in a series of studies investigating associations between depressive symptoms and both retrospective and longitudinal measures of mood instability. Although the COMET study assessed negative affect and not

depressive symptoms, it still suggests that mean levels of negative affect may be important in the experience of mood instability.

Overall, compliance to daily PANAS-SF ratings was high, with little missing data. For high and low MDQ participants respectively, an average of 92% and 94% of mood scores were completed out of the 50 possible sessions over the study. These compliance rates are similar, and even higher than other smartphone studies that have used daily (Duffy et al., 2019; Tsanas et al., 2016), or twice daily reporting schedules (Li et al., 2019). The Automated Monitoring of Symptom Severity (AMoSS) study used a 'Mood Zoom' questionnaire consisting of 6 items (anxious, sad, angry, irritable, elated, energetic) rated daily on a 1-7 Likert scale. Compliance over 12 weeks was found to be 87% for BD patients, 93% for BPD patients and 92% for healthy controls (Tsanas et al., 2016). Similar to Duffy et al., (2019), decline in compliance was observed over time in COMET. Whilst the optimal mood monitoring schedule remains unclear, based on observations from this study, it seems that daily monitoring is practical and tolerated by participants, especially with a brief rating scale such as the PANAS-SF.

A strong association existed between the ALS-SF and the AIM, as previously has been reported in the literature (Oliver & Simons, 2004). Interestingly, high ALS-SF scores at baseline were positively correlated with both negative and positive affect instability across the course of the study, however AIM scores at baseline were only positively correlated with instability in negative affect. This is partly in line with Solhan et al., (2009) who observed that trait measures of mood instability only show modest associations with quantitative indices of mood instability obtained from longitudinal, self-report measures. Furthermore, the ALS-SF showed greater significant differences between high and low MDQ groups at baseline. Whilst the high MDQ group were not patients, this is perhaps in line with previous research suggesting the ALS-SF may be better at differentiating groups than the AIM (Marwaha et al., 2018).

Only one measure of instability was used in the present analyses; the tRMSSD. RMSSD is one recommended time-series approach to quantify mood instability (Faurholt-Jepsen, Geddes, et al., 2019), but other quantifications do exist, e.g. frequency domain methods and entropy (Carr et al., 2018; Tsanas et al., 2016). They were not employed in this analysis because they typically require more data (>100 data points) than the ~50 data points available in the COMET study. Further, other data assumptions were not met for their use, for example, the mean and SD of the data was not constant over the 10-week monitoring period as required by frequency domain analysis. In addition, although there was a low rate of missing data in this study, missing data were not imputed in this analysis. Instead, the RMSSD was adjusted for missing data by taking into account the time between data points. The RMSSD and tRMSSD were still shown to be highly correlated.

Future research may consider collecting data about daily life events, supplementing PANAS-SF ratings that are completed in the participants own environment. It would be interesting to examine whether positive or negative life events are related to instability in PANAS-SF scores over time, perhaps due to reactivity of mood. In addition, more fine-grained measures of affect could be developed, which use response scales that allow for small variations to be identified (e.g. visual analogue scales (VAS)) (Li et al., 2019; Schwartz et al., 2016). Such measures may be able to detect more variability or instability, as an alternative to using Likert scales with fewer possible responses.

2.5 Conclusion

The aim of this analysis was to validate the identification of two groups of participants with low and high mood instability, and to characterise their mood dynamics. This study supports the use of the MDQ as a brief, self-report online screening tool to target such a population. Individuals

recruited to the high MDQ group experienced significant overall mood instability in negative affect, and experienced greater negative affect overall compared to low MDQ participants. The findings suggest that understanding the dynamics of both negative and positive mood are important to contribute to the overall understanding of mood instability. Speculations are not made as to why these dynamics arise; however, the following chapters investigate associations between mood instability, cognitive performance and neural activity that might help to understand the relationship between them.

Chapter 3. Measures of selective attention for neutral and emotional stimuli in high vs. low mood instability

3.1 Introduction

Mood disorders, and mood instability have been linked to deficits in selective attention (Camelo et al., 2013), visual processing speed, visual memory and working memory (Bora et al., 2011; Bourne et al., 2013; Lera-Miguel et al., 2015). It is understood that selective attention – as the mechanisms that prioritise and select information to guide adaptive behaviour – comprise multiple factors. Much of attention research considers how information processing is modulated by top-down or endogenous influences on attention according to our current knowledge, expectations and goals (Desimone & Duncan, 1995). However, attention can also be modulated by bottom-up or exogenous influences such as the emotional or affective salience of a stimulus (Vuilleumier, 2005).

Evidence has shown that attention is prioritised toward emotional, rather than neutral stimuli (Murphy et al., 2010; Vuilleumier, 2005). For example, visual search tasks of facial expressions show that healthy participants are faster to detect negative emotional faces in a crowd of positive faces than vice versa (Hansen & Hansen, 1988) and reaction times (RTs) are faster for locating negative face targets among neutral face distractors than RTs for locating positive face targets (Eastwood, Smilek, & Merikle, 2001). In addition, negative face stimuli are more distracting than positive face stimuli as shown in flanker tasks (Fenske & Eastwood, 2003; Horstmann, Borgstedt, & Heumann, 2006). These studies suggest that when attentional resources are limited, emotional, particularly negative or threatening, information captures attention.

Negative attentional biases are often observed in clinical and subclinical populations with depression and anxiety (Armstrong & Olatunji, 2012; Joormann & Gotlib, 2007; Peckham, McHugh, & Otto, 2010). They are shown across tasks which show faster orientating towards

(Bradley, Mogg, & Lee, 1997; Gotlib et al., 2004; Leyman et al., 2007), and slower disengagement of negative emotional stimuli (Duque & Vázquez, 2015; Fox et al., 2001). Results from attentional bias studies in BD are less clear, some demonstrating mood congruent biases (Bilderbeck et al., 2017; Murphy et al., 1999; Rocca et al., 2009), while others not (Peckham, Johnson, & Gotlib, 2016). If emotional attentional biases are involved in vulnerability to or contribute to mood changes (Browning, Holmes, & Harmer, 2010) then they may also be present in individuals with heightened risk to mood disorders. Rock and colleagues found that healthy participants with high MDQ scores showed no RT differences compared to a low MDQ group on an attentional dot-probe task using threatening negative and positive words (Rock et al., 2010). However, facial stimuli may be more sensitive than words in detecting attentional biases (Pishyar, Harris, & Menzies, 2004).

The tasks used in previous studies do not assess changes related to independent attentional mechanisms and those specifically related to prioritisation of emotional stimuli versus non-emotional stimuli. The Theory of Visual Attention (TVA) is a quantitative theory allowing the separation of various building blocks of attention (Bundesen, 1990). It is a theory based on accuracy whereby measures of attentional processes are unconfounded by motor function (e.g. RT). This study applied the TVA to compare attentional functions in high and low MDQ groups in the absence and presence of emotional stimuli.

The TVA is based on the biased competition model (Desimone & Duncan, 1995) in that stimuli compete for representation in limited capacity visual short-term memory (VSTM). The TVA proposes two mechanisms of selection for visual attention; the selection of objects (filtering) and the selection of categories (pigeonholing), and two attentional control parameters; pertinence and perceptual bias values (Bundesen, 1990; Bundesen & Habekost, 2014; Bundesen, Vangkilde, & Habekost, 2015). Pertinence values are higher for features of an object that should be

attended. A weight equation determines the attentional weight of an object according to the importance of attending to specific features (i.e. high pertinence = high attentional weight). In addition, a rate equation prioritises processing of objects with relevant features. Perceptual bias values control how categorisations of attended objects are made and are higher for relevant categories. The objects and categories with higher pertinence and perceptual bias values are most likely to gain representation in VSTM. Even if one does not buy into the full theoretical background of the TVA, the variables extracted are very informative.

Using two experimental conditions, whole report (in which all objects are targets) and partial report (which includes targets and distractors), the TVA model can estimate attentional parameters for individuals. Whole report experiments produce estimates of VSTM storage capacity, speed of visual processing and threshold of conscious perception of objects, whilst partial report experiments yield estimates of the efficiency of top-down control of attention. When both whole report and partial report trials are combined in one task, this is termed CombiTVA (Vangkilde, Bundesen, & Coull, 2011).

TVA tasks have primarily been implemented using simple, non-emotional stimuli such as letters, digits or symbols. There has been one study using an Eriksen flanker task, with emotional flanker manipulation, that has qualitatively assessed their results in terms of TVA theory (Barratt & Bundesen, 2012). In this task, RTs were slower when identifying a positive target face in the presence of incompatible negative distractors compared to compatible positive distractors, but RTs were comparable when identifying a negative target face in the presence of incompatible positive and compatible negative distractors. This was interpreted as negative faces having higher pertinence values and therefore greater attentional weight than positive faces, reducing the effect of incompatible distractors. In a second experiment, this time with target letters and letter or positive and negative distractor flankers, there was no longer an effect of negative distractors,

suggesting the attentional weights of emotional distractors was low and attentional control was focused on the targets. However, the emotional stimuli used in this study were emoji-type images reflecting sad and happy faces which may not capture or distract attention as much as ecologically valid images. In the present study, photographic neutral and fearful faces were used as stimuli in a CombiTVA task.

The TVA and CombiTVA have been utilised in both healthy participants and clinical groups. As might be expected, consistency of these results varies between clinical groups, but importantly the CombiTVA task allows these attentional mechanisms to be separated. For example, adults with ADHD demonstrated significant reductions of VSTM storage capacity, whilst other attentional parameters were comparable to controls (Finke et al., 2011). TVA based assessment has not been implemented in healthy participants with mood instability.

The goal of the current study was to pilot an adaptation of the CombiTVA task which, along with whole report trials, included two types of partial report trials; (1) one using digit distractors, and (2) another using ecologically valid face distractors depicting both neutral and fearful faces. The analysis firstly aimed to explore whether the proportion of correctly reported targets in whole report trials differed across stimulus exposure durations, and between low and high MDQ groups. It was hypothesised that all participants would correctly recognise more targets with increases in stimulus duration. Secondly, it was explored whether distractor type (digits and face distractors) differentially interfered with recognition and selection of targets. It was hypothesised that the presence of emotional distractors would reduce the accuracy in recognising targets, particularly fearful face distractors compared to neutral distractors, and perhaps to a greater extent in the high MDQ group. Thirdly, differences in model-based TVA estimates assessing discrete components of attention were compared between high and low MDQ groups. It was hypothesised that participants with high mood instability might show subtle reductions across

these discrete attentional measures and that the presence of emotionally valanced distractor types would affect estimates of attentional weights. Lastly, in more exploratory analyses, associations were tested between model-based TVA parameters and measures of mood instability.

3.2 Methods

3.2.1 Participants

Participants were those recruited to the COMET study who met all inclusion criteria as previously outlined in Chapter 2, section 2.2.1. Data from 78 participants (41 high MDQ and 37 low MDQ controls) were available. This sample includes 4 participants in the high MDQ group who completed the baseline screening visit but were excluded from analyses in Chapter 2 due to not completing longitudinal mood monitoring.

3.2.2 General Procedure

The baseline screening visit took place at the NIHR CRF, as described in Chapter 2. At the end of this visit, participants completed a cognitive task, the Combi emoTVA, which assessed their baseline visual processing parameters, attentional bias, and other attentional functions based on the TVA framework.

3.2.3 Combi TVA task

3.2.3.1 *Stimuli*

In order to assess TVA-derived attentional parameters the CombiTVA task was employed with whole and partial report tasks (Vangkilde et al., 2011). Whole report trials involve presentation of six targets, with no distractors, and partial report trials involve presentation of two targets and four distractors. Typically, targets are letters, and distractor stimuli can be digits, as utilised in the present task. For the purpose of this study, the CombiTVA task was adapted to include two further trial types introducing emotional distractor stimuli; partial report of two targets and four

neutral face distractors and partial report of two targets and four fearful face distractors. This adapted version is henceforth referred to as the Combi emoTVA.

The Combi emoTVA task was presented on a monitor of 530 mm width and 297 mm height, a screen resolution of 1920 x 1080 and screen refresh rate of 100 Hz, allowing display times to vary by 10 ms. On each trial, a white fixation cross was presented on a black screen for 1000 ms. Following fixation, there was an interval of 100 ms before presentation of the stimulus display. The stimulus display was randomised on each trial and could be one of five possible stimulus display types:

1. 6T-0D: whole report of six targets presented at durations of 10 ms, 20 ms, 50 ms, 80 ms, 140 ms, and 200 ms in the absence of any distractors
2. 2T-0D: whole report of two targets presented at 80 ms in the absence of any distractors
3. 2T-4D/digit: partial report of two targets, presented at 80 ms, in the presence of 4 digit distractors
4. 2T-4D/fearful: partial report of two targets, presented at 80 ms, in the presence of 4 fearful-face distractors
5. 2T-4D/neutral: partial report of two targets, presented at 80 ms, in the presence of 4 neutral-face distractors

Both whole report and partial report trials were randomly intermixed. Stimuli were presented in six possible fixed spatial locations around an invisible circle (radius = 7.5° of visual angle). Target stimuli could be any letters from a set of 20 capital letters (ABDEFGHJKLMNOPRSTVXZ) chosen randomly on any given trial. Digit distractors could be any number from 1-9 chosen randomly. All target and digit-distractor stimuli were displayed corresponding to 2.7° x 2.3° of visual angle. Neutral and fearful face distractors were grey scale images. There were 84 images of

each neutral and fearful expression. For each partial report trial four images were chosen from predetermined arrays to ensure they were matched for gender. Immediately following presentation of the stimulus, a black-and-white mask appeared at all six spatial locations. The mask appeared for 500 ms before participants were presented with a black screen on which they were prompted to record any letters they had seen by typing them into a standard keyboard in any order. Participants were told to ignore any distractors and not to enter these as responses. After recording all letters seen in one trial, participants pressed 'enter' to submit responses and advance to the next trial. Figure 3.1A shows a single trial in the task, and Figure 3.1B shows the possible conditions.

3.2.3.2 *Procedure*

All participants were provided with standardised task instructions to read and one practice block of 18 trials was completed before the task began. During the practice, responses were monitored to ensure instructions were followed correctly. Following the practice, participants completed 18 blocks of 18 trials, a total of 324 trials of which 162 were whole report six target trials, 81 were whole report two target trials, 81 were partial report digit distracter trials, 81 were partial report neutral face distractor trials and 81 were partial report fearful face distractor trials. Trials were randomised within each block. Participants were informed that their RT was not being recorded, and they should report all the target letters they were "fairly certain" of having seen. At the end of each block, participants were given feedback on their accuracy rate. In order to analyse the TVA, it is desirable to equate the criterion used across participants. Participants were asked to maintain an accuracy range of 80-90% in their reporting of targets; if their accuracy was higher, they were encouraged to be less conservative and guess more, and if their accuracy was lower, they were encouraged to guess less. The task took approximately 40 minutes.

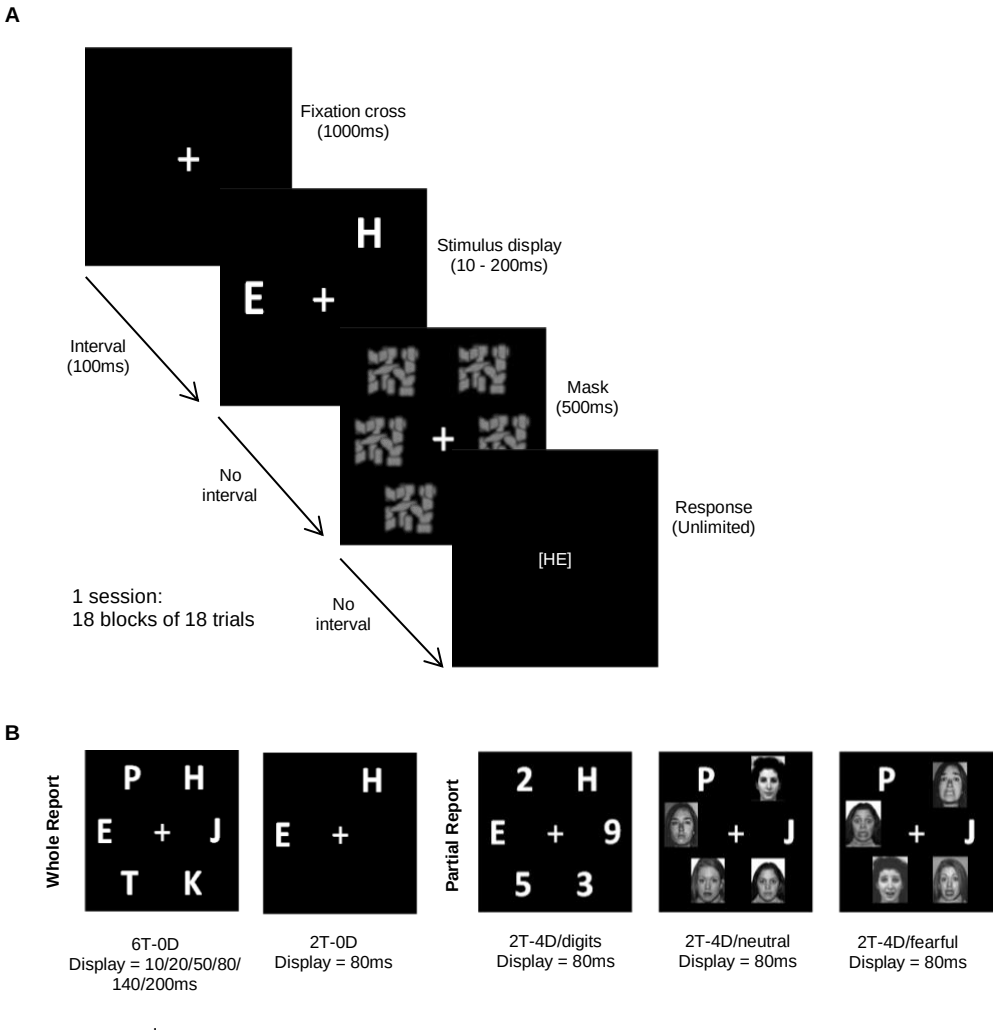


Figure 3.1. **A**. Task schematic showing progression of screens presented during one trial. **B.** The possible trial types, whole and partial report, and their on-screen exposure times.

3.2.3.3 *Estimation of TVA parameters*

The CombiTVA allows the estimation of multiple parameters representing attentional performance across the different task conditions (Vangkilde, Bundesen, & Coull, 2011). These parameters are modelled by TVA based on a maximum-likelihood fitting procedure (Dyrholm et al., 2011; Kyllingsbæk, 2006) and are graphically shown in Figure 3.2. Using this procedure, four parameter estimates were derived: (1) *K*, the capacity of VSTM measured by the number of letters reported from all targets and representing the horizontal asymptote of the fitted curve; (2) *C*, the speed of visual processing measured in letters processed per second, represented by the slope of the curve; (3) t_0, the threshold of conscious perception and the point at which the curve

rises from the abscissa; and (4) α, the efficiency of top-down selectivity defined as the ratio between the attentional weights allocated to a distractor and to a target, estimated by comparing performance in partial report trials (two targets and four distractors) with performance in whole report trials (two targets no distractors only) (Habekost, 2015). This will henceforth be referred to as the distractibility index. Values of α close to zero indicate no distractibility/efficient selection of targets and values close to one indicate high distractibility with no prioritisation of targets compared with distractors.

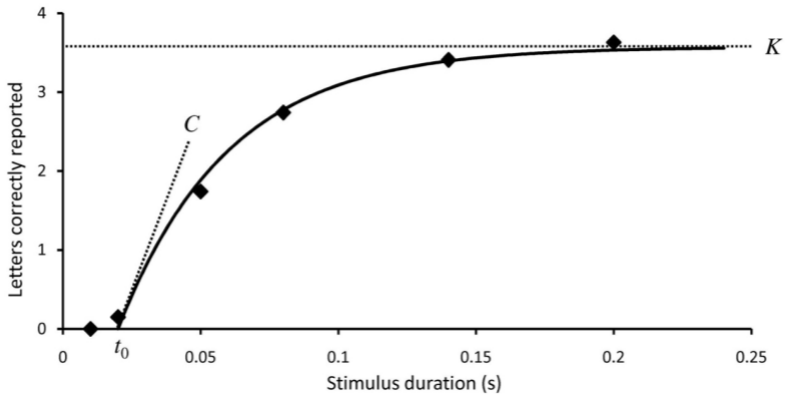


Figure 3.2. Plot taken from (Habekost, 2015), demonstrating the estimation of TVA-based model parameters derived from whole report data, the capacity of visual short-term memory *K*, the speed of visual processing *C* and the threshold of conscious perception t_0. The solid curve represents maximum likelihood fits to the observed data.

When estimating the first three parameters (*K*, *C* and t_0), the change in performance with increasing stimulus exposure times is measured, hence these whole report trials are presented at 10, 20, 50, 80, 140 and 200 ms. As might be expected, participants report very little at 10 ms, but the mean number of targets reported rises steadily with increasing exposure durations. This rise begins to flatten off at the maximum exposure, on average, between three and four targets. Using each participants parameters, *K*, *C* and t_0, the TVA model outputs the number of predicted targets identified at each exposure duration.

When estimating parameters for the distractibility index the model does not require variations in stimulus exposure duration and therefore partial report trials are presented at a fixed exposure duration of 80 ms.

3.2.3.4 *Statistical Analysis*

For the current analysis, data from the PANAS-SF mood questionnaire (Chapter 2) and Combi emoTVA task were used. Baseline demographics were compared between groups using independent samples t-tests or Mann-Whitney U tests as appropriate for continuous data, and chi-square tests for categorical data. Mean accuracy rate was based upon the number of correct targets reported out of correct or incorrect responses made but excluded trials for which there was no response. The mean accuracy was obtained for each exposure duration in whole report trials, and for each distractor condition in partial report trials. Group mean and SEs were calculated for high and low MDQ groups.

To assess mean accuracy in six-target whole report trials, a repeated-measures ANOVA was conducted with exposure duration as the within-subject factor. To assess mean accuracy in two-target partial report trials, a repeated-measures ANOVA was again conducted with distractor type as the within-subject factor. Group (low or high MDQ) was always included as a between-subject factor. Where assumptions of sphericity were violated, Greenhouse-Geisser corrections were applied. Bonferroni-corrected post-hoc comparisons were performed when significant differences were observed.

Data extraction and fitting procedures were performed using Matlab (MathWorks, Inc, version 2016b) and the LibTVA package (Dyrholm et al., 2011; Kyllingsbæk, 2006). TVA models were fit independently for each partial report distractor type (digit, neutral faces and fearful faces), each model including the whole report data. The basic model parameters (K, C, t_0) were

compared between groups using appropriate tests. The distractibility index for each distractor type was log-transformed due to being non-normally distributed and a repeated-measures AVOVA was used to assess differences between distractor types and groups. Spearman's Rho correlations were used to test for associations between negative and positive mood instability quantified by tRMSSD and estimated model parameters.

3.3 Results

3.3.1 Demographics

Due to a computer error during completion of the Combi emoTVA task, nine participants were unable to complete the full number of trials, and their task data was excluded (2 high MDQ and 7 low MDQ). Complete Combi emoTVA task data were available from 69 participants (39 high MDQ; 30 low MDQ controls). By design, participant groups differed significantly in their MDQ score, with high MDQ participants having a higher score (Mdn=9) than low MDQ participants (Mdn=1) (U=.0, p<.001, r=-.86). There were no differences between groups in age ($t(67)$=-.36, p=.72) or gender ($\chi(1)$=1.51, p=.22.). Demographics are shown in Table 3.1.

Table 3.1. Baseline demographics of analysed sample	**High MDQ (*n*=39)**	**Low MDQ (*n*=30)**
Age (mean, range)	25.36 (18-46)	24.77 (18-49)
Female (n, %)	26 (66.7%)	24 (80%)
MDQ score (median, range)	9 (7-13)*	1 (0-4)*
Affect Intensity Measure (AIM) (median, range)	147 (87-192)*	140 (55-182)*
Affective Lability Scale (ALS-SF) (median, range)	41 (18-59)***	20 (18-40)***
ALS-SF – depression/mania (median, range)	21 (8-30)***	10 (8-20)***
ALS-SF – anxiety/depression (median, range)	12 (5-18)***	5 (5-10)***
ALS-SF – anger (median, range)	8 (5-15)***	5 (5-10)***
DSM-IV disorders (n, %)****	10 (25.6%)	0 (0%)

BD-Not otherwise specified (NOS)	2 (5.1%)	-
BD-II	3 (7.7%)	-
Major Depressive Disorder	7 (17.9%)	-
PTSD	1 (2.6%)	-
Past alcohol dependence	2 (5.1%)	-
Past panic disorder	1 (2.6%)	-

SD = standard deviation. *** $p<.001$, ** $p<.01$, * $p<.05$

**** 5 participants had received 1 diagnosis of a DSM-IV Axis-1 Disorder, 4 participants had received 2 diagnoses of DSM-IV Axis-1 Disorders and 1 participant had received 3 diagnoses.

3.3.2 Combi emoTVA task performance

Distributions of task response types (correct response, incorrect response, or no response) are shown in Figure 3.3.

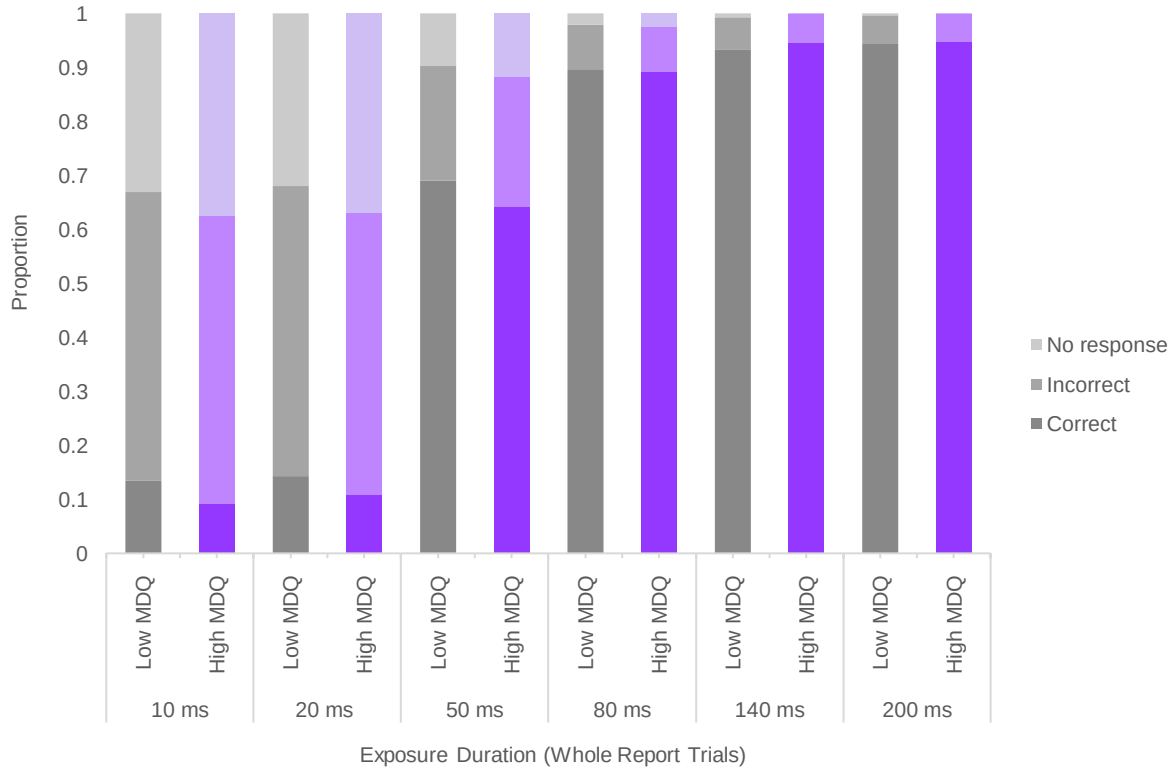


Figure 3.3. The distribution of response types (correct, incorrect, or no response) for each whole report stimulus exposure duration, by low and high MDQ group.

3.3.2.1 *Whole report trials*

Before modelling the data, mean accuracy of reported targets was compared between stimulus exposure durations of 10, 20, 50, 80, 140 and 200 ms in six-target, no distractor trials (6T-0D). As expected, mean accuracy increased with increases in stimulus exposure duration (F(2.13,142.71)=873.23, p<.001, η_{p^2}=.93, Greenhouse-Geisser corrected) (Figure 3.4). Bonferroni-adjusted post hoc comparisons demonstrated significant differences between all stimulus durations (p<.001) apart from between 10 ms and 20 ms (p=1.00) and 140 ms and 200 ms (p=1.00) (see Table 3.2). There were no differences in mean accuracy of reported targets in whole report trials between high and low MDQ groups (F(1,67)=1.09, p=.30, η_{p^2}=.02) and no interaction between stimulus exposure durations and high or low MDQ groups (F(2.13,142.71)=1.25, p=.29, η_{p^2}=.02, Greenhouse-Geisser corrected) (Table 3.3).

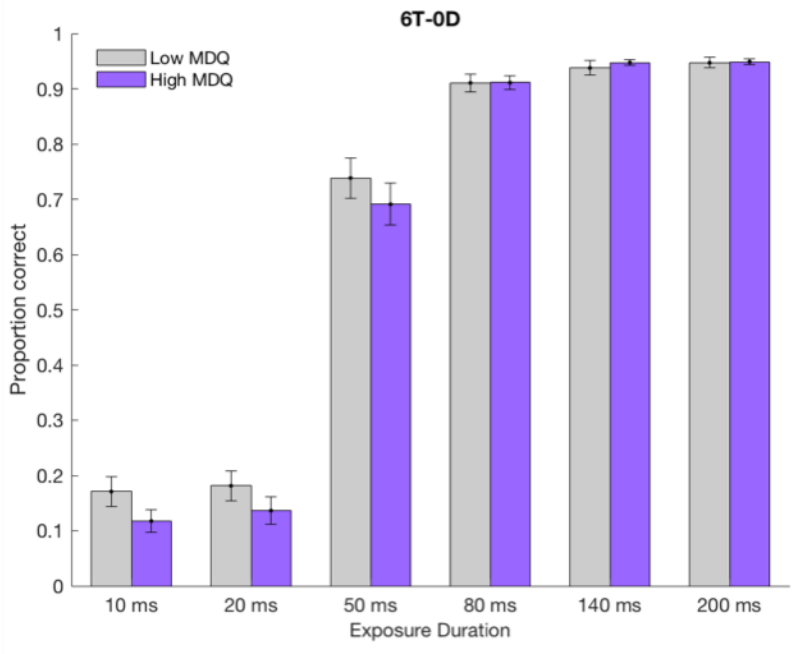


Figure 3.4. Mean accuracy of correctly reported targets (letters) for stimulus exposure durations of 10, 20, 50, 80, 140 and 200 ms in six-target whole report trials (6T-0D). Error bars represent ±SE of the mean.

Table 3.2 Bonferroni adjusted post-hoc comparisons of mean targets reported between stimulus exposure durations in whole report six-target conditions.

Target duration	Target duration	Mean difference (a-b) (se)	Sig.[b]	95% confidence interval	
				Lower Bound	Upper Bound
10 ms	20 ms	-.02 (.01)	1.00	-.04	.01
20 ms	50 ms	-.56* (.02)	.00	-.62	-.50
50 ms	80 ms	-.20* (.02)	.00	-.26	-.13
80 ms	140 ms	-.03* (.01)	.01	-.06	-.01
140 ms	200 ms	-.01 (.01)	1.00	-.02	.01

* Mean difference significant at $p<0.05$. [b]Bonferroni adjusted multiple comparisons.

Table 3.3. Proportion of correctly reported targets for whole report six-target exposure durations, for low and high MDQ participants.

Stimulus exposure duration	Low MDQ Mean (SD)	High MDQ Mean (SD)
10 ms	.17 (.15)	.12 (.13)
20 ms	.18 (.15)	.14 (.16)
50 ms	.74 (.20)	.70 (.24)
80 ms	.91 (.09)	.91 (.08)
140 ms	.94 (.07)	.95 (.03)
200 ms	.95 (.05)	.95 (.04)

3.3.2.2 *Partial report trials at 80 ms*

Mean accuracy of reported targets was compared across two-target, no distractor trials (2T-0D) and for all two-target partial report trials (2T-4D/digits, 2T-4D/neutral faces, and 2T-4D/fearful faces). A repeated-measures ANOVA revealed no main effect of group ($F(1, 67)=1.74$, $p=.19$, $\eta_{p^2}=.03$), or interaction between group and trial type ($F(2.48, 165.98)=1.04$, $p=.37$, $\eta_{p^2}=.02$, Greenhouse-Geisser corrected). However, there was a significant main effect of trial type on the mean accuracy of reported targets ($F(2.48, 165.98)=233.90$, $p<.001$, $\eta_{p^2}=.78$, Greenhouse-Geisser corrected) (Figure 3.5).

Bonferroni-adjusted post hoc comparisons firstly revealed that mean accuracy was significantly higher in 2T-0D trials (M=.84, SD=.12) than 2T-4D/digit trials (M=.57, SD=.17, p<.001), 2T-4D/neutral face trials (M=.70, SD=.16, p<.001), and 2T-4D/fearful face trials (M=.71, SD=.16, p<.001) suggesting worse performance with distraction. Secondly, mean accuracy of reported targets was significantly lower in 2T-4D/digit trials compared to all other trial types presented at 80ms (all p<.001) suggesting that digits were the most distracting of all distractor types. Lastly, there was no difference in the mean accuracy of reported targets between 2T-4D/neutral face trials and 2T-4D/fearful face trials (p=1.00). Emotion did not differentially affect task performance (Table 3.4).

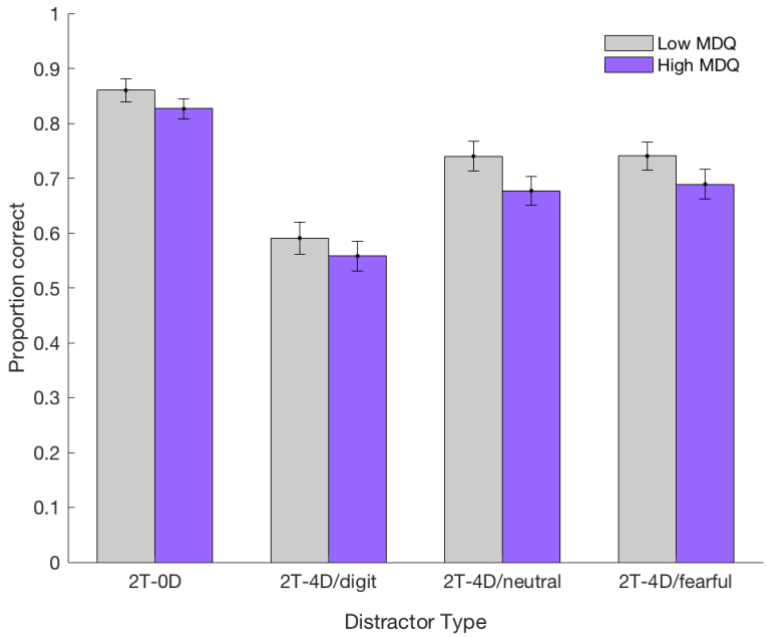


Figure 3.5. Mean accuracy of reported targets in the 2T-0D and each partial report distractor condition; 2T-4D/digits, 2T-4D/neutral, 2T-4D/fearful presented at 80 ms, for low and high MDQ groups. Error bars represent ±SE of the mean.

Table 3.4. Bonferroni adjusted post-hoc comparisons of mean accuracy of reported targets between distractor types in partial report two-target conditions.

Distractor Type (A)	Distractor Type (B)	Mean difference (A-B) (se)	Sig.[b]	95% Confidence Interval	
				Lower Bound	Upper Bound
No distractor (2T-0D)	2T-4D/digits	.27* (.01)	.00	.24	.30
	2T-4D/neutral	.14* (.01)	.00	.11	.16
	2T-4D/fearful	.13* (.01)	.00	.10	.16
Digits (2T-4D/digits)	2T-0D	-.27* (.01)	.00	-.30	-.24
	2T-4D/neutral	-.13* (.01)	.00	-.16	-.11
	2T-4D/fearful	-.14* (.01)	.00	-.17	-.12
Neutral (2T-4D/neutral)	2T-0D	-.14* (.01)	.00	-.16	-.11
	2T-4D/digits	.13* (.01)	.00	.11	.16
	2T-4D/fearful	-.01 (.01)	1.00	-.02	.01
Fearful (2T-4D/fearful)	2T-0D	-.13* (.01)	.00	.16	-.10
	2T-4D/digits	.14* (.01)	.00	.12	.17
	2T-4D/neutral	.01 (.01)	1.00	-.01	.02

* Mean difference significant at the $p<0.001$. [b]Bonferroni adjusted multiple comparisons.

3.3.3 Combi emoTVA model fitting

3.3.3.1 *Quality of TVA model fit*

As described in the methods, using each participants parameters, *K*, *C* and t_0, the TVA model predicts the number of targets identified at each exposure duration. The model predictions for a representative participant are plotted alongside the observed raw data in Figure 3.6A. The model predictions for low and high MDQ groups are shown alongside the averaged observed raw data for each group in Figure 3.6B. The model predictions closely match the observed behavioural data, illustrating a good model fit.

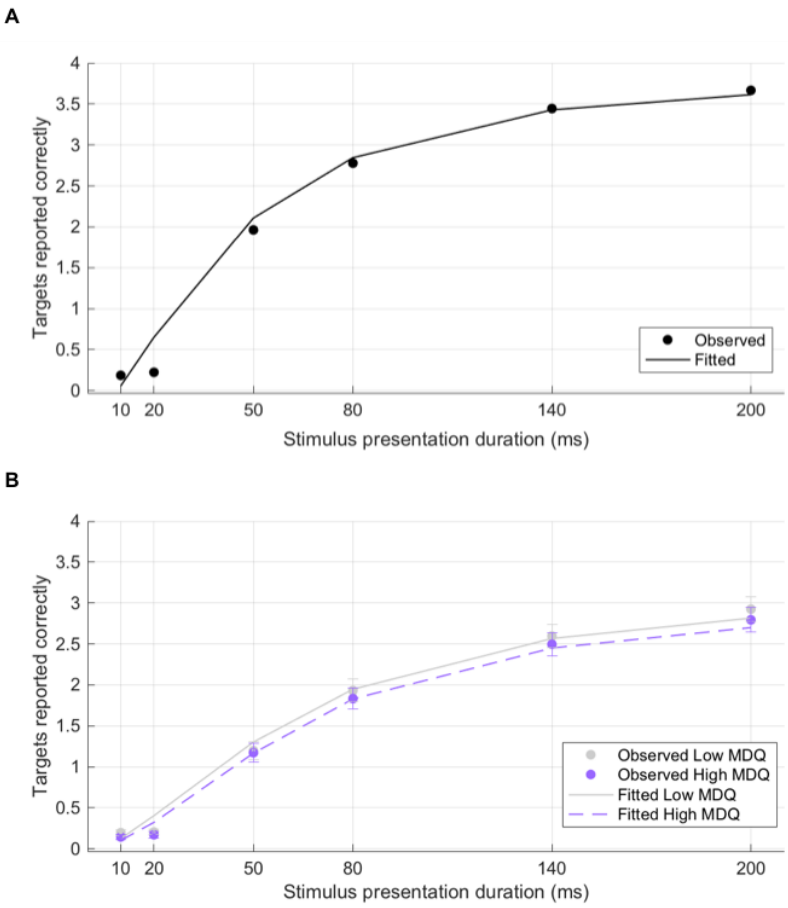


Figure 3.6. A. The black dots show the observed data of mean targets correctly reported from a representative participant. The solid line represents the TVA-based model fits of correctly reported targets which closely follow the observed data. **B.** Whole report observed and fitted performance for both low and high MDQ participants.

3.3.3.2 *Whole report trials*

Independent-samples t-tests were used to compare model parameters between groups. These revealed no significant group differences in mean VSTM capacity (*K*) ($t(67)=.44$, $p=.66$), or mean visual processing speed (*C*) ($U=559$, $p=.89$, $r=-.02$). There was a significant difference in mean perceptual threshold (t_0) between groups, with low MDQ participants displaying lower minimum exposure duration to identify targets compared to high MDQ participants ($U=387$, $p=.02$, $r=-.27$) (Table 3.5 and Figure 3.7A). Correlations between model fit parameters revealed that *K* and *C* were highly positively correlated ($r_s(68)=.66$, $p<.001$, Figure 3.8A), and *K* and t_0 were negatively

correlated ($r_s(68)$=-.32, p=.007, Figure 3.8B). Increased VSTM capacity was associated with faster visual processing speed, and lowered thresholds of conscious perception.

Table 3.5. Mean parameter estimates modelled for whole report data, and partial report data.

Model parameters	**Low MDQ**	**High MDQ**
Whole Report		
K (mean, SD)	3.15 (.85)	3.05 (1.07)
C (mean, SD)	48.38 (21.55)	52.30 (30.86)
$\mathbf{t_{0\ (ms)}}$ (mean, SD)	13.84 (11.84)*	20.07 (13.15)*
Partial Report		
α - digit distractors	.77 (.34)	.75 (.33)
α - neutral face distractors	.22 (.17)	.27 (.19)
α - fearful face distractors	.21 (.16)	.25 (.20)

* Mean difference significant at p<.05.

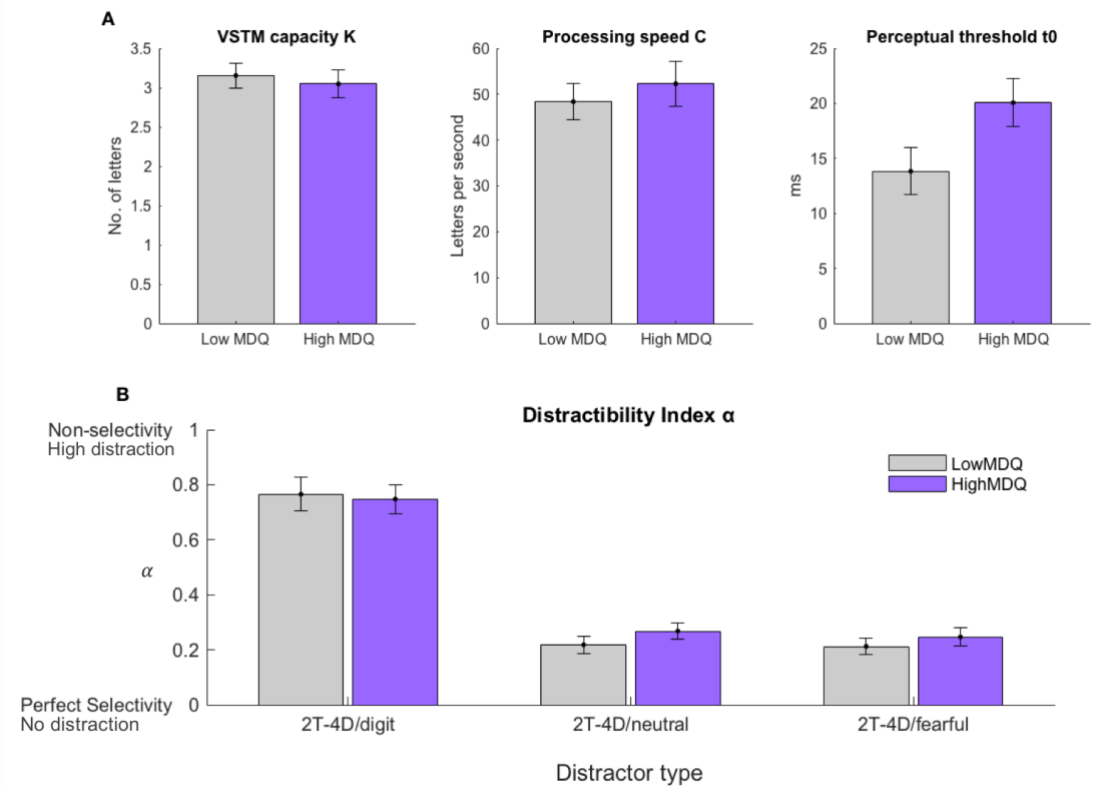


Figure 3.7. **A.** Model fits for whole report data including VSTM capacity (*K*), processing speed (*C*) and perceptual threshold (t_0) between low and high MDQ participants. Note that one participant (1 high MDQ) was excluded from t_0 correlational analysis due to abnormally low estimates in perceptual threshold (less than 0 ms) and one participant (1 high MDQ) was excluded from the *C* correlational analysis due to an abnormally high estimate of visual processing speed (>200 letters per second). **B.** Model fits of the distractibility index estimates (α) in all partial report conditions for both low and high MDQ groups. Values of 0 demonstrate no distraction/perfect selectivity and values of 1 demonstrate high distractibility/non-selectivity. Error bars represent the ±SE of the mean.

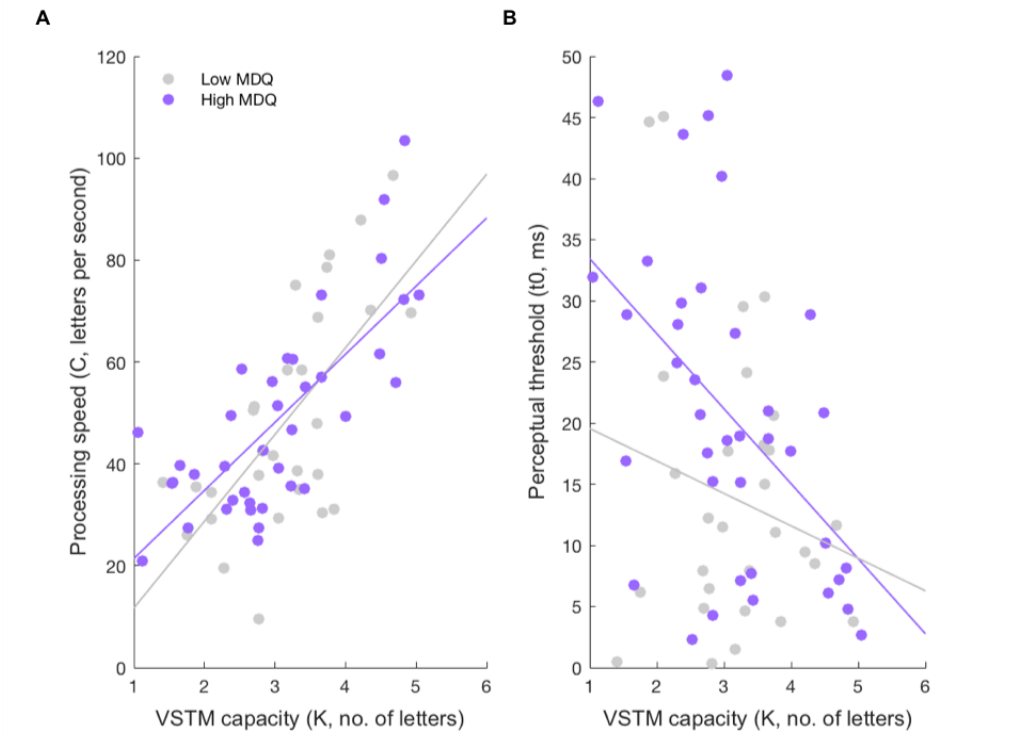


Figure 3.8. A. Significant positive correlation between processing speed (*C*) and VSTM capacity (*K*) in both low and high MDQ participants. **B.** Significant negative correlation between perceptual threshold (t_0) and VSTM capacity (*K*) in both low and high MDQ participants. Fit to all data shows the least-squares (LS) line.

3.3.3.3 *Partial report trials*

The TVA model was fit to each distractor type independently (digit, neutral faces and fearful faces), with each model incorporating the whole report data. This resulted in a parameter of top-down attentional selection of targets (distractibility index α; 0 - no distraction/perfect selectivity, 1 – high distractibility/non-selectivity) in the context of each distractor type. A repeated-measures ANOVA revealed a main effect of distractor type ($F(2,134)=120.85$, $p<.001$, $\eta_{p^2}=.64$) with Bonferroni-adjusted post hoc comparisons demonstrating that the distractibility index was significantly higher for digit distractors compared to neutral distractors ($p<.001$) and fearful distractors ($p<.001$), but not different between neutral and fearful distractors ($p=1.00$) (Table 3.6 and Figure 3.7B). There were no differences between MDQ groups in the distractibility index

across distractor types ($F(1,67)=.01$, $p=.91$, $\eta_{p^2}=.00$) and no interaction between distractor type and group ($F(2,134)=.33$, $p=.72$, $\eta_{p^2}=.01$).

Table 3.6. Mean differences in log transformed distractibility index (α), estimated through TVA-based modelling, between partial report conditions.

Distractor Type (A)	Distractor Type (B)	Mean difference in α (A-B) (se)	Sig.[b]	95% Confidence Interval	
				Lower Bound	Upper Bound
Digits (2T4D/digits)	2T4D/neutral	.53* (.04)	.00	.43	.64
	2T4D/fearful	.55* (.04)	.00	.45	.65
Neutral (2T4D/neutral)	2T4D/digits	-.53* (.04)	.00	-.64	-.43
	2T4D/fearful	.02 (.04)	1.00	-.08	.11
Fearful (2T4D/fearful)	2T4D/digits	-.55* (.04)	.00	-.65	-.45
	2T4D/neutral	-.02 (.04)	1.00	-.11	.08

* Mean difference significant at the $p<0.05$. [b]Bonferroni adjusted multiple comparisons.

3.3.3.4 *Mood instability and attentional parameters*

Correlations were conducted between TVA model parameters and indices of instability in negative mood and positive mood. Four participants in the high MDQ group were excluded from correlational analyses as they did not provide longitudinal mood measures, and tRMSSD could not be calculated (participants are those also excluded from Chapter 2 mood analyses). As t_0 was previously found to differentiate between groups, its association with mood instability was further examined. However, Spearman's Rho correlations revealed that t_0 was not correlated with negative ($r_s(34)=.07$, $p=.69$) or positive levels of mood instability ($r_s(34)=-.10$, $p=.58$) in high MDQ participants. Similarly, no correlation was observed between t_0 and negative ($r_s(30)=-.07$, $n=30$, $p=.70$) or positive mood instability ($r_s(30)=-.13$, $p=.49$) in low MDQ participants.

Further, Spearman's Rho correlations were conducted between distractibility index (α) estimates for digit distractors (given that they were most distracting compared to face distractors) and

mood instability. In high MDQ participants distractibility index for digit distractors was not correlated with negative ($r_s(35)=.16$, $p=.37$) or positive mood instability ($r_s(35)=.16$, $p=.35$). Similarly, for low MDQ participants, distractibility index for digit distractors was not correlated with negative ($r_s(30)=.03$, $p=.86$) or positive mood instability ($r_s(30)=.04$, $p=.84$).

3.4 Discussion

This chapter examined visual and attentional processing in individuals with high and low levels of mood instability, in the absence and presence of emotional distractors. Using the Combi emoTVA task, participants recognised and selected more correct target letters with increases in exposure, starting to plateau at 200 ms in line with previous TVA findings. TVA modelling worked well for this sample, with raw data similar to model predictions. No differences in visual processing and attentional function between groups were observed in TVA model-based parameters measuring VSTM capacity or speed of processing. However, high MDQ participants had a higher threshold of conscious perception compared to low MDQ participants; longer exposure times were required for stimuli to be perceived. Further, while participants performed worse with distraction, there were no differences between groups in accuracy of detecting targets in the presence of any distractor type. This was despite the high MDQ group showing non-significant but qualitatively lower accuracy scores in all distractor conditions.

Inconsistent with a priori hypotheses, digit distractors were more distracting than neutral and fearful face distractors in partial report trials. This resulted in less differentiation between attentional weights of targets and distractors in digit distractor trials. Distractibility was higher for digits, most likely because of their physical similarity to targets. Using face distractors was the main limitation of this task, as due to their dissimilarity to the targets, face distractors may have been less likely to be afforded attentional resource given the task goals. Indeed, the study by Barratt and Bundesen (2012) showed that the effect of negative distractors flankers was no

longer significant when targets were letters, compared to when targets were other emotional distractor flankers, likely due to reductions in their perceptual similarity. This demonstrates the role of top-down selective attention toward items sharing target features (Egeth, Virzi, & Garbart, 1984; Witkowski & Geng, 2019). The PFC has been shown to play a particular role guiding early stimulus distinctions and categorical representations toward those of task relevance (Duncan, 2001), and in governing attentional control in the presence of distractors (Bishop et al., 2004).

No differences in accuracy or distractibility were demonstrated between neutral and fearful face distractors as expected. As introduced at the beginning of this chapter, research in healthy and clinical populations shows that negative emotional stimuli are found to draw attention. This is not replicated in the findings of the current task. A limitation of this task is that recognition of neutral and fearful faces was not assessed. It is possible that neutral faces were interpreted as negative, especially at such short exposures, and thus equally as distracting (Lee et al., 2008). More likely, face stimuli did not provide a sensitive enough manipulation to explore the emotional component to selection in this task. If it were to be redesigned, similar emotional/non-emotional distractors and targets would have to be used to ensure categorisations of objects were similar.

Previous research has highlighted associations between mood instability in clinical populations and greater distractibility to conflicting stimuli in attention demanding tasks, and increased attention toward highly salient stimuli in emotion recognition tasks (Broome et al., 2015). For example, longer RTs to task relevant stimuli were found in the presence of emotional distractors (Kanske et al., 2013; Krause-Utz et al., 2012). It is therefore surprising that differences between high and low MDQ groups were found to exist in the perceptual threshold of stimuli. It would be necessary to replicate and validate this finding. It is possible that processing deficits in

domains such as distractibility, processing speed and VSTM capacity, become apparent in individuals who go on to develop psychiatric disorders (of which mood instability may be feature), in line with previous research. Instead, the results from the present task corroborate those from Rock, Goodwin and Harmer (2010) who found no attentional deficits in a high MDQ sample using an attentional dot-probe task with an emotional manipulation.

The Combi emoTVA task allowed the assessment of discrete and meaningful components of attention that are not often assessed in a single task, or perhaps detected on standard clinical tasks (Bundesen & Habekost, 2014). In this way, it was an appropriate choice of task to use in healthy individuals with high and low mood instability in which visual and attentional processing differences might be relatively subtle. Although these findings are not directly comparable to other TVA based studies in terms of the sample used, the estimated parameters obtained through TVA model fitting are comparable to those of similarly aged participants (Vangkilde et al., 2011). In addition, in the current task, the TVA model fits were found to closely match the observed behavioural data.

There are a number of further limitations to acknowledge. It is possible that group differences may have become apparent at longer stimulus durations. However, the rationale for setting the longest stimuli duration at 200 ms was to avoid saccades (Salthouse & Ellis, 1980). Spatial biases in where participants directed their attention, if not on the fixation cross, cannot be ruled out. Eye tracking would be a useful addition to this task, not only to ensure fixation during trials, but also to assess sensitive physiological measures of visual processing and attention such as pupil dilation and startle response. These are considerations for future research.

3.5 Conclusion

This chapter implemented a novel Combi emoTVA task in order to determine whether deficits in discrete measures of visual processing and attentional deficits, related to both non-affective

and affective stimuli, were present in individuals with high MDQ scores. Through interrogation of both behavioural data and estimates of TVA model-based parameters, there was little evidence of deficits in this group, though they did display higher thresholds of conscious perception at very short exposure durations compared to individuals with low MDQ scores. This finding will benefit from replication in similar samples.

Chapter 4. Implicit learning to guide attention in high and low mood instability

4.1 Introduction

Complementing bottom-up competitive attentional processes such as emotional salience assessed in Chapter 3, a number of top-down factors can guide and prioritise attention during visual processing. Examples include foreknowledge of the spatial location or feature of a target relevant to task goals (Treisman & Gelade, 1980; Wolfe & Horowitz, 2004), and the memory of regularities in the surrounding context in which an item is viewed (Chun & Jiang, 1998). The latter is particularly relevant to the real world, in which multiple objects form part of a complex context, or environment. Although our surrounding environment contains a vast amount of information to process, there are many regularities within it which can be used to guide behaviour towards the most relevant for our current goals (Chun & Jiang, 1998).

In a lab environment, attention to such regularities can be investigated by introducing 'contextual cueing' within visual search tasks (Chun & Jiang, 1998). Participants search for a target ('T') among distractors ('L's'). However, unlike in standard visual search experiments, the specific spatial configuration of distractors is repeated on a proportion of trials. The target in each repeated configuration appears in a consistent location relative to its context, thus, the global spatial layout is predictive of target location (Brady & Chun, 2007; Kunar et al., 2007). Search becomes more efficient over time for targets consistently encountered within repeated contexts, compared to novel contexts. This is termed the contextual cueing effect. When asked explicitly, participants are unable to discriminate between repeated and novel displays, suggesting that attention is guided by incidental and implicit learning (Chun & Jiang, 1998; Jiang & Chun, 2001).

Contextual cueing has previously been tested in psychiatric populations. In one such study, depressed participants did not demonstrate a contextual cueing effect (no facilitation for

repeated contexts), while it was present in participants with schizophrenia (Lamy et al., 2008). However participants with schizophrenia showed slower acquisition of contextual cueing compared to healthy controls, only matching the same facilitation for repeated contexts in the second half of the experiment (Lamy et al., 2008). This suggests that participants with schizophrenia may show a flatter learning curve, but not a global deficit in contextual cueing.

No studies have tested contextual cueing in individuals known to experience mood instability. It was of interest to see whether mood instability is associated with cognitive instability in a way that might disrupt learning or the ability to effectively utilise regularities to guide attention for adaptive performance. Indeed, studies assessing contextual cueing after mood manipulations have demonstrated the effect mood changes can have on attentional processing. Kunar and colleagues presented healthy participants with either fearful or neutral stimuli intended to induce a negative or neutral mood under which to perform the contextual cueing task. Individuals shown negative stimuli, showed a reduced contextual cueing effect compared to participants shown neutral stimuli (Kunar et al., 2014). The authors suggested this was consistent with evidence that emotion can influence the focus of attention, in turn affecting learning, with negative emotions leading to diminished processing of visual items and a narrowing of attention and positive emotions associated with an increased spread of attention (Fenske & Eastwood, 2003; Fredrickson, 2001; Fredrickson & Branigan, 2005; Gable & Harmon-Jones, 2010; Rowe, Hirsh, & Anderson, 2007). In a similar way, instability in mood could lead to more variable performance in implicit learning and contextual cueing when assessed over time.

No studies have investigated parallel measures of contextual cueing, or even cognitive performance, and mood instability. Whilst overall cognitive performance does not seem to show decline over longitudinal follow-up in mood disorders (Arts et al., 2011; Budde & Schulze, 2014; Chaves et al., 2011; Samamé et al., 2014; Santos et al., 2014), some studies have shown that

individuals with BD demonstrate more short-term variability in their mean level of cognitive performance, compared to healthy individuals (Depp et al., 2012, 2008; Gildengers et al., 2009). Short-term variability was assessed using cognitive measures such as visual attention and information processing speed, captured either months or 1-3 years apart. However, repeated assessments over prolonged periods are unlikely to capture variability in cognition that might be due to symptoms that fluctuate at a higher frequency (e.g. daily), such as mood instability.

For the current study, an incremental contextual cueing task was developed, adapted from the original contextual cueing task (Chun & Jiang, 1998), in order to test whether individuals could accumulate knowledge over days to guide behaviour and to test whether this was disrupted by the presence of mood instability. Both mood and cognitive measures were collected simultaneously, 5 days a week over a period of 10 weeks as part of the COMET study.

The analysis firstly aimed to test whether selective attention was different across low and high MDQ groups, by comparing baseline performance in identifying targets in novel context arrays. It was hypothesised that performance on novel arrays would not be different between groups similar to their comparable attentional performance in Chapter 3. Secondly, it was of interest to validate the novel manipulation of the task and ensure participants could learn regularities presented over days, and not just in a single testing session as has previously been shown. Thirdly, it was explored whether individuals with high MDQ scores, and therefore mood instability, demonstrated an impairment in contextual cueing compared to those with low MDQ scores. Specifically, impairment in the recognition of regularities presented in the task environment might result in shallower slopes of learning. Further, associations between instability in mood scores and instability in task performance were tested. Greater instability in mood over time may also be reflected in more variable contextual cueing performance due to frequent mood changes driving the narrowing or widening of attention day-to-day, which in turn

would affect using implicitly learned information integrated over time to guide adaptive behaviour. It was hoped that these findings could help to elucidate cognitive correlates of mood instability and thus aid in the identification of cognitive markers that can be used in the development of novel therapeutic targets for mood instability.

4.2 Methods

4.2.1 Participants

Seventy-four participants (37 high and 37 low MDQ) who completed mood and cognitive tasks for more than three out of ten weeks were included in the current analyses. Their demographics have previously been described in Chapter 2, section 2.3.1.

4.2.2 General procedure

Participants were asked to complete short mood assessments and cognitive tasks, 5 days a week. They completed these on an iPad in their own environment as described in Chapter 2, section 2.2.5. The contextual cueing task took approximately 1-2 minutes to complete each day (depending on participants' response times to find the target). Participants were asked to complete the task in a quiet environment with no distractions and without taking breaks.

4.2.3 Contextual cueing task

For the purpose of this study, the original contextual cueing task (Chun & Jiang, 1998) was adapted to include repeated array configurations across days in addition to within days. This allowed for the exploration of deficits related to memory integration over different time scales. The adapted version of the task consisted of four conditions. Participants were required to identify the location of a target ('T'), hidden among an array of 11 distractor stimuli ('L's) in the following conditions:

1. Novel - 10 different configurations presented each day that were never repeated.

2. Alternate day - 10 different configurations repeated on odd days & 10 different configurations repeated on even days.
3. Daily – 10 different configurations repeated once per day, every day.
4. Within-day – 10 repetitions of 1 configuration within a day (10 trials) that never repeated on another day.

Five-hundred and eighty stimuli configurations were created in a global configuration file for each participant in order to accommodate all conditions. The novel set of stimuli consisted of 500 randomly generated novel configurations, of which 10 different configurations were randomly drawn from each participants' global configuration file each day. The alternate day set of stimuli consisted of 20 different randomly generated configurations, of which the same 10 were drawn from the global configuration file on odd days, and the remaining same 10 for even days. The once daily set of stimuli consisted of 10 different randomly generated configurations, each repeated once per day, each day. The within-day stimuli consisted of 50 different randomly generated configurations, with 10 repetitions of one configuration within a day that never repeated on another day. A total of 40 trials were therefore presented each session across the four conditions. The order of trials was randomised but with one constraint - within-day repeated trials never followed another within-day trial. This was done to circumvent participants noticing trial repetitions within a session.

The task was completed on an iPad 2 with a 9.7-inch (diagonal) screen and 1024 x 768 pixel display. Assuming a 40 cm viewing distance, the visual search array appeared within an invisible 8 x 6 grid of possible locations that subtended approximately 21 x 28 degrees in visual angle at screen centre. The background of the search array was black, and stimuli were white. Each trial display contained 12 stimuli (1 target 'T' and 11 'L' shape distractors). Within each invisible grid of the 8 x 6 display, individual stimuli could appear in the centre, or was randomly jittered within

+/- 0.6 visual degrees (separately for x and y) from the centre. The jitter was the same for a given configuration when repeated. The size of the stimuli was 4.89mm, 0.7 x 0.7 degrees in visual angle (maximum of 25.8 x 25.8 pixels). The orientation of targets and distractors was selected randomly in one of four rotations (0, 90, 180 or 270 degrees) and was the same for repeats of the same configuration.

For three conditions that repeated over different time scales (within-day, once-daily and alternate days), a target always appeared in the same location within any particular configuration. The locations of targets within a configuration were restricted to 10 possible predetermined locations so that targets did not appear at the border, or in the centre of the invisible grid. To ensure the 10 target locations were counterbalanced among novel, alternate-day and once-daily, and within-day conditions, configurations were drawn randomly in sets of 10 when initially being created, with each set containing every target location only once. A target always appeared in every trial. The identities of the distractors within their respective spatial locations were preserved across repetitions. There were no limitations for the location of distractors in each configuration, including target locations used in other configurations.

4.2.4 Task procedure

Task instructions read as follows: 'Tap on the T shape among the L shapes. Be as quick as possible without making mistakes.' Once read, participants pressed an on-screen button to continue and begin the task. There was a pre-stimulus interval of 500 ms before the presentation of the first trial on each day. When the participant correctly selected a target, it turned yellow. However, if they incorrectly selected a distractor, the distractor turned red. Regardless of a correct or incorrect trial, a 'click' noise sounded for 100 ms after each stimulus selection. After an inter-trial-interval (ITI) of 1000 ms, the screen advanced to the next trial. After 40 trials, the task ended. RTs to finding and selecting a target or distractor were recorded as the primary

outcome. Accuracy of selecting the target over a distractor was recorded as a secondary outcome. Task screens are shown in Figure 4.1.

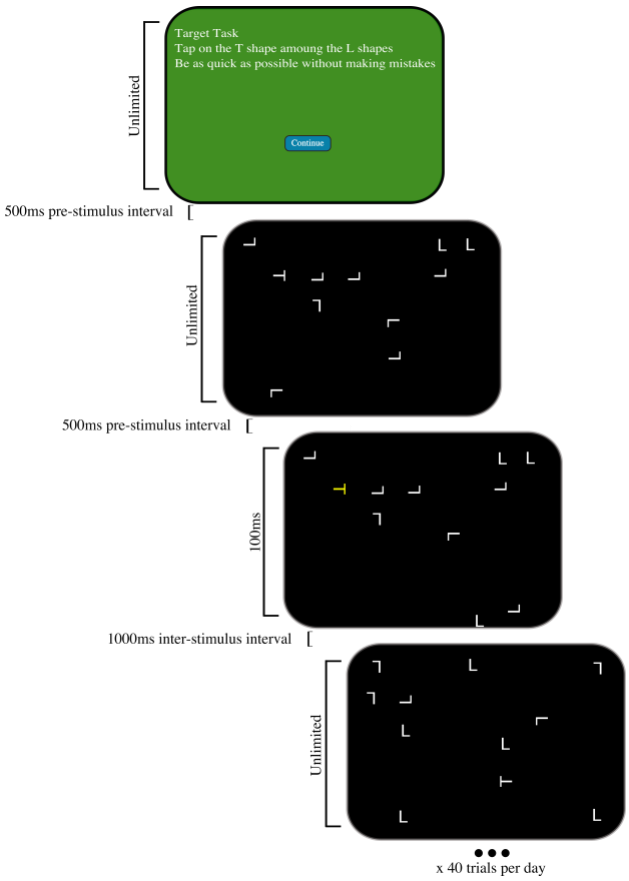


Figure 4.1. Task flow showing the progression of screens during one study session of the contextual cueing task.

4.2.5 Statistical Analysis

4.2.5.1 *Task data cleaning, outliers and accuracy*

Data were cleaned by removing RTs greater than 10,000 ms, thought to be from participants disengaging in individual trials (84 trials in total across participants - .06% of total trials), and RTs less than 0 ms reflecting responses made during the ITI (4 trials in total across participants - .003% of total trials). For each participant, further data cleaning was undertaken to remove outlier trials in which RTs were more than 3 SDs from the mean RT of each condition. This SD cut-off has been used in contextual cueing literature (Chun & Jiang, 2003). In addition, only trials

in which the target was correctly identified e.g. participants located the target 'T' and not a distractor 'L', were included in the main analyses, and error trials were removed. On 336 trials (.25%), a technical error meant that correct or incorrect responses were recorded as NaN values. These trials were also removed (85, 86, 87, and 78 trials removed from the novel, alternate day, daily and within-day conditions respectively). On average, 7.83 trials were removed per participant (breakdown by condition; novel: 7.57 trials (range 3-14), daily: 8.11 trials (range 3-13), alternate days: 7.55 trials (range 2-12), within-day: 8.10 trials (range 3-15)). For each participant, a percentage accuracy score for locating the target was computed for each condition. For both percentage accuracy and outliers, repeated-measures ANOVAs were conducted with condition as within-subject factor and group (low and high MDQ) as the between-subject factor. Where assumptions of sphericity were violated, Greenhouse-Geisser adjustments were applied. Bonferroni-corrected post hoc comparisons were performed when significant differences were observed.

4.2.5.2 *Baseline attentional performance*

For each participant, RT data were epoched into 10 weeks based on how many task sessions were completed by a participant during a 7-day period in the study. Within each epoch, the mean and SD of RTs was calculated for the novel, alternate day, and daily conditions. This resulted in a mean RT and SD of RT for each condition for each of the 10 weeks of the study. The same method was used to epoch mood data in Chapter 2, section 2.2.6.2.

The novel condition of the contextual cueing task provided a baseline attentional performance measure on each day testing. Therefore, mean RT on novel trials was used to assess group differences in baseline attentional performance in the absence of implicit learning. Mean RT on novel trials across the 10 weeks were compared between low and high MDQ groups in a repeated-measures ANOVA with mean RT for each week (1-10) as the within-subject factor, and group as the between-subject factor.

As it was hypothesised that instability in mood may be associated with instability in cognitive performance, Spearman's correlations were performed with measures of instability in mean RT for novel trials (quantified using the tRMSSD, non-normally distributed) and overall mood instability in positive and negative affect.

4.2.5.3 *Contextual cueing across days*

To assess whether contextual cueing and memory integration could be observed over different, longer time scales, performance was compared on the alternate day and daily conditions to the novel condition. Arrays repeated within-day were not considered for this analysis (within-day condition).

To assess change in RT as a function of learning, learning-slope parameters were estimated by applying the power-law function to RTs of novel, alternate day, and daily conditions. Quantifying learning in this way has previously been demonstrated in contextual cueing literature (Chun & Jiang, 2003). Also observed by Chun and Jiang (2003), the power law function yielded better fits to the current data than exponential or linear functions, demonstrated by lower mean squared error values in each condition. For each participant, search slopes were derived from the best-fit line of mean RTs across all days, for each condition. Data were normalised by subtracting the slope of the alternate day and daily conditions from the novel condition for each participant. Differences in the slope of mean RT for each condition were examined in a repeated-measures ANOVA with normalised slopes as the within-subject factor, and group as the between-subject factor.

Spearman's correlations were performed with the normalised slope of learning in the daily condition and overall mood instability in positive and negative affect.

4.2.5.4 *Contextual cueing within a day*

In order to look for any deficits in integrating information into memory at faster time scales, and to compare our findings to standard contextual-cueing studies, performance on within-day repeat and novel conditions of the task were compared. For this analysis, arrays repeated across days were not considered (e.g. alternate days and daily conditions).

For each participant, learning-slope parameters were again estimated by applying the power-law function to derive search slopes from the RTs of each trial (1-10) for novel and within-day conditions each day. Data were normalised by subtracting the slope of the within-day condition from the novel condition for each participant. An independent samples t-test was used to compare differences in the mean normalised slope between groups.

Lastly, Spearman's correlations were performed with measures of instability in the normalised slope of learning in the within-day condition each day (quantified using the tRMSSD, non-normally distributed) and overall mood instability in positive and negative affect.

4.3 Results

4.3.1 Demographics

Participant demographics are the same as those described in Chapter 2.

4.3.2 Data cleaning

There were no differences in the percentage of outliers removed during data cleaning between high and low MDQ groups ($F(1,72)=.16$, $p=.69$, $\eta p^2=.002$) or conditions ($F(3,216)=1.97$, $p=.12$, $\eta p^2=.03$). In addition there was no group by condition interaction ($F(3,216)=.43$, $p=.74$, $\eta p^2=.006$) (Figure 4.2A).

Overall accuracy across conditions was very high, in line with the literature showing accuracy of ~95% (Figure 4.2B). There were no differences in percentage accuracy in locating the target between groups ($F(1,72)=.07$, $p=.79$, $\eta p^2=.001$) or conditions ($F(2.52,181.52)=1.63$, $p=.19$, $\eta p^2=.02$, Greenhouse-Geisser corrected), nor was there a group by condition interaction ($F(2.52,181.52)=0.84$, $p=.46$, $\eta p^2=.01$, Greenhouse-Geisser corrected). The subsequent analyses include only trials in which the target 'T' was correctly identified.

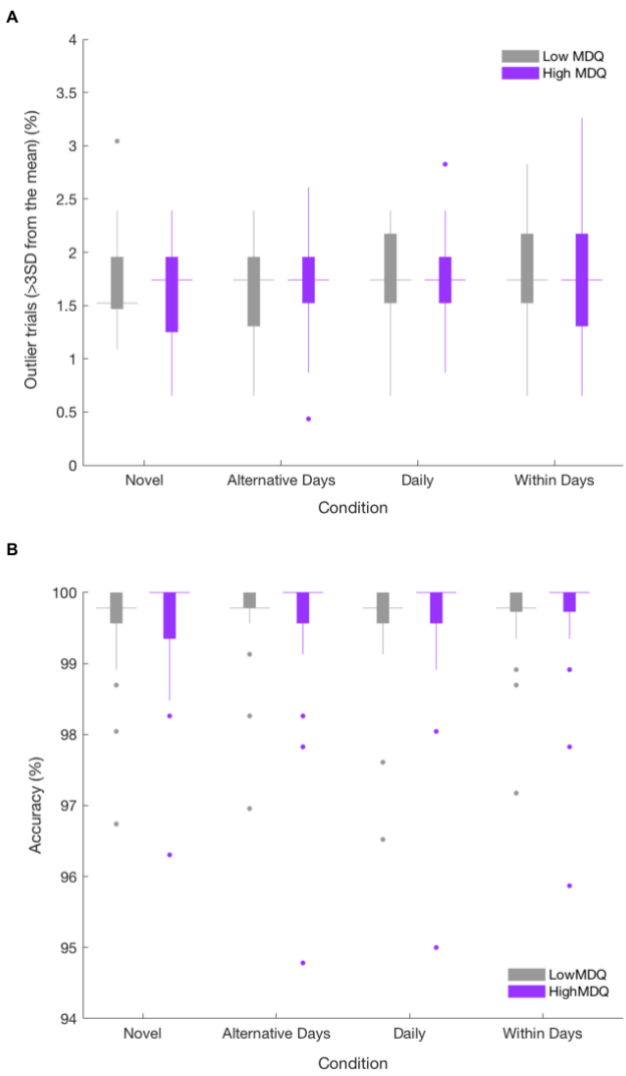


Figure 4.2. A. Overall mean percentage of outlier trials (trials >3SD of the mean RT of each condition per participant) removed from analysis, in each condition, by low and high MDQ groups. **B**. Overall mean percentage accuracy in selecting the target 'T' across conditions, by group. Error bars represent ±SE of the mean.

4.3.3 Overall attentional performance in novel trials

The novel condition of the contextual cueing task allowed assessment of overall attentional performance in the absence of implicit learning. Therefore, mean RT on novel trials across the 10 weeks were compared between groups in a repeated-measures ANOVA. This showed no significant main effect of group ($F(1,62)=.41$, $p=.53$, $\eta_{p^2}=.007$), suggesting comparable

attentional performance in low and high MDQ over the study. There was however, a significant main effect of week (F(5.21,322.82)=5.14, p<.001, η_{p^2}=.08, Greenhouse-Geisser corrected). Mean RT for novel trials at week 1 was significantly higher than weeks 2, 3, 5, 6, 8, 9 and 10 (all p<.02) but not significantly higher than week 4 (p=.08) or week 7 (p=1.00) (Table 4.1). This is likely due to task practice effects. Lastly, there was no significant interaction between week or group (F(5.21,322.82)=.70, p=.63, η_{p^2}=.01, Greenhouse-Geisser corrected).

Table 4.1. Post hoc pairwise comparisons between mean RTs for novel arrays and weeks.

Week (A)	**Week (B)**	**Mean difference (A-B) (se)**	**Sig.**[b]	**95% Confidence Interval**	
				Lower Bound	Upper Bound
1	2	69.01* (18.34)	.02	6.28	131.74
	3	81.07* (21.66)	.02	6.97	155.17
	4	64.51 (19.79)	.08	-3.18	132.20
	5	91.97* (20.36)	.001	22.33	161.60
	6	83.29* (20.06)	.005	14.69	151.89
	7	67.83 (31.39)	1.00	-39.53	175.20
	8	109.16* (25.58)	.003	21.68	196.64
	9	128.77* (24.36)	.00	45.44	212.10
	10	93.74* (18.76)	.00	29.56	157.92

* Mean difference significant at the p<.01. [b]Bonferroni adjusted multiple comparisons.

Spearman's correlations were used to investigate whether individuals who had greater mood instability, also demonstrated greater instability in RT performance for novel trials each day. One high and one low MDQ participant were excluded from this analysis due to showing extreme outlier values in instability of mean RT for novel trials. No associations between instability in daily mean RT for novel trials and negative mood instability (r_s(36)=.14, p=.42) or positive mood instability (r_s(36)=-.18, p=.30) were observed in the high MDQ group. Similarly in the low MDQ group, no associations existed between instability in daily mean RT for novel trials and negative mood instability (r_s(36)=.02, p=.91) or positive mood instability (r_s(36)=.13, p=.45).

4.3.4 Contextual cueing over days

The analysis of contextual cueing over days, the benefit of reduced RTs in finding the target 'T' in repeated arrays versus novel arrays, included the alternate day, daily and novel conditions only. To confirm the presence of contextual cueing over different time scales, and to look specifically at differences in implicit learning between individuals with low and high MDQ, learning slopes were compared between conditions and groups.

The mean RT and slope for each group and condition is shown in Figure 4.3A and 4.3B. To observe benefits in RT facilitated by contextual cueing, data were normalised by subtracting the mean of the slope of the novel condition from the daily and alternate day conditions. A repeated-measures ANOVA of the normalised slopes revealed significant group differences, with the low MDQ group (M=-.02, SD=.02) demonstrating steeper slopes of learning compared to the high MDQ group (M=-.01, SD=.01) (mean difference=-.009, SE=.004) ($F(1,72)=4.27$, $p=.04$, $\eta p^2=.06$ (see Figure 3C). In addition, there was a main effect of condition demonstrating that mean RT slopes for the normalised daily condition (M=-.01, SD=.03) were steeper than those of the normalised alternate day condition (M=-.02, SD=.02) (mean difference=-.01, SE=.003) ($F(1,72)=9.84$, $p=.002$, $\eta p^2=.12$); conditions repeated more often (daily<alternative days) lead to facilitated recognition of targets, demonstrating contextual cueing over days. There was no significant interaction between low and high MDQ groups and condition ($F(1,72)=1.07$, $p=.31$, $\eta p^2=.02$).

There were no associations between normalised slope of learning in the daily condition and negative mood instability ($r_s(37)=-.03$, $p=.88$) or positive mood instability ($r_s(37)=.03$, $p=.86$) in the high MDQ group. Similarly, no associations between normalised slope of learning in the

daily condition and negative mood instability ($r_s(37)=-.07$, $p=.68$) or positive mood instability ($r_s(37)=-.19$, $p=.27$) were observed in the low MDQ group.

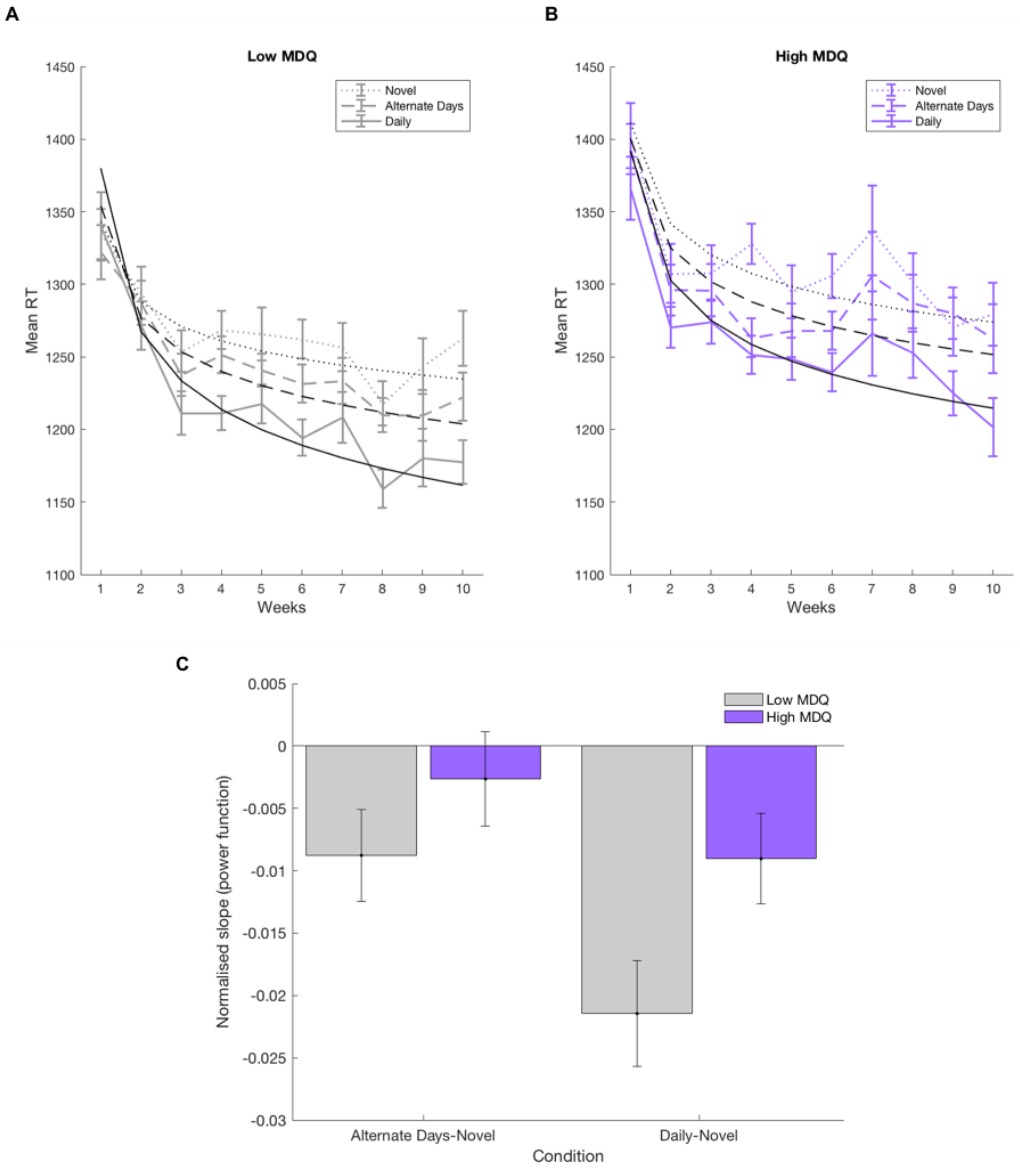


Figure 4.3. **A.** Best fitting power-law functions (black lines) shown with mean RTs (average within epoch) for each condition in low MDQ and **B.** high MDQ groups. **C.** Mean cueing slope, fit by a power-law function, between the novel condition and alternate day and daily condition (repeat conditions – novel), for low and high MDQ groups. Error bars represent ±SE of mean.

4.3.5 Contextual cueing within a day

The analysis of contextual cueing within days included the within-day and novel conditions only. Like original contextual cueing studies, the benefit of reduced RTs in finding the target in repeated arrays versus novel arrays within each daily session was investigated. This allowed the investigation of any differences between low and MDQ groups that might be present in contextual cueing across faster time scales, compared to across days, and allowed the investigation of whether mood interfered with learning and utilising regularities within a session.

The group mean RT and slopes for the novel and within-day conditions are shown in Figure 4.4A and 4.4B, with the slope for within-day trials decreasing compared to novel trials demonstrating contextual cueing. Data were normalised by subtracting the mean of the slope of the novel condition from the within-day condition. An independent samples t-test revealed no significant difference in performance slopes between MDQ groups ($t(72)=-1.46$, $p=.15$) (Figure 4.4C) although slopes were slightly steeper for individuals with low MDQ (M=-.054, SD=.03) than high MDQ (M=-.043, SD=.04).

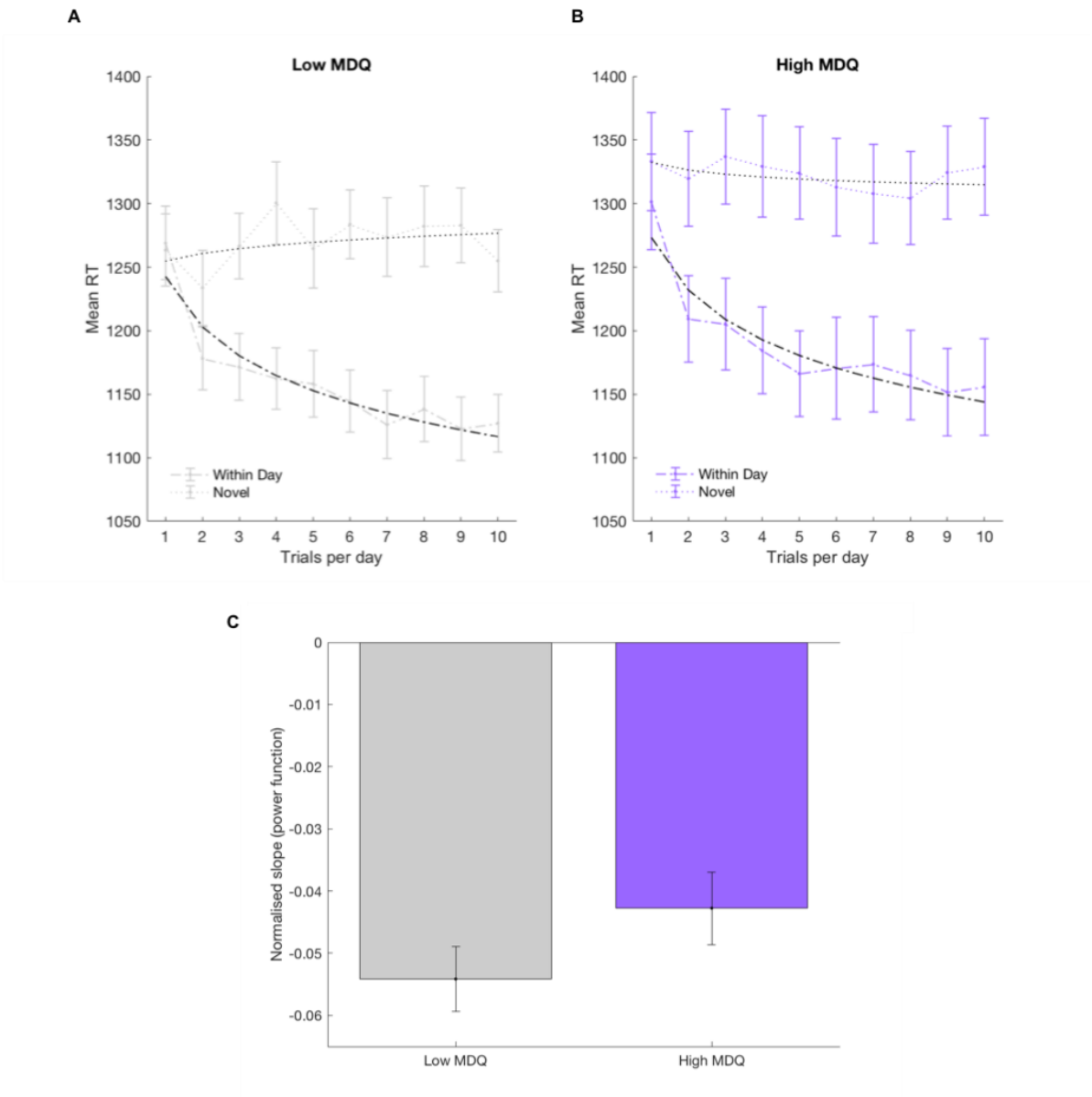


Figure 4.4. **A.** Best fitting power law functions (black lines) shown alongside mean RTs for each condition in low MDQ and **B.** high MDQ groups. **C.** Mean reduction in slope each day (within-day – novel), fit by a power function, shown for low MDQ and high MDQ groups. Error bars represent ±SE of mean.

Spearman's correlations were used to investigate whether greater mood instability was associated with greater instability in normalised within-day learning slopes each day. One high MDQ participant was excluded from this analysis due to showing extreme outlier values in instability of learning slopes. In the high MDQ group, no associations were observed between instability in within-day learning slopes and negative mood instability ($r_s(36)=.13$, $p=.47$) or positive mood

instability ($r_s(36)$=-.19, p=.27). Similarly in the low MDQ group, no associations were observed between instability in within-day learning slopes and negative mood instability ($r_s(37)$=.05, p=.75) or positive mood instability ($r_s(37)$=.15, p=.37).

4.4 Discussion

The present chapter sought to address a number of aims. The first investigated whether baseline attentional performance differed between groups. Using mean RTs of novel trials as an indicator of baseline attentional performance, no difference was observed between participants with high and low MDQ. Further, levels of mood instability did not correlate with instability in daily RTs. The second aim sought to demonstrate a novel adaptation of the original contextual cueing task, in which contexts were repeated across days to facilitate implicit learning of regularities over longer time scales. Importantly, using fitted learning slopes as an indicator of learning, high MDQ participants were impaired at building and using contextual regularities across days compared to low MDQ participants. The third aim investigated differences between groups on contextual cueing performance over short time frames, more in line with the original contextual cueing task. This time fitted learning slopes were not statistically different between groups, suggesting high MDQ participants did not show impairments in building and using contextual regularities within a session, and no relationship between mood instability and learning over short time frames.

This study has shown that it is possible to measure daily cognitive performance in order to investigate parallel measures of cognition and mood instability. In order to obtain a sensitive measure of daily cognitive performance, the contextual cueing task was successfully adapted to assess learning-based attention over short (within-day) and longer (across days) time scales. The within-day condition is most comparable to other studies that show reduced search times for repeated compared to novel contexts. However, due to testing outside of a lab-environment,

fewer trials (10) were presented for repeated (within-day) and novel contexts each day, in order to ensure testing sessions were kept short and participants remained engaged. Nevertheless, the contextual cueing effect was robust, in line with previous studies that also detect it after relatively few trials (Chun & Jiang, 1998; Tseng & Li, 2004). Further, RTs to identify targets were comparatively similar to those seen in lab-based contextual cueing experiments. Compared to studies that show disrupted contextual cueing in psychiatric populations such as MDD and schizophrenia (Lamy et al., 2008), individuals with high MDQ scores did not show significantly different slopes of learning to those with low MDQ scores in the within-day condition.

The across day conditions developed in this task were completely novel. Previous contextual cueing studies have varied the frequency with which contexts are presented *within* a session to alter the degree of learning-based attention (Zang et al., 2018; Zinchenko et al., 2018). For example, Tseng et al., (2011) presented novel configurations along with four configurations that repeated three times, four that repeated twice and four that repeated just once in each block. The authors observed that search became more efficient for configurations presented more frequently, which they interpreted as a function of associative memory strength (Tseng et al., 2011). In COMET, a similar pattern was observed across days, rather than blocks, with search more efficient for configurations presented daily compared to on alternate days.

Importantly, the findings show shallower slopes of learning across days in individuals with high MDQ scores. This is unlikely to be due to general attentional deficits given no group differences were observed in RTs for novel trials. It instead suggests these individuals may be slower at detecting and using regularities in the environment in order to guide adaptive behaviour over time. If general mechanisms of learning regularities are deficient, this could affect regulation of mood through slower learning and integration of outcomes in different situations. It would be interesting to examine whether the learning of regularities in the context of reward or emotional

state is additionally and differentially impaired in individuals with high levels of mood instability. Indeed, in healthy controls, it has been shown that rewarding contexts can accelerate the time in which implicit learning is observed, and both consistent and inconsistent feedback can result in faster and slower learning, respectively (Tseng & Lleras, 2013). In addition, in explicit learning tasks, associations have been noted between emotional state, learning of reward outcomes, and mood instability (Eldar & Niv, 2015).

There are a number of strengths and limitations to the contextual cueing design used. Firstly, stimuli and their configurations were devoid of meaning. This eliminated confounders such as familiarity or salience associated with prior knowledge of object locations that might be observed using natural scenes (Chun & Jiang, 1998; Võ & Wolfe, 2013). Secondly, contextual cueing provides a measure of implicit learning thought to be less susceptible to ceiling effects than explicit learning (Klinge et al., 2018). However, in this study, participants were not required to perform tests in order to assess explicit knowledge of target locations within repeated configurations (Chun & Jiang, 2003). It therefore cannot be confirmed whether contextual cueing was fully implicit, especially given participants completed up to 50 tasks (Smyth & Shanks, 2008). Lastly, conclusions about how learning influences attention and guides adaptive behaviour are limited as only one type of incidental, implicit learning was measured in the absence or more ecologically valid or meaningful associations (Scholl & Klein-Flügge, 2017), and only RTs were collected as outcome measures. Nevertheless, this task design has revealed specific differences in attention-based learning between high and low MDQ groups for which to generate further hypotheses.

4.5 Conclusion

This chapter shows that it is feasible to develop an incremental contextual cueing task to assess cognitive performance over different timescales, outside of a lab-based testing environment. In

addition to this being the first observation of contextual cueing over days, it was found that individuals with high mood instability are impaired at integrating information over longer timescales (daily) but perform similarly to individuals with low mood instability over shorter timescales (within a day). This has implications for understanding the role of learning-based attention over shorter and longer time scales and helps to elucidate cognitive correlates of mood instability.

Chapter 5. Neural correlates of Mood Instability

5.1 Introduction

Much of what is known about resting-state neural activity in at-risk or clinical populations is largely based upon fMRI. Whilst fMRI has great spatial resolution, it is an indirect measure of neuronal activity. Non-invasive electrophysiological methods such as electroencephalography (EEG) and MEG, which provide direct measures of neuronal activity, are important to advance our understanding (Uhlhaas et al., 2017). The high temporal resolution of EEG and MEG is necessary to capture local and long-range synchronisation of oscillations. These neuronal oscillations reflect the temporally coordinated activity of neuronal populations, within different frequency ranges, and influence neural communication within and between networked brain areas (Buzsáki & Draguhn, 2004; Buzsáki, Logothetis, & Singer, 2013; Varela et al., 2001; Wang, 2010). It has been suggested that disruptions in the coordination of neural oscillations, or in the communication between large-scale networks, may be markers of psychiatric disorders (Alamian et al., 2017; Mathalon & Sohal, 2015; Schnitzler & Gross, 2005; Uhlhaas & Singer, 2012; Voytek & Knight, 2015).

Both EEG and MEG detect coordinated activity of neuronal populations, primarily reflecting summation of postsynaptic currents of pyramidal neurons (Buzsáki, Anastassiou, & Koch, 2012; Lopes da Silva, 2013). While EEG measures the electrical currents generated by this activity, MEG detects the magnetic fields that accompany the electrical currents, leading to important differences. Electrical activity can be distorted by tissues such as the skull and scalp whereas the magnetic field is relatively unaffected (Hari & Salmelin, 1997; Vorwerk et al., 2014). Magnetic fields decay faster with distance than electrical fields, yielding sharper gradients that emphasize neocortical activity. Further, MEG sensors are only sensitive to tangential sources of magnetic fields from cortical pyramidal neurons in sulci (Baillet, 2017). When this information is coupled

with sophisticated source reconstruction algorithms, MEG is a powerful method to explore modulations in neuronal activity (Gross, 2019).

EEG has been used as a tool to observe dysfunctional neural communication in psychiatric disorders, particularly in schizophrenia in line with the dysconnection hypothesis (Friston et al., 2016). While MEG has been less utilised, it is increasingly recognised as a valuable tool in psychiatry. Indeed, dysfunctional resting-state oscillatory activity and connectivity observed with MEG has been reported in patients with schizophrenia, autism spectrum disorder and Alzheimer's disease compared to healthy controls (Uhlhaas et al., 2017). A small but growing body of MEG research has assessed resting-state activity in individuals with mood disorders such as BD and MDD that are also likely to experience mood instability (Alamian et al., 2017). The following paragraphs briefly summarise some of these findings and the diverse methods by which they are investigated.

Al-Timemy and colleagues (2014) compared resting-state spectral properties including power spectral density (PSD) and median frequency (MF) between BD and healthy participants. They found significantly lower MF in BD patients in the posterior brain region compared to healthy controls (Al-Timemy, Fernandez, & Escudero, 2014). Moreover, relative power modulations in delta (1.5-4 Hz) and theta (4-8 Hz) in posterior regions were found to be higher in BD patients than healthy controls (Al-Timemy et al., 2014). These findings were in line with resting-state EEG studies that demonstrate increases in delta and theta power, even in euthymic BD (Degabriele & Lagopoulos, 2009). Jiang and colleagues (2016) compared oscillatory activity in MDD patients and healthy controls. Using a Hanning taper to calculate spectral power, the authors observed decreased theta (4-8 Hz) and alpha (8-14 Hz) in frontocentral and posterior regions respectively, and increased beta (14-30 Hz) in frontocentral regions. In addition, depression severity was negatively correlated with alpha power, demonstrating how spectral

changes might map onto symptoms. Although these results are not in line with those reported by Al-Timemy et al., (2014), differing methods of spectral analysis could account for these findings.

Other studies have applied non-linear analysis methods such as Lempel–Ziv complexity (LZC), which examines the rate of occurrence of finite sequences within a time series (Lempel & Ziv, 1976). Fernandez et al., (2018) found that MDD patients showed significantly higher LZC scores than patients with BD and healthy controls, suggesting different patterns of neural complexity (Fernández et al., 2018). In addition to characterising alterations in the frequency of the MEG signal, a small number of studies have assessed resting-state connectivity patterns. For example, increased synchronisation of delta oscillations (2-4 Hz) and decreased synchronisation of beta (12-24 Hz) was seen in euthymic BD compared to healthy controls (Chen et al., 2008) and impaired prefronto-thalamic connections in the alpha band were observed in treatment-resistant MDD patients that were subsequently rescued in responders to transcranial magnetic stimulation (Li et al., 2013). This highlights the functional importance of networks in symptomology and their potential for treatment biomarkers.

The aforementioned studies were conducted in sensor-space, but source-space localisation can further provide important links to findings from rsfMRI. In MDD patients compared to healthy controls, FC between the subgenual ACC (sgACC) and hippocampus was reduced, and FC between right insular-temporal regions and the amygdala and thalamus, and the left insular-temporal regions and posterior regions of the frontal lobe was increased in individuals with MDD (Nugent et al., 2015). Another study reported increased FC in alpha and beta band between the sgACC and dorsolateral prefrontal cortex (DLPFC) in MDD, but decreased connectivity over the same frequencies in healthy controls. In MDD patients, greater FC between the sgACC and DLPFC was associated with remission at follow-up (Wang et al., 2019). This is in line with fMRI studies that implicate disrupted FC between the DMN and CLN in

mood disorders and changes related to successful treatment (Mayberg, 2003; Salomons et al., 2014). However, the above methods of estimating FC aggregate activity over the data acquisition period, assuming stability over time. Instead, evidence from fMRI and MEG demonstrates FC is dynamic (Baker et al., 2014; Hindriks et al., 2016; Vidaurre et al., 2016).

Recent analytical methods take advantage of the high temporal resolution of MEG to enable the assessment of functional network dynamics. Developments have shown how Hidden Markov Modelling (HMM) can be used to observe time-varying oscillatory dynamics in terms of their spatial and spectral properties, in a data driven way (Baker et al., 2014; Vidaurre et al., 2016). Unlike other methods used to capture network dynamics, such as sliding time window approaches (De Pasquale et al., 2010), the HMM does not require pre-specified data window lengths, but extracts relevant timescales directly from the data. Importantly, the HMM identifies time-points at which unique spectral and spatial patterns (referred to as states) repeat in the data (Vidaurre et al., 2016). Patterns of activity across repeated visits to these states can be concatenated to provide well characterised estimates of state dynamics, for example, the rate of state switching, or the average time spent within a state at each visit. When applied to the amplitude envelope of source reconstructed resting-state MEG data, the HMM revealed network dynamics on fast timescales of 100-200 ms (Baker et al., 2014). In addition, spatial topographies of states were similar to well-known RSNs, including the DMN, DAN, sensorimotor network and visual network (Baker et al., 2014). This approach has now been developed further to identify states from the raw time courses of MEG data (Vidaurre, Hunt, et al., 2018) which will be used in the current analysis.

There have been a number of applications of the HMM, particularly to explore the dynamics of large-scale functional networks in healthy populations (Quinn et al., 2018; Vidaurre, Abeysuriya, et al., 2018). Of note, the temporal organisation of large-scale networks has been found to be

both heritable and related to behaviour, with important implications for their role in cognition (Vidaurre, Smith, & Woolrich, 2017). Applications in psychiatry are in their infancy, but the HMM has been used to explore how patients with Alzheimer's disease (AD) (Sitnikova et al., 2018), and neurodevelopmental disorders (Hawkins et al., 2020) might differ from healthy control participants. The current study adds to this growing literature, by applying the HMM to assess neural dynamics in a population with mood instability.

The aim of this work was to characterise resting-state oscillatory brain activity in individuals with high levels of mood instability compared to those with low levels of mood instability. To achieve this, three analytical methods were used to explore MEG resting-state activity as there is no 'best way' to analyse the data (Başar et al., 2016). Firstly, differences in the MEG spectral power were examined in sensor-space, and secondly in source-space between individuals with high and low levels of mood instability. Thirdly, a Time-Delay Embedded Hidden Markov Model (TDE-HMM) (Quinn et al., 2018; Vidaurre, Hunt, et al., 2018) was used to characterise the temporal dynamics underlying changes in spectral power, across the whole raw time course of the data. Whilst global differences in MEG power spectra might not be observed due to mood instability being dynamic in nature, the TDE-HMM might reveal inherently different brain dynamics in individuals with high levels of mood instability. Further, the COMET data was combined with a larger normative dataset from the UK MEG Partnership grant and a separate TDE-HMM was computed to assess the robustness of findings in a larger sample.

5.2 Methods

5.2.1 Experimental Design

The current MEG dataset was acquired as part of the COMET study. The present analysis focuses on resting-state MEG data acquired at baseline (between weeks 0 to 1). T1-weighted structural scans were collected at baseline to be used in conjunction with MEG data during pre-

processing. In addition, participant demographic information (age, gender), and mood instability measures (tRMSSD of PANAS-SF mood scores) were utilized during data analyses (previously described in Chapter 2).

5.2.2 Participants

It had been intended that all participants recruited to the COMET study would undergo MEG scanning. However, due to technical failures, the MEG scanner was out of operation for a substantial proportion of time during data collection. Therefore, MEG scan data at baseline were only available for 26 individuals; 14 high MDQ and 12 low MDQ (Table 5.1). Only 12 of these individuals underwent scanning at study endpoint (weeks 9-10); 8 high MDQ and 4 low MDQ. Due to unequal groups and fewer participants at follow-up, endpoint data was not used in the current analyses.

Table 5.1. Demographics of COMET MEG sample	**High MDQ (n=14)**	**Low MDQ (n=12)**
Age (mean, range)	24 (19-42)	27 (20-49)
Female (%)	8 (57.1%)	8 (66.7%)
MDQ score (median, range)	9 (7-13)***	2 (0-3)***
ALS Total score (median, range)	36.50 (19-55)***	21 (18-32)***
AIM Total score (mean, SD)	150.08 (19.78)	130.08 (31.28)

*** denotes significant differences between groups at $p<.001$.

5.2.3 Data acquisition

MEG data were acquired at OHBA on a passively shielded Elekta Neuromag 306-channel scanner (comprising 204 planar gradiometers and 102 magnetometers). Participants were seated in the scanner and instructed to remain still and awake. Immediately prior to data acquisition a Polhemus 3D tracking system recorded positions of 4 fixed Head Position Indicator (HPI) coils secured to the participant's scalp and approximately 200 distributed points covering the scalp surface, forehead and nose, all relative to nasion and left and right preauricular fiducial landmarks. The four fixed HPI coils were intermittently energised from 293–321 Hz, which

allowed for continuous measurement of head position within the MEG helmet during the scan. MEG data were digitized at 1000 Hz with a .03 Hz high pass filter. Visual fixation, blinks and saccades were continuously monitored using an infrared eyetracker (Eyelink 1000). Vertical and horizontal electrooculograms (EOGs) and left and right wrist electrocardiogram (ECG) were also measured to enable artefact detection and removal during data pre-processing. MEG was recorded for 10 minutes in an eyes-open resting-state condition whilst participants fixated on a black cross on a white background 1 meter away. Participants were asked to look at the cross, let their mind wonder and think of nothing in particular.

Within 1 week of each MEG scan, T1-weighted structural whole-brain MR images, including ears and nose, were acquired for co-registration of MEG data (repetition time (TR) = 3,000 ms, echo time (TE) = 4.71 ms; flip angle = 8°; field of view (FoV)= 256 millimetres; voxel dimension = 1 millimetre isotropic, acquisition time = 8 mins 48s). Scans were acquired on a Siemans Trio 3T scanner located at the OCMR.

5.2.4 Data pre-processing

MEG data were pre-processed in Matlab R2017a using the OHBA Software Library (OSL: https://ohba-analysis.github.io/osl-docs/). Data pre-processing followed the exact pipeline previously implemented in Quinn et al., (2018). Each pre-processing stage is shown in Figure 5.1A and described below.

The raw MEG data was processed with MaxFilter version 2.2 (Elekta Neuromag). Using MaxFilter, external noise sources were separated from the MEG signal arising from neuronal activity using a signal space separation (SSS) algorithm (Taulu, Simola, & Kajola, 2005). Further, MaxFilter automatically detected bad channels, filtered 50 Hz line-noise, and HPI coil signals (from 293–321 Hz), and adjustments for head movement were compensated for utilising

measurements from the HPI coils. Maxfiltered data were down sampled to 250 Hz to reduce computational demands during further analysis. In order to remove slow drifts and high frequencies in the data, a band-pass filter was applied from 1-45 Hz.

Subsequent pre-processing of each participants data used an automated pipeline, removing any biases. Bad segments were identified as outliers in the SD of the MEG signal, in non-overlapping windows of 1 second, computed across all sensors (Quinn et al., 2018; Rosner, 1983). Time windows of the data identified as bad segments (e.g. movement artefacts) were marked and removed from following pre-processing and data analysis steps (Quinn et al., 2018). A temporal Independent Component Analysis (ICA) tool was used to identify re-occurring noise components across the length of the data that correlated with EOG and ECG channels recorded during data collection. Independent Components with correlations larger than r=.5 were automatically rejected and removed from the data. All rejected components were checked manually to ensure that only components containing consistent and clear biological artefacts were selected for rejection by the correlation threshold. If no components were automatically identified in a dataset, manual rejection of artefacts was undertaken. Eye-blink and cardiac components were manually identified by the combined inspection of the spatial topography, time course, and frequency spectrum. Examples of these artefacts are shown in Figure 5.1B and 5.1C. An average of 3 components, including both cardiac and eye-blinks, were removed from each dataset. Lastly, the magnitude of signal variance from both magnetometers and planar gradiometers was normalised. This was particularly important to avoid the magnetometers dominating the covariance matrix estimation during subsequent beamforming (Woolrich et al., 2011).

The following pre-processing steps were applied to data for the purpose of source-space analyses and HMM. Coregistration between participants' structural MRI and MEG data was performed

using OSL tool RHINO (Registration of Headshapes Including Nose). This aligned the MRI coordinates with the Polhemus points across the scalp, forehead and nose, and fiducial landmarks. For 4 out of 26 participants, Polhemus points on the nose were not collected during data acquisition. Therefore, coregistration for these participants was performed using only fiducial landmarks. Aligned data were then positioned within the MEG sensor-space. Coregistration was visually inspected for each individual to ensure good quality alignment. None had to be manually adjusted.

Continuous sensor data were source transformed using a scalar linearly constrained minimum variance (LCMV) beamformer (Van Veen et al., 1997; Woolrich et al., 2011). The beamformer used adaptive spatial filters to weight sensor measurements based on a pre-specified spatial location (Woolrich et al., 2011). For each participant, source-space neural activity was estimated at each point across an 8 mm whole-brain grid within MNI (Montreal Neurological Institute) space. Defining the grid in MNI space ensured that the number of grid points, and their locations, were consistent across each participants' data.

The data were then parcellated into 39 regions providing coverage of the cortex. The same parcellation, from the Human Connectome Project (Van Essen et al., 2013), has been previously used to analyse FC in resting-state MEG data (Colclough et al., 2015; Colclough et al., 2016; Quinn et al., 2018). Time courses for each parcel were estimated from the first principle component analysis (PCA) of the voxel time courses within each parcel, with voxel contributions weighted by the size of the parcellation. Correction for spatial leakage between voxel time-courses was applied across the whole network using a symmetric-multivariate orthogonalization procedure described in Colclough et al. (2015).

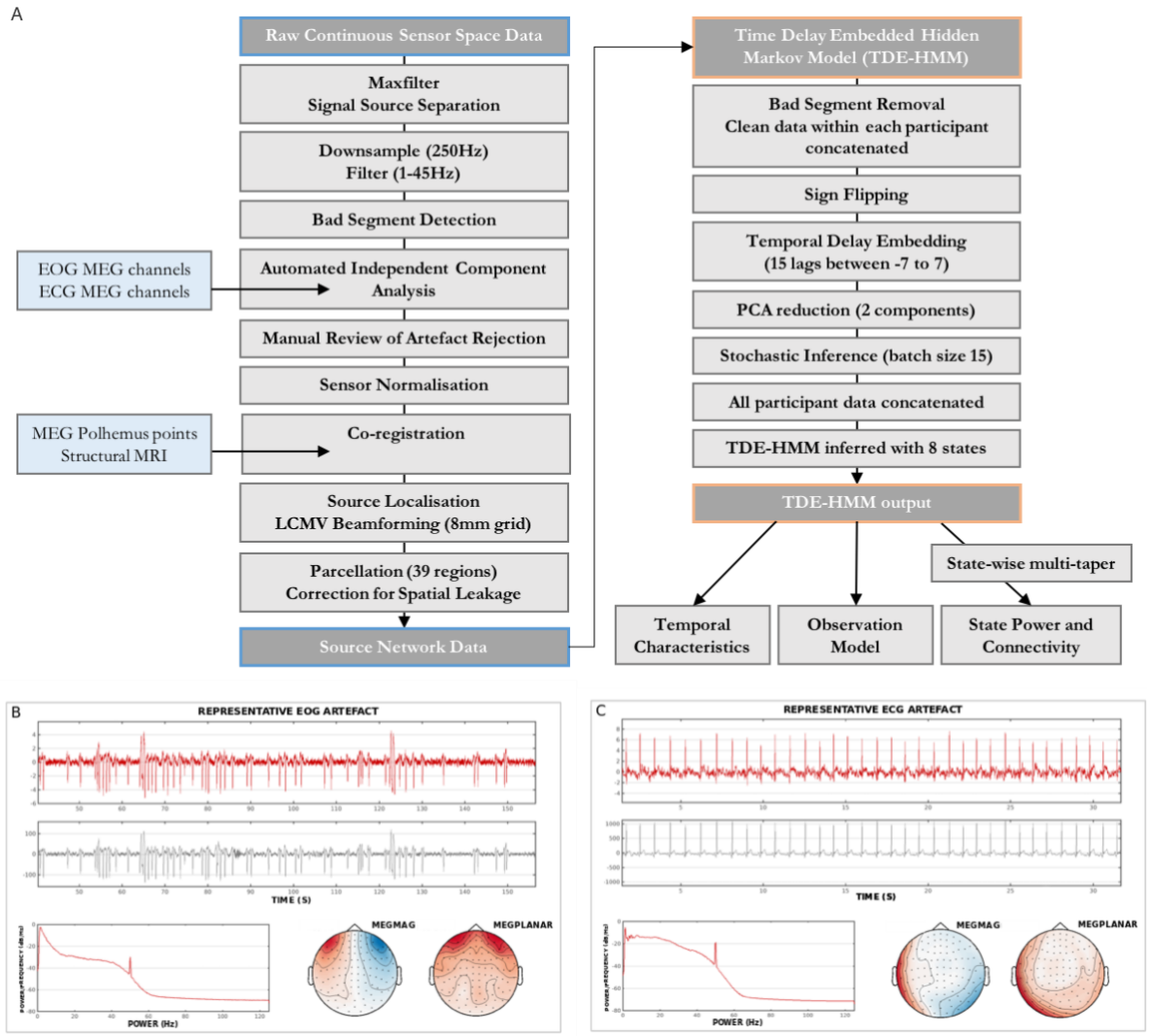


Figure 5.1. A. Schematic of MEG data pre-processing pipeline and implementation of the TDE-HMM. Figure based upon and adapted from Quinn et al., (2018) **B.** Example of electrooculogram (EOG) component rejected during Independent Component Analysis using OSL toolbox in SPM 12. The top panel shows the time course of the component, in this instance marked red indicating a rejected artefact component (other components not containing artefacts would be displayed in green). Eye-blink artefacts typically exhibited a repeated blink structure in the time course and very structured spatial topographies. This correlates with the covariate time course of the EOG, shown directly below in grey, which is recorded via electrodes placed vertically and horizontally on the left eye. The bottom left graph shows the power spectral density of the rejected component. The 50-Hz line noise is also observed in the power spectrum. The bottom right plots show the spatial topographies of the rejected component, in both magnetometers (MEGMAG) and planar gradiometers (MEGPLANAR). The topographies clearly indicate a visual artefact, with activity surrounding the left and right eye areas. **C.** Example of electrocardiogram (ECG) component rejected during Independent Component Analysis using OSL toolbox in SPM 12. Cardiac component time courses strongly resembled typical ECG signals. The top panel again shows the time course of the rejected artefact component. This tightly

correlates with the covariate time course, shown directly below in grey, of the clear ECG signal which is recorded via electrodes placed on the left and right wrist. The bottom left graph shows the power spectral density of the rejected component. The bottom right plots show the spatial topographies of the rejected component, in both magnetometers (MEGMAG) and planar gradiometers (MEGPLANAR). Topographies of ECG components typically show activity that spread across the left and right sides of the brain.

5.2.5 Data analysis

5.2.5.1 *Sensor-space frequency analysis*

For this analysis, data were utilised from 204 planar gradiometers. Both planar gradiometers and magnetometers, after Maxfilter with SSS, have been found to demonstrate similar results (Garcés et al., 2017). However, planar gradiometers were used in the current analyses because they have greater sensitivity to sources directly below the sensors, are less affected by environmental noise (Hansen, Kringelbach, & Salmelin, 2010) and are more easily interpretable (Gross et al., 2013).

An estimate of power spectral density (PSD) was computed for each participant using Welch's method (Welch, 1967). The data were divided into non-overlapping Hanning windows of equal lengths (256 samples). In each data window a modified periodogram was calculated by computing the squared magnitude of the discrete Fourier transform (Welch, 1967). The average of these individual periodograms over the time series resulted in the PSD, an estimate of power at each frequency (129 frequencies, 0-125 Hz) for each sensor (204). Averaging over periodograms is known to decrease variance in the estimation of the PSD. This method was implemented in Python 3.7 using the Signal Processing package (scipy.signal.welch).

Power spectra were averaged across frequency bands; delta (1-4 Hz), theta (4-8 Hz), alpha (8-13Hz), beta (13-30 Hz). This data was passed into an Ordinary Least Squares (OLS) general linear model (GLM). The OLS GLM had a design matrix with four regressors; 3 categorical regressors including high MDQ, low MDQ and gender (male/female) and one parametric

regressor, age (Figure 5.2.). Both gender and age regressors were z-transformed to normalise variance so that units of the parameter estimates were comparable. The mean power at each sensor within each frequency band was modelled by all four regressors and summarised at the group level. The parameter estimate for each regressor was summarised by a Contrast of Parameter Estimate (COPE) value. A mean contrast, across all participants, and a differential contrast to assess group differences (high MDQ<low MDQ) was computed from the parameter estimates. To account for variance in the differential contrast, group-level stats were performed on the t-statistics rather than the COPE values.

To determine statistical significance for group-level parameters, non-parametric permutations were used, a standard approach in analyses of neuroimaging data (Nichols & Holmes, 2003; Winkler et al., 2014). The main effects were permuted by sign-flipping, and the differential contrast by row-shuffling. Five-thousand permutations were computed. To correct for multiple comparisons, the maximum statistic of each main effect and contrast was taken across each frequency band and sensor and was statistically significant from baseline if it was above the 95th percentile of the null distribution. As this study is exploratory and hypothesis generating, results will report significant sensors both before and after this correction.

5.2.5.2 *Source-space parcellation*

The source-localised and parcellated data were transformed to the frequency domain using Welch's method, in the same way as the sensor data. The same OLS GLM was used to obtain model outputs for each regressor and the differential contrast of interest, but this time, parameter estimates were computed for the frequency band of each parcel.

General Linear Models (GLMs) for sensor-space and source-parcellated data were computed in Python 3.7 using in-house GLM tools.

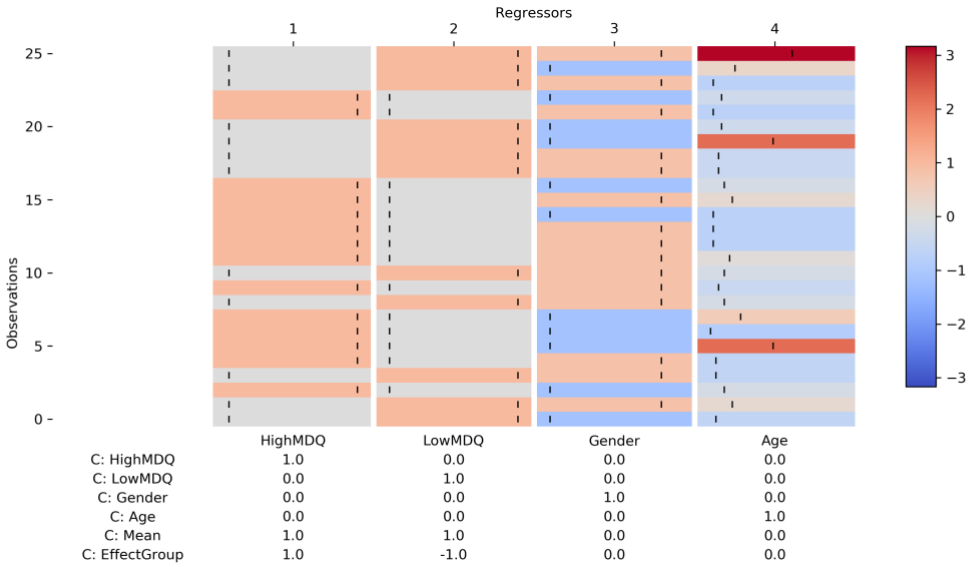


Figure 5.2. Group design matrix. This shows four regressors that were specified in the model, and six contrasts; 5 main effects and 1 differential contrast.

5.2.5.3 *Hidden Markov Modelling*

The HMM is a statistical model that assumes a time series can be characterised by a hidden sequence of states, (*k*). The HMM requires that the number of hidden states are pre-determined. Each state relates to part of a time series with unique but measurable properties (Rabiner & Juang, 1986). At each time point (*t*), one state is assumed to be active. Additionally, a Bayesian Inference provides a posterior probability of each state being active at each time point. The probability of a state being active depends on the state active at the previous time point (*t-1*). This is known as the Markov assumption. The Viterbi algorithm is used to determine the most probable state at each time point (Bishop, 2006). Each state has its own observation model defined by the probability distribution of the observed data when the state is active (Vidaurre et al., 2016). Time-courses for each state are constructed from the observation model. Importantly, the HMM does not imply that there is only one active state in the brain at any one time, rather that the activity at a certain time point is best described by a particular state.

There are several variants of the HMM which are distinguished by their underlying observations. A previous study by Baker et al., (2014) applied an HMM to the amplitude envelope of MEG data using a Gaussian observation model (AE-HMM). The AE-HMM enables the characterisation of temporal events from the data. More recently, Vidaurre et al., (2016, 2018) have used a multivariate autoregressive model to describe the raw time courses of MEG data (HMM-MAR). In the current study, we applied a Time-Delay Embedded HMM (TDE-HMM).

The TDE-HMM uses a multivariate Gaussian distribution model, similar to that of the AE-HMM, and is described in technical detail in Vidaurre, Hunt, et al., (2018) and Quinn et al., (2018). However, the TDE-HMM models a time-delay embedding of raw time-courses of the data, as opposed to the power envelope of the data as in Baker et al., (2014). Each state captures periods of time that have distinct patterns of auto-covariance which is, in turn, closely related to the power spectrum. It characterises spectrally resolved events in the data, that is, it detects recurrent patterns of network activity that show spatially distinct changes in power in addition to changes in phase-coupling, meaning features are both spectrally and temporally resolved. Power and phase coupling are defined as a function of frequency, and different networks are active or inactive at distinct periods in time. Whilst information about the power and phase-coupling of states is defined at a group-level, information about when a state is active or inactive is generated at an individual level.

5.2.5.4 *Model Implementation*

The TDE-HMM was implemented following procedures in Vidaurre, Hunt, et al., (2018) and Quinn et al., (2018), using the HMM-MAR toolbox (https://github.com/OHBA-analysis/HMM-MAR). Bad segments of the data detected during the aforementioned pre-processing were removed from the dataset. The remaining clean segments of the data were concatenated for each subject. Locations of missing bad data segments were accounted for

during the HMM inference to avoid the model assuming continuity in the remaining data that were temporally separated.

Data from each participant had been beamformed individually during previous source reconstruction. As a result, the sign of the reconstructed dipoles could be arbitrarily different across subjects (+ or -). This was problematic for group-level averaging as phase-coupling could be minimised in either direction leading to effects cancelling at the group level. To overcome this, a sign flipping algorithm was applied (Vidaurre, Hunt, et al., 2018). The sign-flipped source reconstructed time-courses from all participants were concatenated prior to HMM inference.

The source reconstructed time-courses, X, were of size (NxT), where N is the number of parcels and T the number of timepoints. A time delay-embedding procedure was implemented creating a matrix of lagged data observations for each timepoint in X. Each embedded sample creates a vector, Y, of length (N*L) where L represents the number of lags. The number of lags was set to 15, between values -7 to 7, which corresponds to a ±30 ms lag given the data are down sampled at 250 Hz (Quinn et al., 2018). The embedded time series is the concatenation of these lags into the embedded matrix, Z, of size (N*LxT). For computational reasons, the first dimension of Z is reduced by PCA to the 2 largest components, resulting in a final data matrix of (2NxT). Stochastic inference was used to further reduce computation time (Vidaurre, Abeysuriya, et al., 2018).

The TDE-HMM was inferred with 8 states to the concatenated data of all participants. The model inference was repeated 10 times and the repeat with the lowest value of free energy (best explaining the data with the fewest parameters) was retained for further analysis. The free energy is the sum of; (1) the negative log likelihood (NLL) term, a measure of how likely the parameters maximally fit the data, and (2) the Kullback-Leibler (KL) divergence, a distance measure between

inferred parameters and the prior distribution which penalises unlikely distributions in the model according to the prior distribution (Joyce, 2011).

5.2.5.5 *State power and connectivity*

State power and connectivity were computed after the TDE-HMM inference. A state-wise multi-taper, applied to each state and parcel, was used to gain an estimate of power and phase-locking coherence from the raw data weighted by the posterior probability of each state (Quinn et al., 2018). By combining this information, the multi-taper provided time-frequency representations of power spectral density (PSD) (1-40 Hz for each state) and coherence (or FC).

5.2.5.6 *Temporal Characteristics*

A number of temporal characteristics relating to the dynamics of the states were estimated from the Gamma time course of the HMM inference. The output was a time course of posterior probabilities representing the probability of a state being active at each time point, and a Viterbi path, containing the most likely sequence of states. Four temporal characteristics were calculated;

- Fractional occupancy (FO) – the proportion of time spent in each state, over the time course of each participant's data.
- State life times (LTs) – the mean time spent in a state at each visit.
- Interval times (ITs) – the time elapsed between visits to a state.
- Switching rate (SR) – the global rate of switching between all states over the time course of a participant's data.

The HMM inference also returns the transition probabilities of each state in a kxk matrix, that is, how likely it is to be in state j if state i was active beforehand. Any differences in state temporal statistics between groups of high and low MDQ participants were tested using independent

samples t-tests. In addition, correlations between state temporal dynamics and mood instability (as measured by the tRMSSD of positive and negative PANAS-SF scores over 10 weeks) were tested with Pearson correlations. Analyses were undertaken in Matlab R2017a.

5.2.5.7 *Spectral Modes*

In order to aid visualisation of the power spectral density (PSD), a non-negative matrix factorisation (NNMF) was computed to decompose the data in more data driven frequency bands (Berry et al., 2007). The NNMF was repeated until the spectral modes were unimodal and reflected separate, interpretable frequency bands approximately corresponding to delta/theta, alpha and beta bands. The state-wise power maps and functional connectivity networks were then estimated for each spectral mode (Quinn et al., 2018). Remaining networks after NNMF were those networks that were not expected to come from a Gaussian distribution. In addition, it enabled power and FC to be viewed as they varied across frequencies in each brain state.

5.2.5.8 *UK MEG partnership data*

The MRC UK MEG Partnership (UKMP) Grant (https://meguk.ac.uk) is a collaborative project between 8 MEG sites based at universities in the UK. Together they have collected resting-state MEG data from more than 500 healthy individuals, that have all undergone extensive screening procedures. Two MEG resting-state datasets from the University of Oxford and University of Cambridge were acquired for use in this thesis.

To supplement the relatively small COMET sample, and to ensure that estimates of the TDE-HMM applied to COMET data were sensible, a second TDE-HMM was implemented combining COMET data with Oxford and Cambridge datasets from the UKMP. Applying the TDE-HMM to a large combined dataset allowed greater confidence in the distribution that the COMET parameters were estimated from. For example, it is less likely that estimates in the

power and network connectivity of states are skewed by a small number of participants that might sit at the tails of the distribution. If outputs from the independently estimated TDE-HMMs were similar, this would provide reassurance that estimations based on the COMET data alone were robust.

UKMP datasets from Oxford and Cambridge were collected on identical MEG scanners to that used in the collection of COMET data (Elekta Neuromag 306-channel). This ensured that differences in acquisition were minimised between the normative UKMP sample and the COMET data. The Oxford UKMP data consisted of 73 scans (participants aged 20-80, 48% female) and the Cambridge data consisted of 79 scans (participants aged 18-78, 49% female), each lasting 8 minutes. Including the COMET data, this resulted in a total of 178 resting-state MEG scans.

The normative datasets were pre-processed using the same pipeline as COMET data. A second TDE-HMM was then inferred with 8 states to combined COMET and UKMP data. The methods were identical to those described in section 5.2.5.4. Of note, MDQ data were not available for the two UKMP datasets. Therefore, associations between state dynamics estimated from the combined COMET and UKMP samples and mood instability were only undertaken in COMET participants.

5.3 Results

5.3.1 Mood instability

Analyses of mood data from the subsample of COMET participants who completed MEG scanning (n=26) showed a similar pattern to that observed when the full cohort had been analysed (n=74) (see Appendix 2).

5.3.2 Sensor-space frequency analysis

The average topographies for each frequency are shown in Figure 5.3A. Figure 5.3B shows power spectra averaged over all sensors for low and high MDQ. All participants showed declines in spectral power with increasing frequency, with the exception of an alpha peak at approximately 10 Hz.

The first analysis assessed whether any global differences in sensor-space power spectra existed between individuals with high and low levels of mood instability. The differential group contrast (high<low MDQ) computed from the OLS GLM showed that, compared to the low MDQ group, the high MDQ group exhibited decreases in delta power (1-4 Hz) focused around frontal and left and right temporal sensors. No differences were found between groups in theta power. In addition, the high MDQ group showed increased alpha power in occipital and right temporal sensors and decreased beta power in a cluster of occipital sensors (Figure 5.4). While these sensors showed significant differences after non-parametric permutation testing at $p<.05$, they did not survive correction for multiple comparisons across sensors.

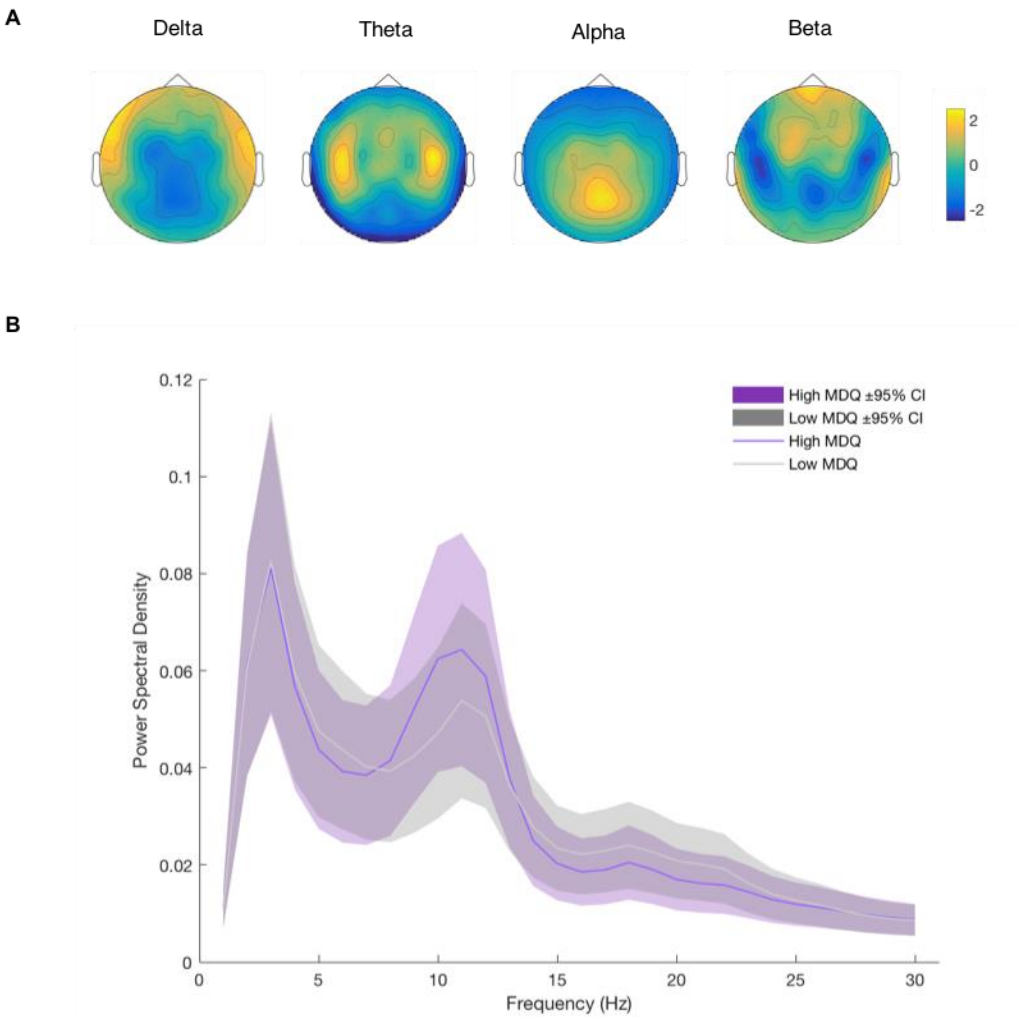


Figure 5.3. A. Topographical plots represent mean power spectral density (PSD) across all participants, modulated by frequency. Units shown are z-scored PSD. For visualisation, planar gradiometers were combined to obtain a single value under each sensor. **B.** Mean power spectra of low MDQ and high MDQ groups, over all sensors. Patch represents the +/-95% confidence intervals (CI).

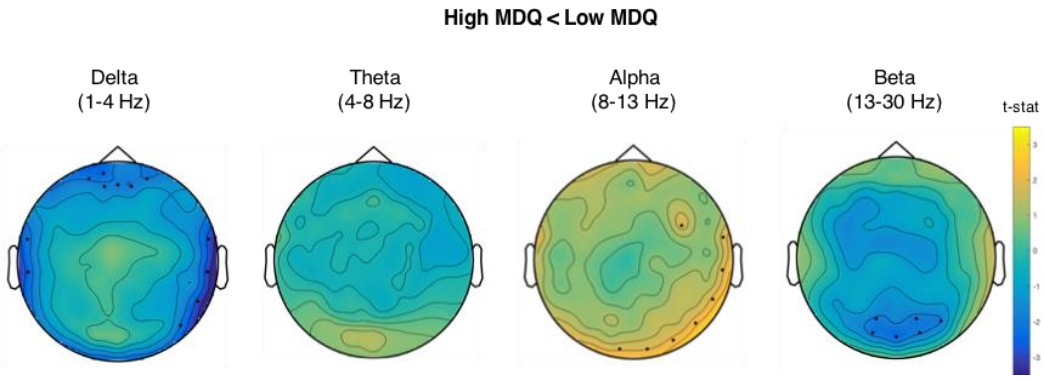


Figure 5.4 Statistical analysis of sensor-space MEG data. Group contrast of high MDQ<low MDQ across delta, theta, alpha and beta frequency bands shown topographically. Yellow indicates increases in power, and blue indicates decreases in power. Marked sensors indicate those showing significant increases or decrease after non-parametric permutation testing (95% significance threshold), but before correction for multiple comparisons across sensors. Units displayed are t-statistics. For visualisation, planar gradiometers were combined to obtain a single value under each sensor.

5.3.3 Source-space parcellation analysis

The mean PSD maps for each frequency across all participants is shown in Figure 5.5A. Figure 5.5B shows power spectra averaged over all parcels for low and high MDQ. All participants showed declines in spectral power with increasing frequency, with the exception of an alpha peak at approximately 10 Hz.

The presence of global differences in spectral power between individuals with high and low levels of mood instability was again explored in source-space. Results from the differential group contrast (high<low MDQ) showed that high MDQ participants demonstrated decreased delta power (1-4 Hz) in parcels located in the left frontal lobe including the paracingulate gyrus, right frontal lobe including the insular cortex, and the middle temporal gyrus. Decreased theta power (4-8 Hz) was observed in the same left frontal parcel including the paracingulate gyrus shown to exhibit reduced delta power. Increased alpha power was observed in two parcels located in the occipital lobe and the right lateral occipital cortex in high MDQ participants compared to low

MDQ participants. High MDQ participants further showed decreased beta power compared to low MDQ participants in a parcel located in the occipital lobe (Figure 5.6). Although these parcels showed significant differences after non-parametric permutation testing at $p<.05$, they did not survive correction for multiple comparisons across parcels.

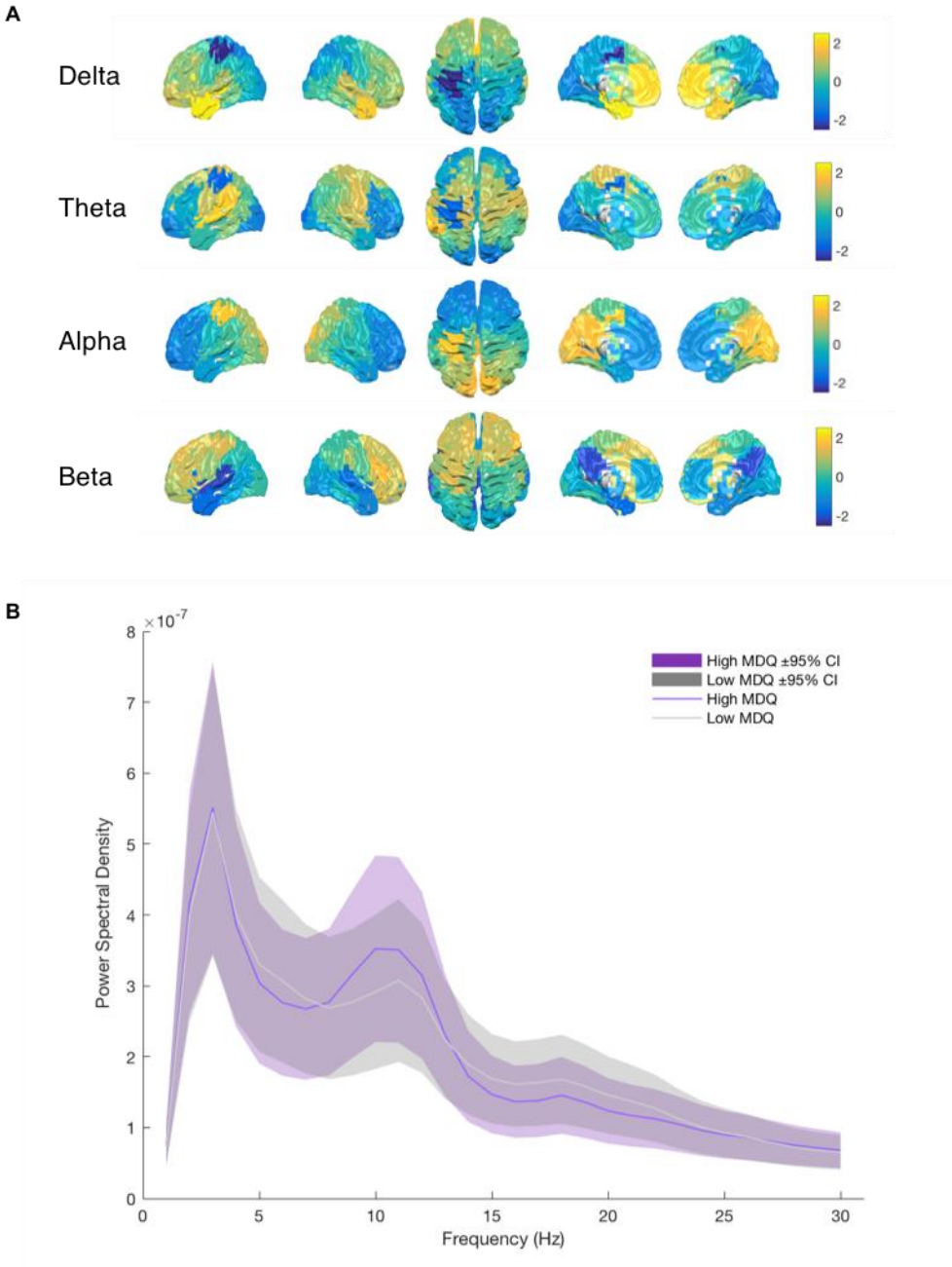


Figure 5.5. A. Source-space mean power spectral density (PSD) across all participants, modulated by frequency. Units shown are z-scored PSD. **B.** Mean power spectra of low MDQ and high MDQ groups, over all parcels. Patch represents the +/-95% confidence intervals (CI).

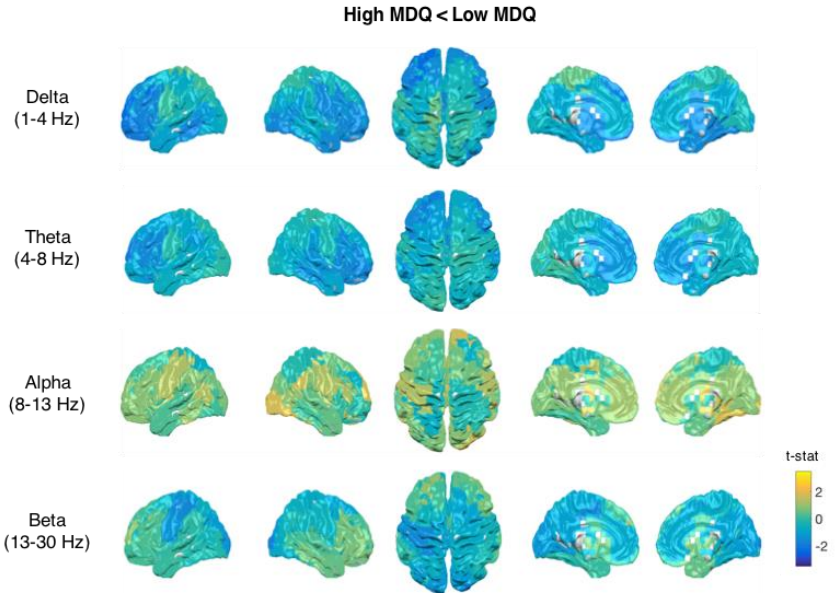


Figure 5.6. Statistical analysis of source-parcellated MEG data. Group contrast of high MDQ<low MDQ across delta, theta, alpha and beta frequency bands shown topographically. Yellow indicates absolute increases in power, and blue indicates absolute decreases in power. Units displayed are t-statistics.

5.3.4 TDE-HMM analysis – COMET data

5.3.4.1 *State power and connectivity*

The TDE-HMM was inferred with 8 states on the concatenated data of all participants, in order to derive states that were common to both low and high MDQ groups. This revealed interpretable and distinct brain networks of coordinated broadband oscillatory activity (1-40Hz), from the raw time courses of the resting-state MEG data. Figure 5.7 shows the mean activation maps (or PSD) and coherence networks of all 8 states. The states include sensorimotor networks (State 1 and State 6), frontal networks (State 2 and State 7), a frontolimbic network (State 3), an occipital-parietal network (State 4) and visual networks (State 5 and State 8).

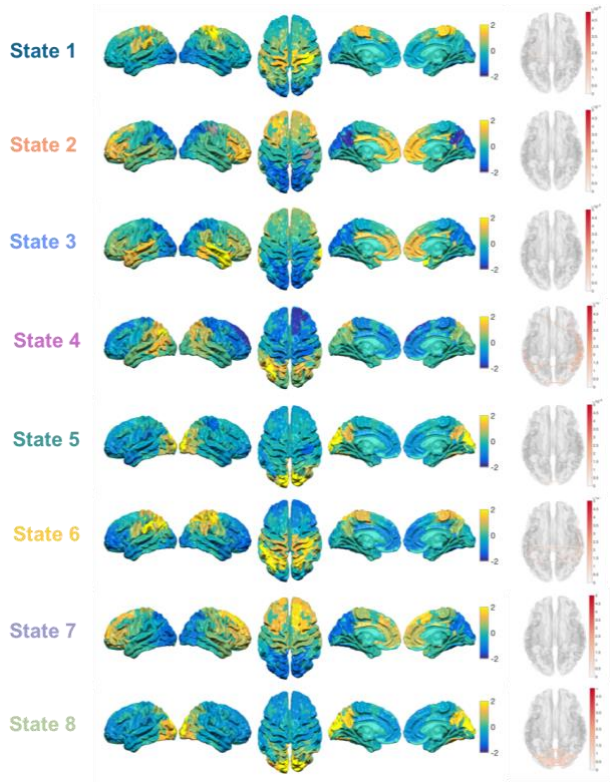


Figure 5.7. Mean broadband activation maps and coherence networks of each 8 states. These were computed from the state-wise multi-taper, applied after the TDE-HMM inference. Mean activation is z-scored across parcels. In the mean activation maps, yellow represents brain parcels in which the mean activation was found to be increased, and blue represents brain parcels in which the mean activation was found to be decreased, in a particular state.

The probabilistic state time course shows the probability that each state was active at a certain time point in the data (Figure 5.8A). As can be seen, no one state dominated the time-course in this small section of the data, though some were more or less probable to occur e.g. State 4 was more likely to be active in the first 400 ms, and less likely to be active in the following 600 ms. The accompanying Viterbi path (Figure 5.8B) shows the most likely sequence of states in this section of the data. In addition, the probability of state-to-state transitions are shown in Figure 5.8C. The most probable transition at a certain time point (t) to the next (t+1) was from State 2 to State 7. The probability of transitioning from State 4 to States 1, 2, 5 or 7, was very low.

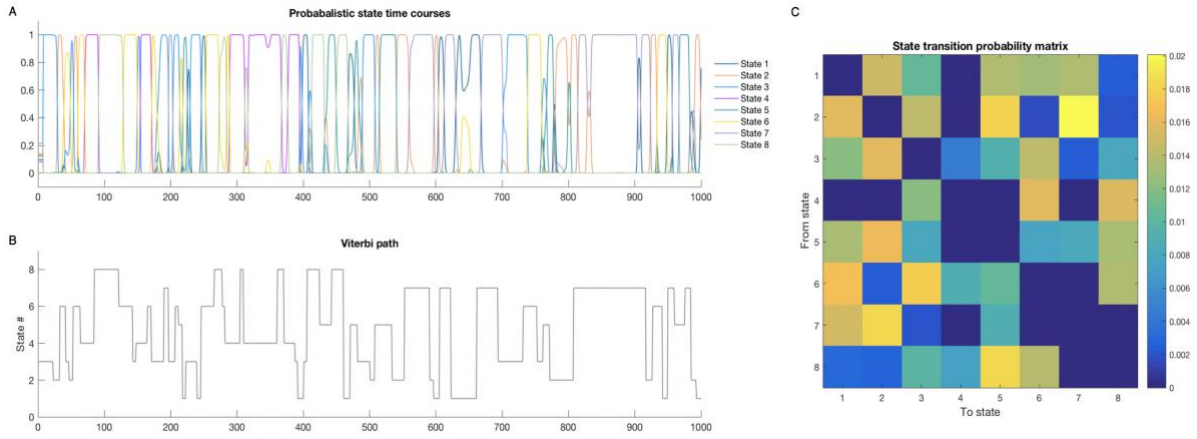


Figure 5.8. A. The probabilistic state time course of each 8 states shown for 1000 ms of MEG data. The probability of being in a state is shown by the y axis (0 being not probable and 1 being highly probable). Only one state is probable at a certain moment in time. **B.** The Viterbi path displaying the most likely sequence of states during the 1000 ms of MEG data shown. **C.** The state transition probability matrix depicting the probability of moving from a state (y axis) to another state (x axis).

5.3.4.2 *Temporal Characteristics*

Temporal characteristics were estimated from the probabilistic state time-course. States 1-3 and 5-8 exhibited similar fractional occupancies of around 10-20%, however State 4 demonstrated a lower fractional occupancy of around 5%. The greatest variance in fractional occupancy occurred in State 7. Average state life times were approximately 50-100 ms, demonstrating fast transient brain states, similar to Baker et al., (2014) and Quinn et al., (2018). Average interval times of States 1-3 and 5-8 were approximately 500 ms. However, the interval time of State 4 was much longer, this state taking on average 2 seconds to reoccur, consistent with its reduced fractional occupancy. Importantly, all states were visited by each participant during the resting-state scan (Figure 5.9).

There were no differences between low and high MDQ groups in state fractional occupancies or interval times (Figure 5.9A and 5.9C). Life times of State 5 were shorter in high MDQ than low MDQ participants ($t(24)=-2.23$, $p=.04$) (Figure 5.9B and Table 5.2) however, this difference was no longer significant after correction for multiple comparisons. There were no group differences

in the life times of all other states. Further, there were no group differences in the global rate of switching between all states ($t(24)=1.12$, $p=.28$) (Figure 5.9D).

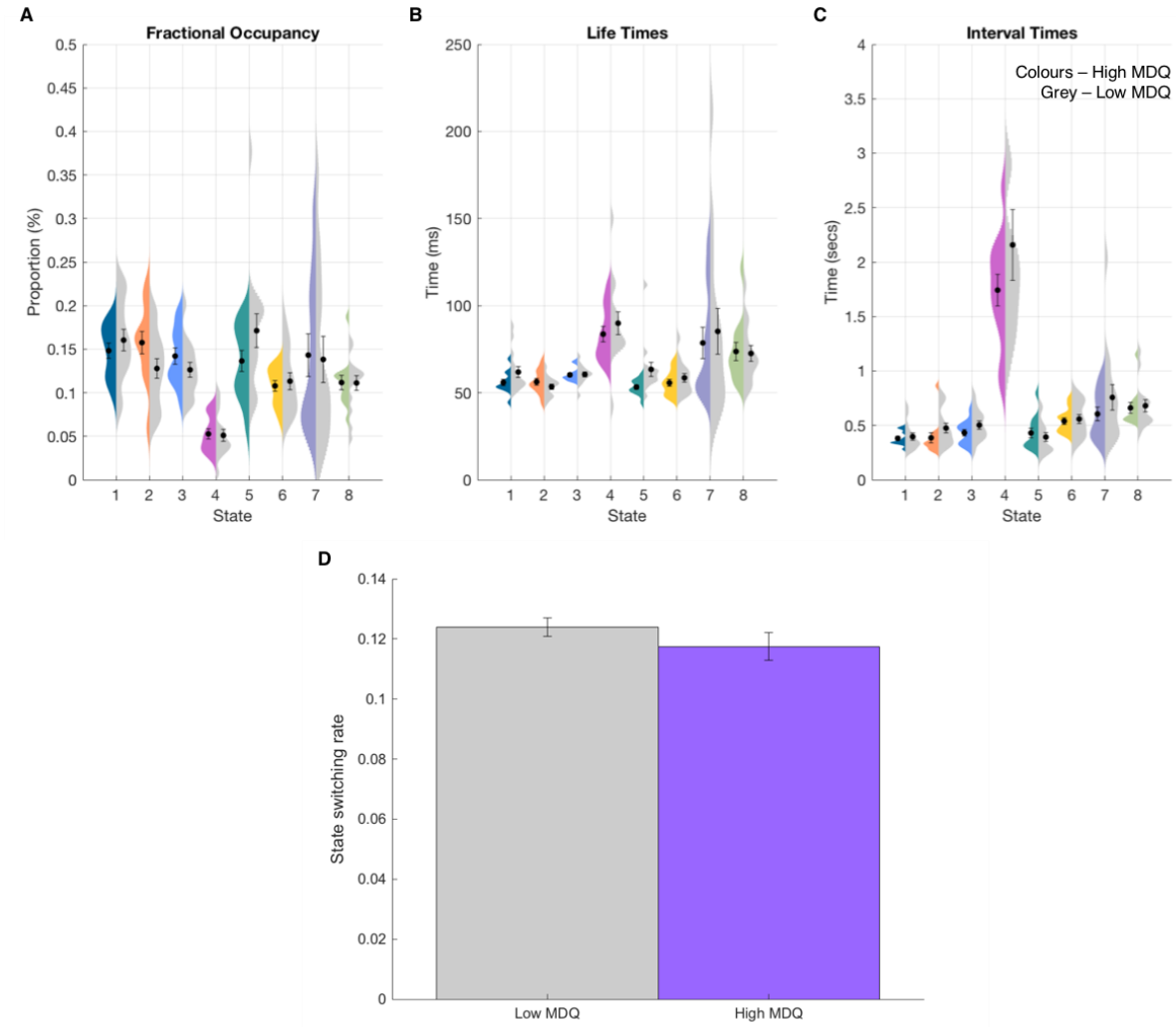


Figure 5.9. Temporal characteristics of the resting-state MEG data, including **A.** fractional occupancies, **B.** life times, and **C.** interval times. The distribution plots show the mean (black dot) and standard error of the mean (error bars) for each state, for both low (grey) and high MDQ (colour) groups. State switching rates for low and high MDQ groups are shown in **D.** Error bars represent ±SE of mean.

Table 5.2. State temporal characteristics by group		Fractional Occupancy (mean, SD)	Life Times (mean, SD)	Interval Time (mean, SD)
State 1	**Low MDQ**	.15 (.03)	55.88 (6.31)	.38 (.07)
	High MDQ	.16 (.05)	61.90 (11.65)	.40 (.12)
State 2	**Low MDQ**	.16 (.04)	56.23 (6.73)	.39 (.16)
	High MDQ	.13 (.04)	53.44 (5.66)	.48 (.17)
State 3	**Low MDQ**	.14 (.03)	60.27 (3.85)	.43 (.10)
	High MDQ	.13 (.03)	60.53 (5.41)	.50 (.14)
State 4	**Low MDQ**	.05 (.02)	83.70 (15.33)	1.74 (.50)
	High MDQ	.05 (.03)	89.94 (24.43)	2.16 (1.21)
State 5	**Low MDQ**	.14 (.04)	53.26 (4.44)	.43 (.15)
	High MDQ	.17 (.07)	63.39 (15.14)	.39 (.15)
State 6	**Low MDQ**	.11 (.02)	55.69 (6.93)	.54 (.11)
	High MDQ	.11 (.04)	58.57 (9.27)	.56 (.15)
State 7	**Low MDQ**	.14 (.09)	78.61 (31.19)	.61 (.22)
	High MDQ	.14 (.10)	85.28 (49.19)	.76 (.44)
State 8	**Low MDQ**	.11 (.03)	73.70 (18.21)	.66 (.17)
	High MDQ	.11 (.03)	72.57 (16.95)	.68 (.21)

5.3.4.3 *Spectral Modes*

In addition to viewing the broadband HMM states, the frequency content of each state was observed. Spectral modes obtained from the NNMF broadly corresponded to delta/theta, alpha and beta frequency bands. They can be viewed in Figure 5.10 alongside the estimated power maps and phase coherence networks for each spectral mode. The sensorimotor networks (State 1 and State 6) were shown to display the greatest power in the beta band. Further, frontal networks (State 2 and State 7) and the frontolimbic state (State 3) were characterised by increased power in delta/theta bands. Increases in power tended to show increases in phase-coupling. State 4 showed the greatest power and phase-coupling in the theta band in frontal areas. In addition, State 5 and 8 showed greatest power in the beta frequency, but greatest phase coupling in occipital alpha. The observed frequency content of the described states is

comparable to power and phase-coupling networks previously identified in Quinn et al., (2018), who also applied the TDE-HMM.

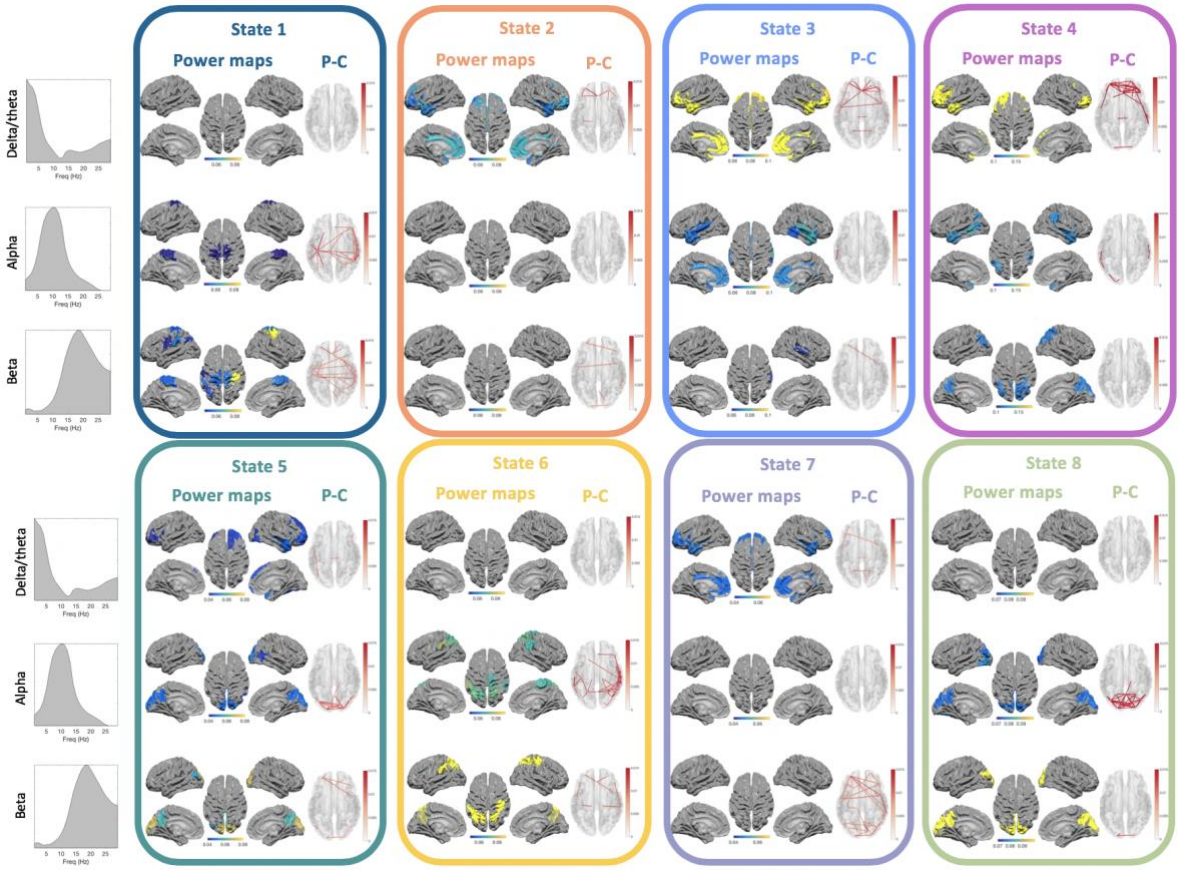


Figure 5.10. Spectrally resolved state power maps and coherence networks for all 8 states inferred by the TDE-HMM. The output of the NNMF, used to decompose the data in more data driven frequency bands, is shown on the left-hand side. The top, middle and bottom rows within each state description represent delta/theta, alpha, and beta power. Power maps show the top 15% of parcels.

5.3.4.4 *Associations with mood instability*

Although there were no differences in the global rate of switching between participant groups, increases in negative mood instability were negatively associated with decreases in state switching rates in the high MDQ group (r=-.62, n=14, p=.02). This association was absent in the low MDQ group (r=.30, n=12, p=.34) (Figure 5.11A). A Fisher's Z-test showed that these two correlations were significantly different from each other (Z=-2.3, p=.02).

Increases in negative mood instability were further associated with lower fractional occupancy of frontolimbic State 3 (r=-.75, n=14, p=.002) and corresponding increased interval times of State 3 (r=.61, n=14, p=.02) in the high MDQ group (Figure 5.11B and 5.11C). Again, associations were absent in the low MDQ group between negative mood instability and both fractional occupancy (r=.02, n=12, p=.95) and interval times (r=-.07, n=12, p=.82) of State 3. Fisher's Z-test showed that the correlations between negative mood instability and fractional occupancy for both low and high MDQ groups were significantly different from each other (Z=-2.1, p=.03). Similarly, the correlations between negative mood instability and interval times in both low and high MDQ groups were also trend significantly different from each other (Z=1.73, p=.08).

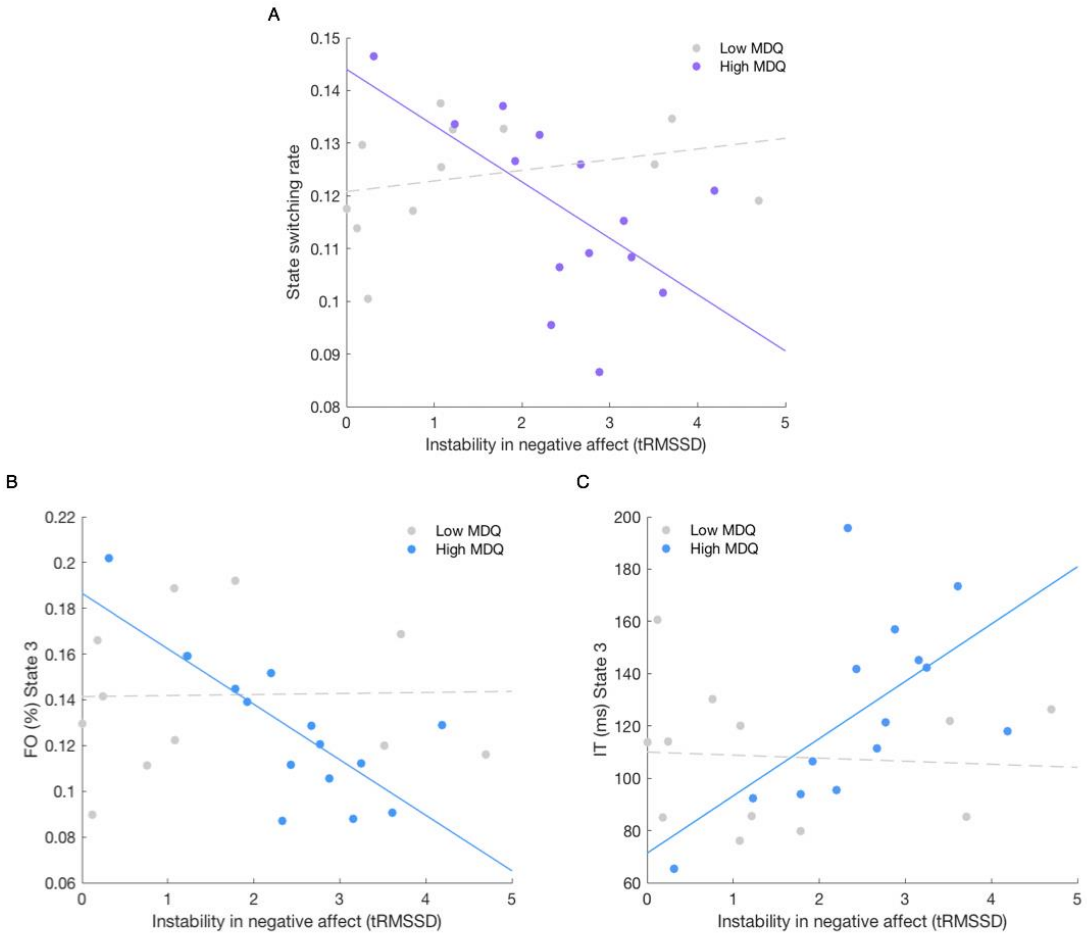


Figure 5.11. A. Pearson's correlation between the global rate of switching and instability in negative affect (as calculated using the tRMSSD) for both low and high MDQ groups. **B.** Pearson's correlation between the fractional occupancy of frontolimbic State 3 and instability in negative affect. **C.** Pearson's

correlation between the interval time of State 3 and instability in negative affect. For all figures, low MDQ is shown in grey, with correlations shown with a dashed line. High MDQ is shown in purple, or the relevant state colour, with significant correlations shown in a solid line.

5.3.5 TDE-HMM analyses – Combined COMET and UKMP Normative data

In order to assess whether the results of the COMET sample were comparable to larger samples of data obtained from healthy individuals, the COMET dataset was combined with two normative datasets acquired as part of the MRC UK MEG Partnership Grant (UKMP). Importantly, the following TDE-HMM results are independently estimated from the previously reported TDE-HMM using COMET data only.

5.3.5.1 *State power and connectivity*

Figure 5.12 shows the mean broadband activation maps and coherence networks of all 8 states estimated from the TDE-HMM. Again, distinct networks can be observed including frontal, sensorimotor, and visual networks.

5.3.5.2 *Temporal Characteristics*

Temporal characteristics of the combined UKMP and COMET sample showed that States 1-6 and State 8 had fractional occupancies of between 10-20%. State 7 had much lower fractional occupancy, around 5%. Average state life times were approximately 50-100 ms and average interval times were approximately 500 ms, with the exception of State 7 that exhibited much longer interval times of around 2 seconds, in line with its reduced fractional occupancy (Figure 5.13). These global temporal characteristics were comparable to the previous TDE-HMM applied to COMET data only. In addition, in other work applying the HMM, it is common to see one state that exhibits particularly low fractional occupancies and longer interval times.

One-way ANOVAs were used to test for differences in the temporal characteristics of each state between the four groups (high MDQ, low MDQ, Cambridge UKMP and Oxford UKMP). Only significant group differences that remained after Bonferroni correction for multiple comparisons are reported here, along with the adjusted *p*-values.

Group differences were observed in the fractional occupancy of State 1 ($F(3,174)=7.15$, $p<.001$). High MDQ participants demonstrated higher fractional occupancies than Cambridge UKMP ($p=.01$) and Oxford UKMP participants ($p=.01$). Low MDQ participants also demonstrated higher fractional occupancies than Cambridge UKMP ($p<.01$) and Oxford UKMP participants ($p<.01$). Group differences were also found in the fractional occupancy of State 3 ($F(3,174)=8.93$, $p<.001$) in which the high MDQ sample demonstrated significantly lower fractional occupancy than both Cambridge ($p<.01$) and Oxford ($p<.01$) UKMP participants. Lastly, group differences were also observed in the fractional occupancy of State 8 ($F(3,174)=5.17$, $p=.002$) in which Cambridge UKMP participants showed significantly lower fractional occupancies than the Oxford UKMP participants ($p<.01$) (Figure 5.13A and Table 5.3).

Group differences in life times were observed in the same states that exhibited group differences in fractional occupancies. In State 1, high MDQ participants demonstrated longer life times than Cambridge ($p=.03$) and Oxford UKMP participants ($p=.02$), ($F(3,174)=3.93$, $p=.009$). In State 3, high MDQ participants demonstrated shorter life times than Cambridge ($p<.001$) and Oxford UKMP participants ($p<.001$), ($F(3,174)=10.07$, $p<.000$). In State 8, high MDQ participants demonstrated longer life times than low MDQ participants ($p=.02$) and Cambridge UKMP participants ($p<.01$), ($F(3,174)=4.84$, $p=.003$) (Figure 5.13B and Table 5.3).

When considering interval times, low MDQ participants demonstrated briefer interval times for State 1 than the Cambridge UKMP participants (p=.02), but did not differ from other participants (F(3,174)=4.57, p=.004). Again in State 3, high MDQ participants demonstrated significantly longer interval times than Cambridge (p<.001) and Oxford UKMP participants (p<.001), (F(3,174)=10.13, p<.000) (Figure 5.13C and Table 5.3). State 3 was the only state in which high MDQ participants consistently differed from the UKMP normative sample, across all three temporal characteristics. In State 5, Oxford UKMP participants demonstrated shorter interval times than low MDQ participants (p=.01) and high MDQ participants (p=.006), (F(3,174)=6.16, p=.000). Lastly, no significant group differences existed in the state switching rate between groups (Figure 5.13D).

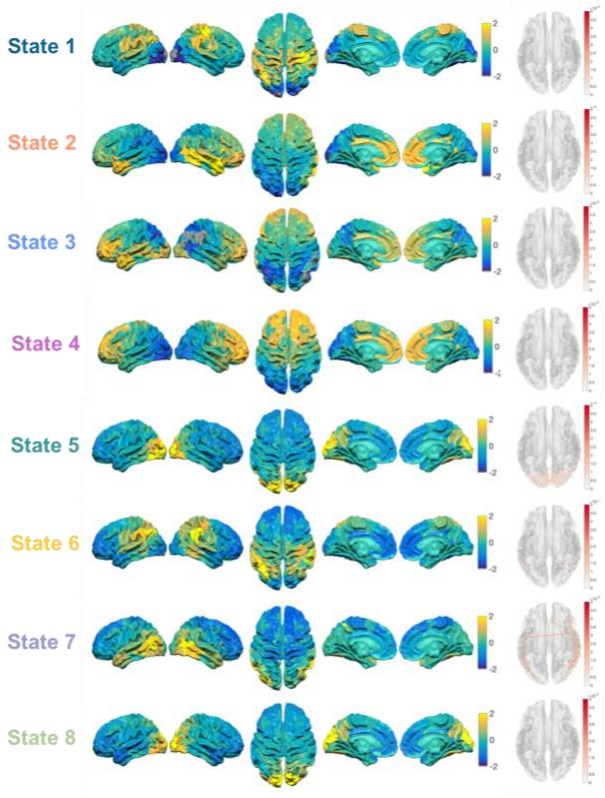


Figure 5.12. Mean broadband activation maps and coherence networks of each 8 states. These were computed from the state-wise multi-taper, applied after the TDE-HMM inference. Mean activation is z-scored across parcels. In the mean activation maps, yellow represents brain parcels in which the mean activation was found to be increased, and blue represents brain parcels in which the mean activation was found to be decreased, in a particular state.

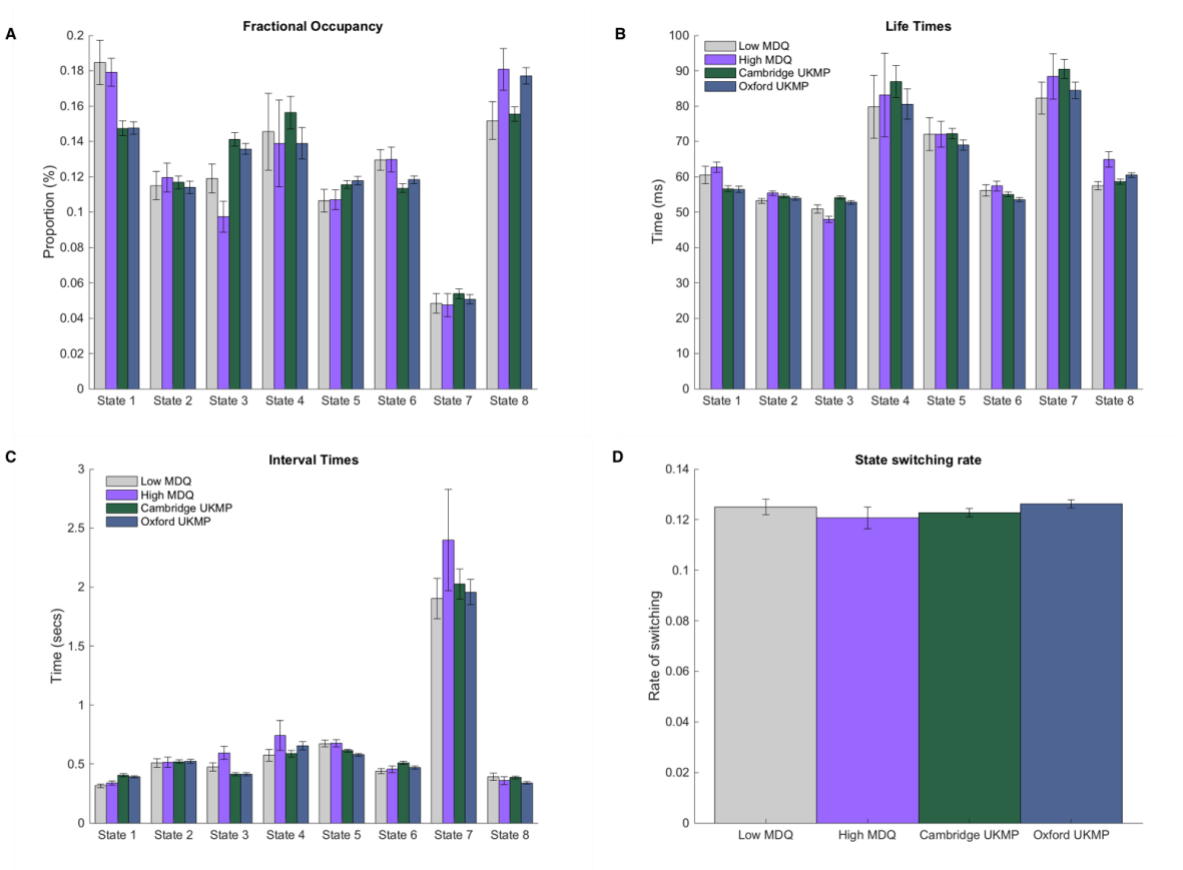


Figure 5.13. The global temporal statistics describing **A.** the fractional occupancies, **B.** life times, **C.** interval times and **D.** state switching rates, for Low MDQ, High MDQ, Cambridge UKMP and Oxford UKMP participants. Error bars represent the ±SE of the mean.

Table 5.3. State temporal characteristics by group		FO (mean, SD)	LTs (mean, SD)	ITs (mean, SD)
State 1	**Low MDQ**	.18 (.04)	60.49 (8.68)	.32 (.05)
	High MDQ	.18 (.03)	62.71 (5.53)	.34 (.06)
	Cambridge	.15 (.04)	56.62 (6.93)	.40 (.11)
	Oxford	.15 (.03)	56.48 (7.59)	.39 (.08)
State 2	**Low MDQ**	.12 (.03)	53.14 (2.48)	.51 (.13)
	High MDQ	.12 (.03)	55.33 (2.51)	.51 (.16)
	Cambridge	.12 (.03)	54.58 (4.47)	.52 (.15)
	Oxford	.12 (.03)	53.88 (4.68)	.52 (.14)
State 3	**Low MDQ**	.12 (.03)	50.87 (3.98)	.48 (.13)
	High MDQ	.10 (.03)	47.94 (3.14)	.60 (.21)
	Cambridge	.14 (.03)	54.10 (4.31)	.41 (.12)
	Oxford	.14 (.03)	52.72 (4.05)	.41 (.10)
State 4	**Low MDQ**	.15 (.08)	79.78 (30.76)	.58 (.17)
	High MDQ	.14 (.09)	83.17 (44.22)	.74 (.47)
	Cambridge	.16 (.08)	86.93 (39.65)	.59 (.25)
	Oxford	.14 (.08)	80.58 (36.38)	.65 (.31)
State 5	**Low MDQ**	.11 (.02)	72.06 (16.08)	.67 (.10)
	High MDQ	.11 (.02)	72.04 (13.84)	.68 (.12)
	Cambridge	.12 (.02)	72.24 (12.75)	.61 (.09)
	Oxford	.12 (.02)	69.00 (12.25)	.58 (.10)
State 6	**Low MDQ**	.13 (.02)	56.12 (5.65)	.44 (.08)
	High MDQ	.13 (.03)	57.40 (5.30)	.46 (.11)
	Cambridge	.11 (.02)	55.03 (5.85)	.51 (.12)
	Oxford	.12 (.02)	53.43 (4.98)	.47 (.10)
State 7	**Low MDQ**	.05 (.02)	82.25 (15.52)	1.90 (.59)
	High MDQ	.05 (.02)	88.41 (24.23)	2.40 (1.60)
	Cambridge	.05 (.03)	90.51 (24.09)	2.03 (1.14)
	Oxford	.05 (.02)	84.47 (20.12)	1.96 (.90)
State 8	**Low MDQ**	.15 (.04)	57.45 (4.23)	.39 (.10)
	High MDQ	.18 (.04)	64.87 (8.32)	.36 (.13)
	Cambridge	.16 (.04)	58.59 (6.47)	.39 (.10)
	Oxford	.17 (.04)	60.46 (5.91)	.34 (.10)

5.3.5.3 *Spectral Modes*

The estimated power maps and phase coherence networks for each spectral mode are shown in Figure 5.14. Sensorimotor networks, States 1 and 6, were shown to display the greatest power and phase coupling in the beta band. Frontal networks, States 2 and 7, were dominated by greatest power and phase coupling in the delta/theta band. State 3 again showed a fronto-limbic network, characterised by increased power and phase coupling in the low frequency delta and theta band. State 4 showed greatest power and phase coupling in the beta band, but also activation in the delta and theta band. Finally, a visual occipital network was observed in State 5, most prominent in the alpha band, and an occipital-parietal network was observed in State 8 with power and phase coupling evident in both alpha and beta frequency bands.

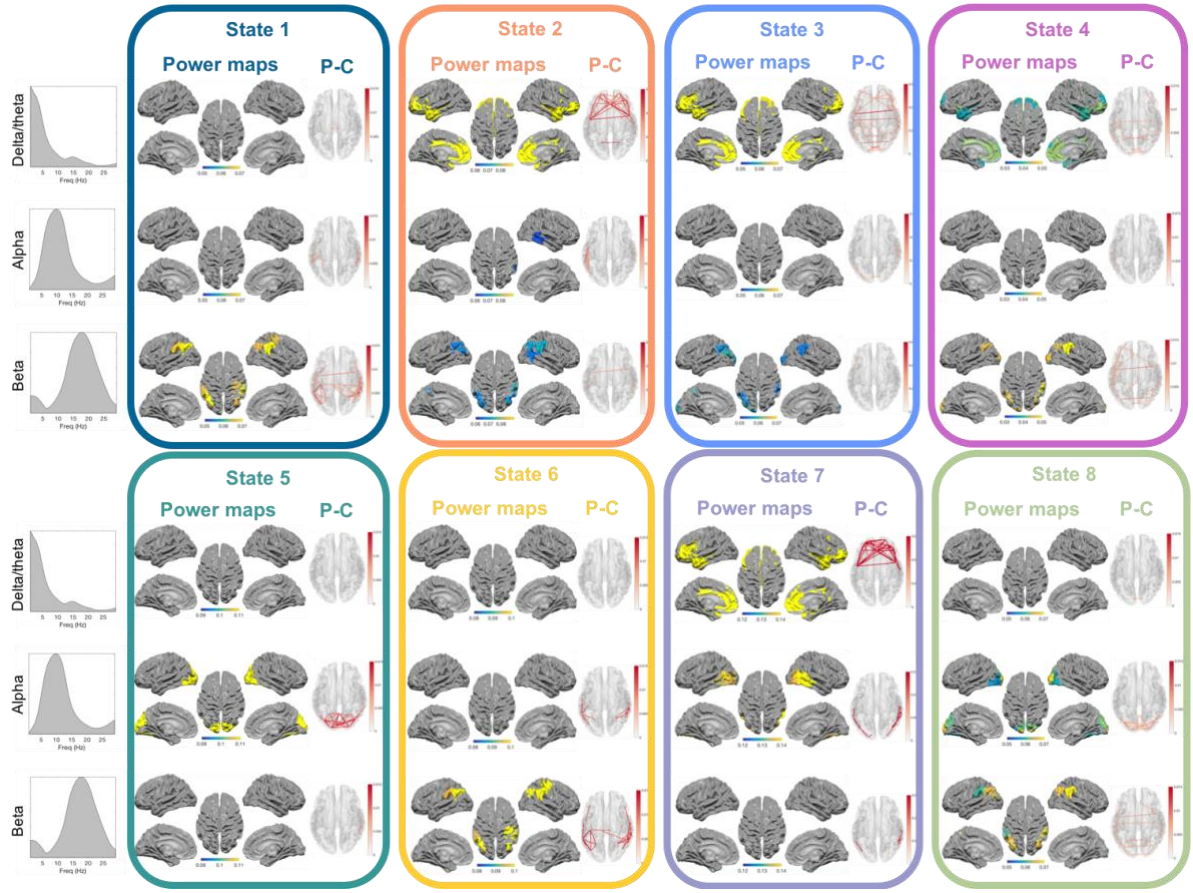


Figure 5.14 Spectrally resolved state power maps and coherence networks for all 8 states inferred by the TDE-HMM for combined UKMP and COMET data. The output of the NNMF, used to decompose the data in more data driven frequency bands, is shown on the left-hand side. The

top, middle and bottom rows within each state description represent delta/theta, alpha, and beta power. Power maps show the top 15% of parcels.

5.3.5.4 *Replication of associations between state dynamics and mood instability*

It was investigated whether associations between state dynamics and mood instability observed in the COMET TDE-HMM (section 5.3.4.4) were also present in the independently estimated combined COMET and UKMP TDE-HMM.

In the COMET participants only, increases in negative mood instability were significantly negatively associated with decreases in state switching rates in the high MDQ group (r=-.56, n=14, p=.04), but not in the low MDQ group (r=.26, n=12, p=.41). This association did not exist when considering positive mood instability. Further, increases in negative mood instability were significantly associated with lower fractional occupancy of frontolimbic State 3 in the high MDQ group (r=-.52, n=14, p=.05) and corresponding increased interval times of State 3, though this correlation did not reach significance (r=.43, n=14, p=.12). Again, there was no association between negative mood instability and fractional occupancy of State 3 in the low MDQ group (r=.23, n=12, p=.42) (Figure 5.15).

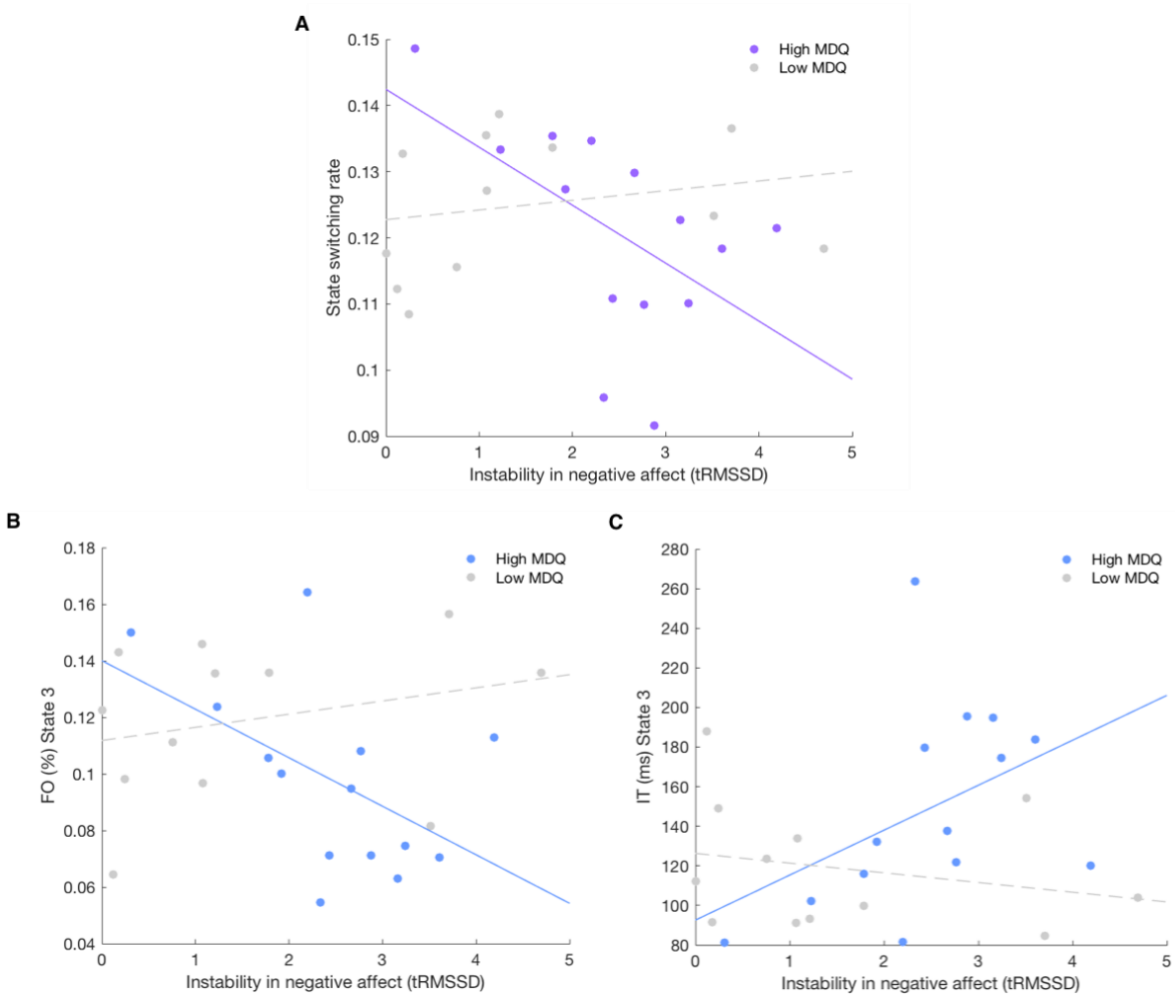


Figure 5.15. Replication of correlations between mood instability and state dynamics in the Combined COMET and UKMP Normative TDE-HMM. **A.** Pearson's correlation between the global rate of switching and instability in negative affect (as calculated using the tRMSSD) for low and high MDQ groups only. **B.** Pearson's correlation between the fractional occupancy of frontolimbic State 3 and instability in negative affect. **C.** Pearson's correlation between the interval time of State 3 and instability in negative affect. For all figures, low MDQ is shown in grey, with correlations shown with a dashed line. High MDQ is shown in purple, or the relevant state colour, with significant correlations shown in a solid line.

5.4 Discussion

This chapter introduced the first investigation of mood instability using an electrophysiological approach. Sensor-space and source-localised time-frequency analyses revealed that, compared to individuals with low mood instability, individuals with high mood instability demonstrated reductions in low frequency delta and theta power in frontal and temporal regions, increases in

alpha power in occipital and temporal regions, and decreases in beta power in occipital regions. To further explore resting-state dynamics, a TDE-HMM with 8 states was applied to COMET data revealing distinct brain networks with frequency specific modulations in power and phase coupling that demonstrated fast transient brain states. Higher levels of negative mood instability in high MDQ participants was associated with decreased overall state switching, reduced proportion of time spent in the frontolimbic state, and increased time between state visits to this state. In addition, a larger, normative sample was included to ensure that resulting state networks from the COMET TDE-HMM were not poorly estimated from using a relatively small sample. In this independent analysis, the combined COMET and UKMP TDE-HMM showed that state networks were robust and associations between high levels of negative mood instability and reductions in overall state switching, reductions in fractional occupancy and increases in interval times of the frontolimbic state, could be reproduced.

Results from both sensor- and source-level frequency analyses were complementary. Due to being exploratory, group differences were explored at the whole brain level, across multiple frequency bands. The current findings suggest that individuals with high levels of mood instability might display reductions in low frequency power in frontal regions, although none of these results remained significant after conservative corrections for multiple comparisons across sensors/parcels. The findings are partly in line with reduced spectral power in theta band in frontocentral sensors of MDD patients (Jiang et al., 2016). However, additional findings in this study, such as increases in alpha power and decreases in beta power in occipital regions, have not been observed in MEG recordings of psychiatric populations.

Of course, the MEG literature within which to view these findings is very small. Turning to EEG, a recent review of 184 studies examined differences in spectral power across psychiatric populations including MDD, BD, ADHD and anxiety (Newson & Thiagarajan, 2019). The

authors noted similarities between disorders, with most eyes-open EEG studies showing increases in delta and theta when studies assessed absolute power differences, but a trend towards no differences between patients and healthy controls when studies assessed relative power. Further, eyes-closed versus eyes-open conditions also affected the reported direction of overall power difference within disorders such as BD, demonstrating how methodological differences have important effects on findings and their interpretation (Newson & Thiagarajan, 2019). In addition, whilst the above findings might be in contrast to those observed in COMET, the present findings focus on the effect of mood instability, regardless of whether individuals met disorder specific criteria. Further work should aim to replicate the present findings using similar methods in individuals known to experience mood instability.

To further examine the spectral content of the signal from COMET data, a TDE-HMM was employed. The TDE-HMM provides richer information about underlying spectral features of the data including whether they are specific to certain networks, whether they are frequency specific, and descriptions of their temporal dynamics. This method was chosen over sliding-window approaches as these require pre-specification of timescales (or window lengths) from which to observe network dynamics, which must be long enough to provide a good estimation of the data, but short enough to capture the fast dynamics in the data. In comparison, the HMM learns the timescales directly from the data, which in itself carries interesting information (Quinn et al., 2018).

The TDE-HMM applied to COMET data revealed temporal characteristics that were comparable to those estimated in previous implementations of the model (e.g. Quinn et al., 2018). State dynamics such as fractional occupancy, life times, interval times and rates of state switching were similar between MDQ groups. Although no group differences were observed in state dynamics, higher levels of negative mood instability in the high MDQ group were

associated with decreased state switching. State switching is likely to subserve fast dynamic brain functions. It has been suggested that during rest, functional networks display transient and repeated shifts over time, continuously exploring multiple network configurations, and building a 'dynamic repertoire' (Deco, Jirsa, & McIntosh, 2011). This 'dynamic repertoire' of states allows the flexibility to more quickly adapt to the most optimal network configuration required for a task (Deco et al., 2011). The rapid reorganisation of functional networks in this way supports the computational demands of cognitive processing (Bressler & Tognoli, 2006).

Given the above, one interpretation is that decreases in state switching in individuals with higher mood instability might reflect reduced exploration between certain network configurations, and possibly those that support mood regulation. This is consistent with the fact that higher negative mood instability in the high MDQ group was associated with decreased proportion of time spent in the frontolimbic state, with increases in interval times to this state. In line with this possibility, the only other study to date assessing neural markers of mood instability in fMRI, found that increased instability in negative mood (feeling down) was associated with reduced connectivity between the salience network and other networks (Servaas et al., 2017).

The COMET sample was relatively small due to being unable to scan all study participants. Despite this, in an independent TDE-HMM applied to both COMET and UKMP data combined, the above associations between negative mood instability and state dynamics in COMET participants were reproduced. This is reassuring having used a small sample, relatively novel analysis method, and in a population that has not been studied using MEG previously. Networks estimated in the combined TDE-HMM were more robust yet demonstrated remarkably similar organisation to the COMET dataset alone. This demonstrates that aggregation of data across studies and multi-sites is a feasible approach and may strengthen smaller datasets from hard to recruit, at-risk or clinical samples. Nevertheless, it would be

necessary to replicate these results in a larger, independent sample of individuals with low and high MDQ.

The HMM requires a number of pre-specified parameters. Of particular importance is the number of states. Initial exploratory work on the COMET dataset, not included in this thesis, has applied the TDE-HMM with a number of pre-specified states, including 4, 6, 8, 10 and 12. Eight states were chosen for the current analysis as it provided a useful description of the data and interpretations did not change by adding further states. Associations between negative mood instability and similar frontal networks were also seen across these analyses.

Lastly, further work on this dataset will consider utilising data from the second MEG session that COMET participants underwent after 10 weeks of mood monitoring. Although not all participants completed their second MEG scan, it would be interesting to observe any longitudinal changes in the dynamics of neural measures in a small subset of individuals, or whether these remain stable over time. Given that task datasets were also recorded during the same MEG scanning sessions, additional analysis will explore whether the state dynamics of task-based networks are associated with indices of mood instability.

5.5 Conclusion

This is the first application of the TDE-HMM to assess mood related neural dynamics. Negative mood instability may be associated with state dynamics, particularly fronto-limbic dynamics, and this warrants further exploration. This finding was replicated in a separate TDE-HMM combined with normative data.

Part 2 – OxCaMS: The effect of L-type calcium channel antagonism for Mood Instability.

Chapter 6. Mood stabilising effects of calcium channel antagonism

6.1 Introduction

The following body of work, which makes up the remainder of this thesis explored the putative role of L-type calcium channel (LTCC) antagonists as a potential treatment for mood instability and associated mood disorders.

Licenced LTCC antagonists such as verapamil and nifedipine have long been used as treatments for hypertension and angina. The idea of repurposing LTCC antagonists for potential treatments in mood disorders is not new. After original reports of altered calcium levels in BD (Carman & Wyatt, 1979; Jimerson et al., 1979; Weston & Howard, 1922), a small number of double-blind RCTs investigated the efficacy of LTCC antagonist verapamil to reduce mania/depressive symptomatology compared to lithium (Garza-Trevino, Overall, & Hollister, 1992; Giannini, Taraszewski, & Loiselle, 1987; Mallinger et al., 2008; Pal Singh, 2008) or placebo (Dubovsky et al., 1986; Janicak et al., 1998). Although a recent meta-analysis found no evidence for the effectiveness of LTCC antagonists, the previous studies may have underestimated their therapeutic potential (Cipriani et al., 2016). Notably, verapamil has poor BBB permeability and is therefore unlikely to produce desired effects in the brain (Doran et al., 1985). The efficacy of other LTCC antagonists have only been tested in observational studies and not in RCTs (Cipriani et al., 2016).

Since these studies, genomic and molecular-based studies have provided evidence supporting LTCCs and $Ca_V1.2$ as a therapeutic target (Zamponi et al., 2015). As previously described in Chapter 1, LTCC genes such as *CACNA1C,* which encodes the voltage-gated LTCC $Ca_V1.2$ protein, are associated with psychiatric disorders such as BD. *CACNA1C* has also been found to be associated with phenotypes known to be disturbed in psychiatric disorders, such as circadian

activity and memory (Craddock & Sklar, 2013; Ferreira et al., 2008). In addition, studies showing altered Ca^{2+} homeostasis in BD and the role of Ca^{2+} in the hypothesised mode of action of lithium treatment (Berridge, 2014; Warsh et al., 2004) are consistent with the view that antagonism of LTCCs is likely to be therapeutically relevant (Berridge, 2014).

Existing LTCC antagonists, however, are not suitable for repurposing for psychiatric use. This is due to the fact that LTCCs are not specific to the human brain and have potential for peripheral side-effects. Nevertheless, if the use of current LTCC antagonists were shown to be associated with psychiatric benefits, this would encourage the development of more brain-selective LTCC antagonists (Atkinson et al., 2019; Harrison, Tunbridge, et al., 2019). This is possible given that LTCC genes encoding the α_1 subunit, and their isoforms, are expressed differently in the brain compared to the heart, producing some brain-enriched or brain-specific isoforms (Clark et al., 2020; Striessnig et al., 2014).

The above considerations provided the rationale for an exploratory, experimental medicine study of calcium antagonism for mood instability: the Oxford study of Calcium channel Antagonism, cognition, Mood instability and Sleep (OxCaMS) (Atkinson et al., 2019). Since LTCC genes contribute to a number of psychiatric disorders and phenotypes, LTCC antagonism could be beneficial when treating transdiagnostic features such as mood instability and cognitive or neural dysfunction. OxCaMS was a double-blind placebo-controlled study. Participants with high levels of mood instability completed a 2-week pre-randomisation phase in the absence of any intervention, during which measures of mood, cognition, sleep, and neural activity were assessed. This was followed by a 2-week randomisation phase to either nicardipine SR (30 mg twice daily) or placebo, during which all measures were repeated. Nicardipine SR is an BBB-penetrant LTCC antagonist of the dihydropyridine type. The study design allowed for within- and between-participant comparison of outcomes. An experimental medicine approach was chosen as so little

is known about the behavioural, cognitive or neural effects of LTCC antagonism, and indeed its mechanisms. In this case, a full clinical trial was not justified or feasible. This thesis focuses on two particular outcomes from the OxCaMS study; mood instability and neural activity at rest.

The current chapter assessed whether LTCC antagonism reduced mood instability, that is, whether indices of mood instability, measured using the tRMSSD, were reduced post-randomisation in the nicardipine SR group, compared to placebo. If indices of mood instability were reduced during calcium-channel antagonism, this would support the development of more selective LTCC antagonists for use in psychiatric disorders. It would also provide the rationale for a larger clinical trial in patients, particularly those with BD, to assess whether reductions in mood instability also reduce the likelihood of further mood episodes.

6.2 Methods

The most relevant aspects of the OxCaMS study for this DPhil are described in the methods of this thesis. The full methods can be viewed in the published protocol (Atkinson et al., 2019). The study received ethical approval from the Health Research Authority, Oxfordshire Research Ethics Committee (17/SC/0029). Contributions to this study are outlined in Appendix 1.

6.2.1 Participants

Potential participants were recruited via: (1) advertisements at the University of Oxford and in the local community and (2) the SCNi cohort. Only students in the SCNi cohort who had consented to take part in further studies, and who met initial eligibility criteria for the OxCaMS study, were contacted to take part.

Participants were aged 18-35. Due to the successful identification of healthy individuals with low and high mood instability in COMET (Chapter 2), the MDQ tool was used as a screening tool

for identifying high mood instability in the OxCaMS study. Inclusion criteria included participants who experienced seven or more symptoms on question 1 of the MDQ, in addition to indicating that several of these symptoms had occurred over the same period of time and had caused at least mild functional impairment. The inclusion criteria were more stringent than that used in the COMET study to ensure targeting of individuals who experienced persistent and significant mood instability. Initial exclusion criteria assessed via online assessment included regular psychotropic drug use within the last 12 weeks ('as required' use of psychotropic medication was permitted at the principle investigators discretion, if it was deemed not to compromise safety or affect data quality), contraindication(s) to nicardipine (as documented in the Summary of Product Characteristics for Cardene) and harmful alcohol or substance use.

6.2.2 Overall study procedure

An overview of the study procedure is shown in Figure 6.1. OxCaMS was a 4-week experimental medicine study, utilising a randomised, double-blind, placebo-controlled design. It comprised a 2-week pre-randomisation period during which a number of baseline assessments were completed, followed by randomisation to nicardipine SR (30 mg twice daily) or placebo and a further 2-week post-randomisation phase during which the same assessments were continued or repeated to assess any effects of nicardipine SR or placebo over this period.

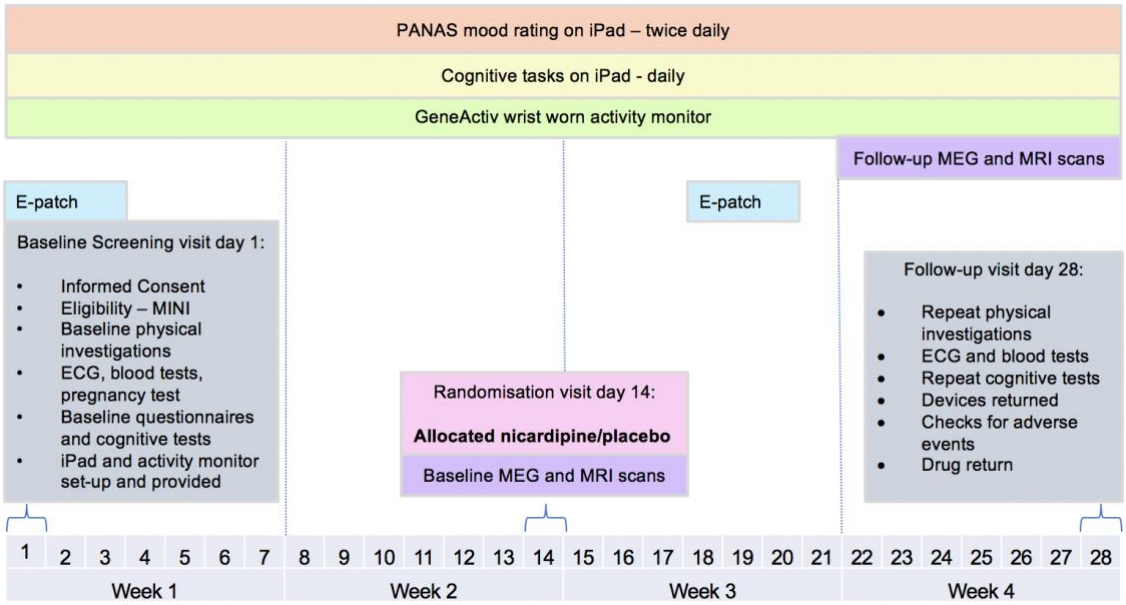


Figure 6.1. Overview of OxCaMS study procedures. Taken and adapted from Atkinson et al. (2019).

6.2.3 Randomisation and dosing schedule

Randomisation was implemented by an external trial manager at the Department of Psychiatry, University of Oxford, using a computer-generated schedule that minimised on gender. Participants were allocated to nicardipine SR or matched placebo on a 1:1 basis. Dispensing of nicardipine SR or placebo was completed by Oxford Health research pharmacists, CRF staff, or OxCaMS study clinicians. Clinicians, researchers, and participants remained blind to allocation for the duration of the study.

The sustained release formulation of nicardipine 30 mg (nicardipine SR) was used, allowing for twice daily dosing. The SR formulation lowers maximal concentration (C_{max}) of the drug, decreasing side effects associated with vasodilation. This in turn helped to maintain blinding. In addition, the chosen dosing schedule had previously been well tolerated when used in a study of normotensive young adults (Sun et al., 1990). Steady-state plasma levels of nicardipine SR are usually reached within 3 days.

6.2.4 Pre-randomisation assessments

Participants who satisfied initial online screening were invited to a baseline screening visit at the NIHR CRF, which took approximately 5 hours. After providing informed consent, participants were screened using the Mini International Neuropsychiatric Interview (MINI) by a trained researcher or clinician to identify the presence of any Axis-1 disorder. Participants meeting criteria for a lifetime Axis-1 disorder (other than psychosis) were not excluded, unless safety or data quality were likely to be compromised. Eligible participants provided demographic information; underwent a physical examination including blood pressure, BMI, and electrocardiogram measures; and blood samples were obtained for routine checks and for isolation of lymphocytes for studies of calcium signalling and calcium channel gene expression. Females underwent pregnancy testing. Participants completed a number of screening and self-report questionnaires on an iPad via Qualtrics Software (Qualtrics, Provo, UT) including the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993), Barratt Impulsiveness Scale (BIS) (Patton, Stanford, & Barratt, 1995), ALS-SF (Oliver & Simons, 2004) and AIM (Larsen, 1984) (see Atkinson et al., 2019 for full list). In addition, they completed a battery of cognitive tasks including the N-back (1-, 2-, and 3-back conditions; Farrell et al., 2012; Martens et al., 2019), the CombiTVA (described in Chapter 2, without emotional distractors), the emotional test battery (ETB) (Harmer et al., 2009), a stop-signal task (Logan, Schachar, & Tannock, 1997), and the National Adult Reading Test (NART) (Nelson & Willison, 1991) as a proxy measure for verbal IQ. Lastly, participants were taught how to complete longitudinal mood measures over the 4-week study period on an iPad with which they were provided, as described below.

6.2.5 Longitudinal monitoring

Every day during the 4-week study period participants completed short mood and cognitive assessments, delivered by the True Colours system. The True Colours system automatically sent

prompts to participants to complete all assessments, and if they had not been completed within 1 hour, a further prompt was sent. All daily tasks took less than 10 minutes in total. All data were automatically recorded and stored.

6.2.5.1 *Mood monitoring*

The PANAS-SF was used to monitor changes in daily mood. In OxCaMS, participants were asked to complete mood ratings twice daily, once in the morning and once in the evening.

6.2.5.2 *Cognitive assessment*

Three cognitive tasks developed for the COMET study were used to assess cognition alongside mood instability in OxCaMS including 'Whack-a-T' (Chapter 4), 'Fractals', and 'Wheel of Fortune' (Atkinson et al., 2019). The cognitive data are not included as part of this thesis.

6.2.6 Brain scanning

Prior to randomisation (on or prior to day 14) and at the final study visit (on or the week prior to day 28), participants underwent MEG scanning and MRI/fMRI at OHBA. The scanning protocols for each scan were identical pre- and post-randomisation. MEG scanning consisted of a 10-minute, eyes-open, resting-state scan, followed by a precision working-memory task (~ 35 min), a visual gamma task (~ 15 min) adapted from (Hoogenboom et al., 2006), and a gripper task to measure cortico-muscular coherence (~ 15 min). MRI/fMRI consisted of a T1-weighted structural MRI scan, a 10-minute, eyes-open, resting-state scan, a gambling task (~ 30 min), a gender discrimination emotional facial expression task (~ 12 min) (Godlewska et al., 2016), and an arterial spin labelling (ASL) sequence to help distinguish cerebrovascular from neural effects of nicardipine SR. Only resting-state MEG data and structural MRI data are considered in this thesis (Chapter 7).

6.2.7 Post-randomisation assessments

After the 2-week randomisation period, participants attended a final visit during which they repeated a number of assessments from the baseline screening visit. These included the physical examination, blood samples, questionnaires and the battery of cognitive tasks (except the NART). They completed questionnaires assessing the tolerability and acceptability of all devices and medication, of their understanding of the mood questionnaires and cognitive tasks, and, to assess the success of blinding, participants were asked to guess their allocation (nicardipine SR, placebo or unsure). Participants returned all devices and any unused medication.

6.2.8 Statistical Analyses of mood and questionnaire data

Baseline demographics were compared between nicardipine SR and placebo groups using independent samples t-tests for normally distributed, continuous data and chi-square tests for categorical data where appropriate.

6.2.8.1 *Task compliance*

During the 4-week study, participants monitored their mood twice daily (morning and evening) using the PANAS-SF. Days for which task data were not submitted were not interpolated in the current analysis. Compliance to mood monitoring was assessed for each participant by computing the percentage of PANAS-SF data points provided during the number of days spent in both the pre- and post-randomisation phases of the study. Compliance data exhibited a negatively skewed distribution. Using the Box-Cox procedure (Box & Cox, 1964) implemented using the MASS package in R (version 7.3-49) (Venables & Ripley, 2002), compliance values were power transformed (λ=3.9) to approximate a normal distribution. Using the transformed data, a repeated-measures ANOVA compared task compliance between groups and assessed any differences pre- and post-randomisation.

6.2.8.2 *PANAS-SF Mood Questionnaire*

Analyses included only mood data submitted from day 4 pre- and post-randomisation (e.g. day 4 – 14 and day 18 – 28). These time periods were chosen in order to ensure that analyses of mood and mood instability took into account delays in achieving steady state plasma levels of nicardipine SR (up to 3 days) during the post-randomisation phase of the study.

Overall mean and instability of daily positive and negative affect scores on the PANAS-SF were computed independently over the pre- and post-randomisation phases of the study. Mood instability was quantified using the tRMSSD, based on its successful implementation and sensitivity in COMET data (Chapter 2).

To test for any differences in the degree of change in outcome measures from pre- to post-randomisation between groups, change scores were computed (post- minus pre-randomisation). Change scores for mean affect and mood instability were compared between groups using independent-samples t-tests.

Analysis of covariance (ANCOVA) is commonly used when, despite randomisation, there are baseline differences in variables of interest (Twisk et al., 2018). While some studies use change scores to take account of such chance imbalances, this method does not in fact control for baseline differences and results in biased effect estimates of the change score (Vickers & Altman, 2001). For example, participants with a higher negative affect score at baseline are more likely to experience a high change score with these being negatively correlated (regression to the mean) (Bland & Altman, 1994; Clifton & Clifton, 2019; Vickers & Altman, 2001). An ANCOVA was therefore implemented to control for baseline differences in the primary outcome of interest, mood instability. For the ANCOVA, post-randomisation change scores were used as the

dependant variable, group as the independent variable, and pre-randomisation scores as the covariate.

6.2.8.3 *Maintenance of blinding*

Bang's blinding index (BI) was used to statistically assess the success of blinding (Bang, Ni, & Davis, 2004). This method was chosen as, compared to other available methods such as Cohen's Kappa, Bang's BI considers 'unsure' responses in its calculation. Whilst James' BI also considers these 'unsure' responses, Bang's BI provides a number of advantages. Firstly, it weights decisive responses greater than 'unsure' responses (Arandjelović, 2012). Secondly, Bang's BI is able to provide estimates of the success of blinding in both active and control arms of the study. Lastly, Bang's BI simplifies interpretability of the results with values from -1 to 1, with -1 indicating that all participants guessed the allocation they did not receive, 0 indicating that all participants randomly guessed their allocation (confirming successful blinding) and 1 indicating that all participants correctly guessed their allocation (Bang et al., 2004; Kolahi, Bang, & Park, 2009).

6.3 Results

The original aim was to recruit 40 volunteers; 20 randomised to nicardipine SR and 20 randomised to placebo. A total of 286 individuals completed the initial online screening assessment. Of these, 254 individuals did not meet inclusion criteria, could not commit to participating in the study, or did not reply to multiple communications from the study team. Due to delays in study set-up, and difficulty identifying eligible participants, the study was terminated (in September 2019) after 32 participants had been recruited. Of these, one participant did not meet eligibility criteria during the study screening visit, and another was withdrawn for not showing evidence of mood instability during the pre-randomisation period. For the remaining 30 participants, 15 were randomised to nicardipine SR and 15 to placebo. The study consort diagram is shown in Figure 6.2.

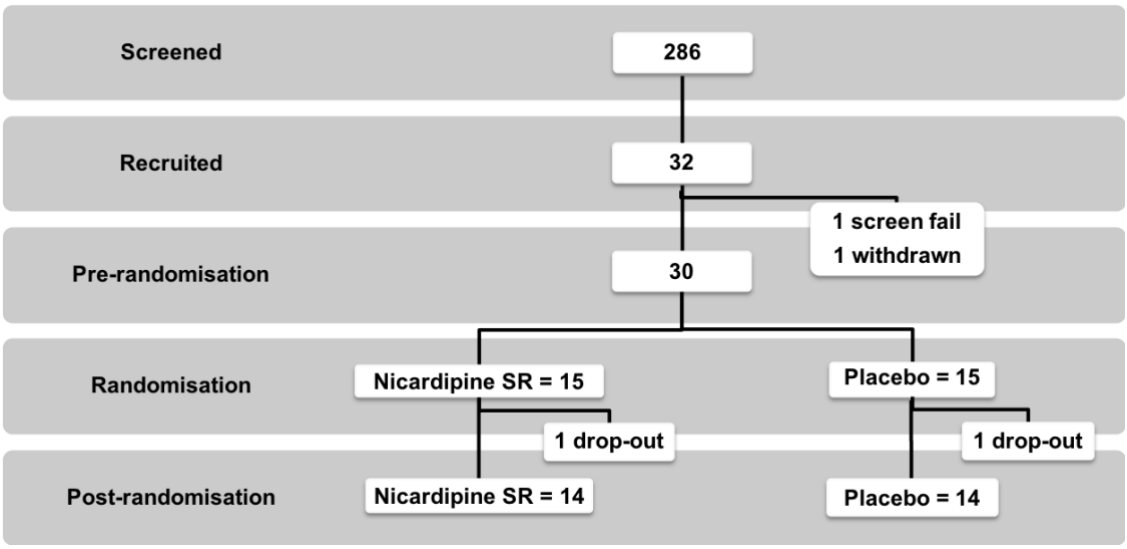


Figure 6.2. Consort diagram showing participant flow through phases of the OxCaMS study.

6.3.1 Baseline group differences

There was a difference between groups in age, with those randomised to nicardipine SR being slightly younger than those randomised to placebo (24 ± 4 vs. 28 ± 5, $t(28)=-2.31$, $p=.028$, Figure 6.3A). There were no differences in gender between allocation ($\chi(1)=.14$, $p=.71$).

Groups did not significantly differ in their baseline MDQ scores ($t(28)=1.06$, $p=.30$, Figure 6.3B). Further, there were no baseline differences in trait affect intensity measured by the AIM (166.27 ± 23.10 vs. 151.33 ± 22.90, $t(28)=1.78$, $p=.08$, Figure 6.4A). However, groups did show significant differences in trait affect lability, with the nicardipine SR group demonstrating higher total scores on the ALS-SF than the placebo group (52.27 ± 9.89 vs. 44 ± 11.53 respectively, $t(28)=2.11$, $p=.04$, Figure 6.4B). Particularly, differences in affect lability were most notable in the anxiety/depression subscale of the ALS-SF, with the nicardipine SR group demonstrating higher scores than the placebo group (15.20 ± 3.47 vs. 11.20 ± 3.82 respectively, $t(28)=3.00$, $p=.006$). No further group differences were observed for the depression/elation subscale (23.33 ± 4.95 vs. 21.4 ± 5.77, $t(28)=.99$, $p=.33$) or anger subscale of the ALS-SF (13.73 ± 3.56 vs. 11.4 ± 4.39, $t(28)=1.60$, $p=.12$). Demographics of participants are presented in Table 6.1.

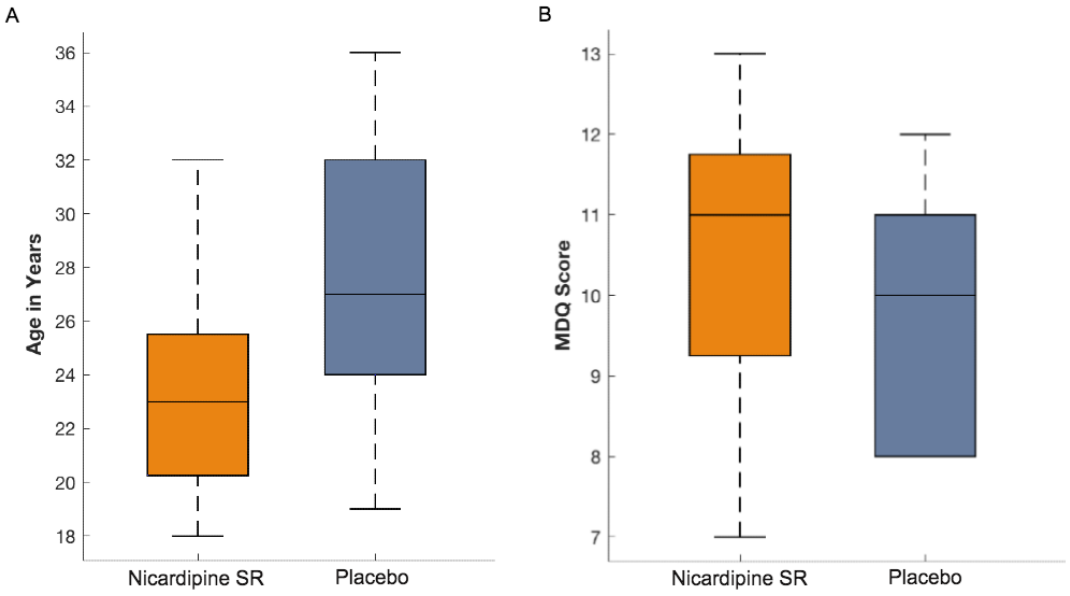


Figure 6.3. A. Boxplot of age in years, by group allocation. **B.** Boxplot of MDQ scores at study entry, by group allocation. Note that only individuals with MDQ scores of 7 or above were recruited for the study.

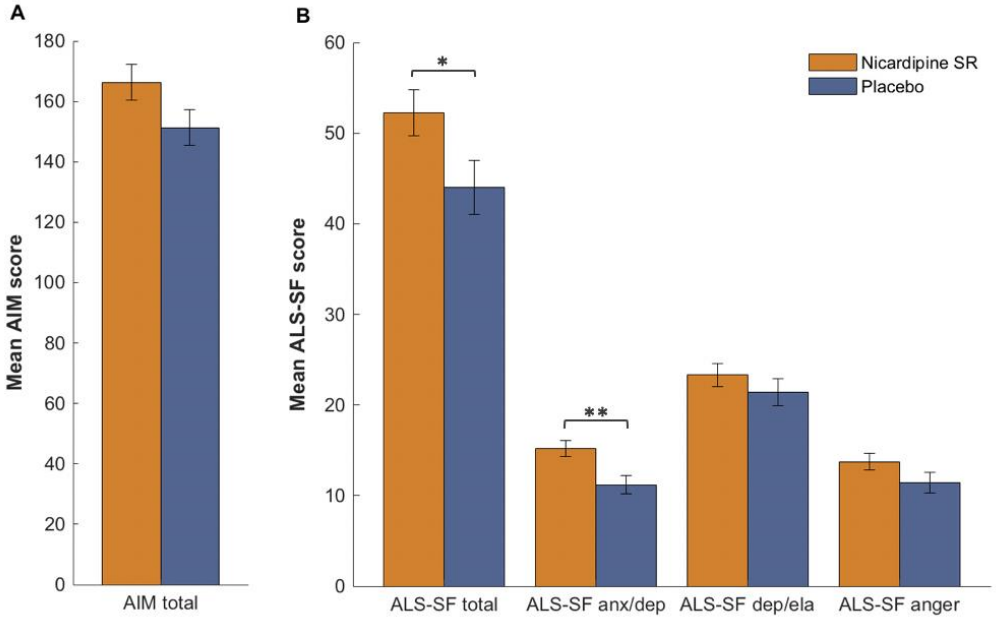


Figure 6.4. A. Bar plot of mean AIM scores for nicardipine SR and placebo groups pre-randomisation**. B.** Bar plots of Mean ALS-SF scores from left to right; total score, anxiety and depression subscale score, depression and elation subscale score and anger subscale score for nicardipine SR and placebo groups pre-randomisation. Error bars represent ±SE of mean. *p<.05 **p<.01.

Table 6.1. Baseline demographics of participants	Nicardipine SR *n*=15	Placebo *n*=15
Age (mean; SD)	24 (4)*	28 (5)*
Female (*n*; %)	10 (67%)	9 (60%)
MDQ score (mean; SD)	10 (2)	10 (2)
Affect Intensity Measure (AIM) (mean; SD)	166.27 (23.10)	151.33 (22.90)
Affective Lability Scale (ALS-SF) (mean; SD)	52.27 (9.89)*	44 (11.53)*
ALS-SF – depression/mania (mean; SD)	23.33 (4.95)	21.4 (5.77)
ALS-SF – anxiety/depression (mean; SD)	15.2 (3.47)**	11.20 (3.82)**
ALS-SF – anger (mean; SD)	13.73 (3.56)	11.4 (4.39)
Barratt Impulsiveness Scale (BIS) (mean; SD)	78.07 (11.42)	68.73 (9.39)
BIS motor	26.87 (4.93)	24.67 (3.89)
BIS attention	28.73 (4.70)	25.20 (6)
BIS non-planning	22.47 (3.78)	18.87 (3.94)
AUDIT score (median; range)	7.33 (5.02)	6.13 (6.22)
SCI score (mean; SD)	13.87 (7.29)	14.20 (7.88)
Ethnicity (*n*; %)		
White British	11 (73%)	7 (46.67%)
White Other	3 (20%)	4 (26.67%)
Asian British	0 (0%)	1 (6.67%)
Asian	0 (0%)	1 (6.67%)
Hispanic	1 (7%)	0 (0%)
North African	0 (0%)	1 (6.67%)
Black Caribbean	0 (0%)	1 (6.67%)
Highest Level of Education (*n*; %)		
O-Level/GCSE	2 (13%)	2 (13%)
A-Level/AS-Level/Scottish Highers	4 (27%)	2 (13%)

Undergraduate degree or Level 5 NVQ Diploma	5 (33%)	4 (27%)
Master's or doctorate degree	4 (27%)	7 (47%)
MINI DSM-IV Diagnoses – Current (*n*; %)	13 (87%)†	11 (73%)†
Major Depressive Episode	9	10
Major Depressive Episode with melancholic features	5	4
Dysthymia	3	4
Mood Disorder with psychotic features	1	1
Generalised Anxiety Disorder	5	3
Panic Disorder	8	3
Agoraphobia	5	6
Social Phobia	4	2
Obsessive Compulsive Disorder	3	2
MINI DSM-IV Diagnoses – Lifetime (*n*; %)	13 (87%)†	11 (73%)†
Manic Episode	2	3
Hypomanic Episode	11	7
Alcohol Abuse/Dependence	1	2
Substance Abuse/Dependence	0	1

SD = standard deviation. ** $p<.01$, * $p<.05$. †Note that participants could meet criteria for multiple DSM-IV diagnoses.

6.3.2 Compliance with longitudinal mood monitoring

Compliance with mood-monitoring over the 4-week study period was assessed. Two participants withdrew from the study after being randomised (1 nicardipine SR group; 1 placebo group) and as a result submitted very little mood data post-randomisation (1 day and 5 days, respectively). They were excluded from the analyses of mood data leaving 14 participants in each group who completed longitudinal monitoring and therefore the study. A repeated-measures ANOVA on the transformed data demonstrated that there was no significant difference in compliance

between groups ($F(1,26)=2.83$, $p=.11$, $\eta p^2=.10$), but there was a significant difference in compliance between time-points, with compliance rates post-randomisation (M=31.53, SE=3.56) being lower than pre-randomisation (M=41.40, SE=3.25) (mean difference=-9.87, SE=2.82, $F(1,26)=12.23$, $p=.002$, $\eta p^2=.32$). There was no interaction between group and time-point ($F(1,26)=.75$, $p=.39$, $\eta p^2=.03$). Whilst transformed data are reported in the text, Table 6.2 displays the untransformed data for interpretability.

Table 6.2. Compliance to mood monitoring schedule	**Nicardipine SR *(n*=14)**		**Placebo *(n*=14)**	
	Pre	**Post**	**Pre**	**Post**
PANAS-SF data points provided (median; range). Max. number of data points possible: 26-32	25 (16-29)	24 (11-30)	28 (18-30)	26 (12-29)
Compliance rate untransformed (median; range)	89.64% (53.3-96.43%)	82.86% (39.29-93.75%)	96.67% (60-100%)	89.29% (42.86-96.67%)

6.3.3 Mean affect scores pre- and post-randomisation

Group mean positive and negative affect scores are shown in Table 6.3. Independent samples t-tests were conducted to assess group differences in mean positive and negative affect change scores. For mean negative affect, there was no difference in change scores between treatment groups, ($t(26)=-.05$, $p=.96$). Similarly, for mean positive affect, there was also no difference in change scores between treatment groups ($t(26)=1.24$, $p=.23$). Individual participant data for pre- and post-randomisation mean affect are shown in Figure 6.5A and 6.5B.

Table 6.3. Mean affect scores and mean instability on subscales of the PANAS-SF questionnaire	Nicardipine SR (*n*=14)		Placebo (*n*=14)	
	Pre	**Post**	**Pre**	**Post**
Mean negative affect (mean, SD)	10.84 (2.50)*	11.28 (2.52)	8.33 (2.54)*	8.81 (3.12)
Mean positive affect (mean, SD)	12.22 (2.32)	13.41 (3.55)	11.76 (3.82)	11.92 (3.87)
tRMSSD negative affect (mean, SD)	8.95 (3.70)**	6.57 (4.14)	5.14 (2.49)**	4.54 (2.91)
tRMSSD positive affect (mean, SD)	9.05 (3.64)	6.89 (4.17)	9.69 (4.59)	7.29 (4.64)

*Nicardipine SR and placebo groups found to be significantly different at baseline, p<.05, and **p<.01

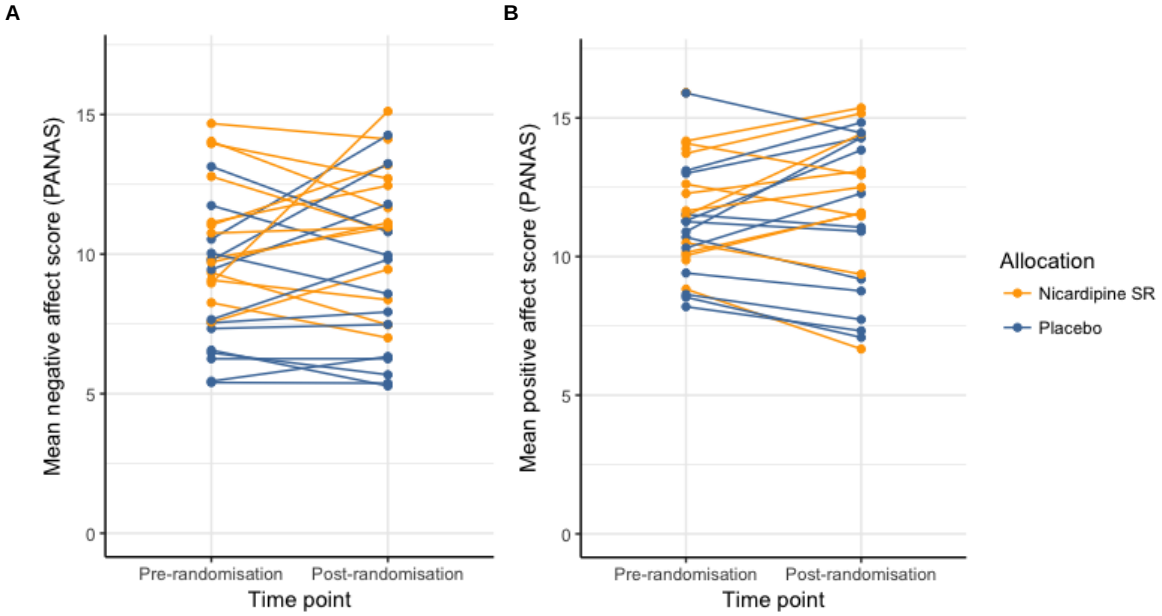


Figure 6.5. A. Individual participant data shown for mean negative and **B.** positive scores on the PANAS-SF pre- and post-randomisation, for nicardipine SR (orange) and placebo (blue).

6.3.4 Instability in mood pre- and post-randomisation

6.3.4.1 *Change scores*

Group mean instability in positive and negative affect (tRMSSD) is shown in Table 6.3. Independent samples t-tests were conducted to assess group differences in change scores in positive and negative mood instability from pre-post randomisation. For instability in negative affect, there was no difference in change scores between treatment groups ($t(26)$=-1.21, p=.24)

(Figure 6.6A). Similarly, for instability in positive affect, there was also no difference in change scores between treatment groups ($t(26)=.17$, $p=.87$) (Figure 6.6B). Individual participant data for pre- and post-randomisation mood instability in both negative and positive affect is shown in Figure 6.7A and 6.7B.

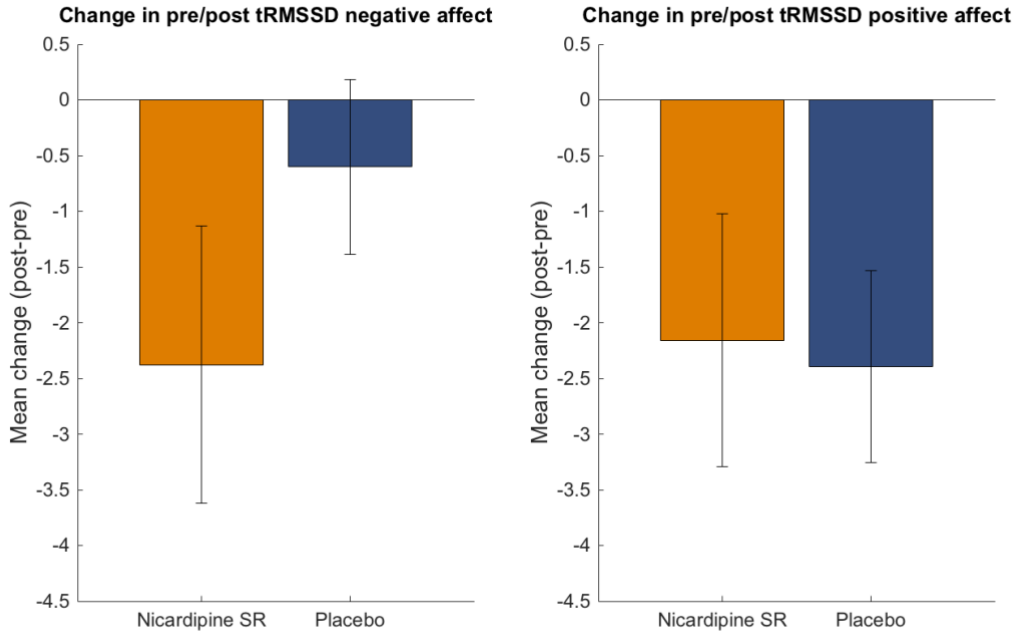


Figure 6.6 A. Degree of change (post-pre tRMSSD negative affect scores) for nicardipine SR (orange) and placebo (blue) groups. **B.** Degree of change (post-pre tRMSSD positive affect scores) for nicardipine SR (orange) and placebo (blue) groups. Error bars represent ±SE of mean.

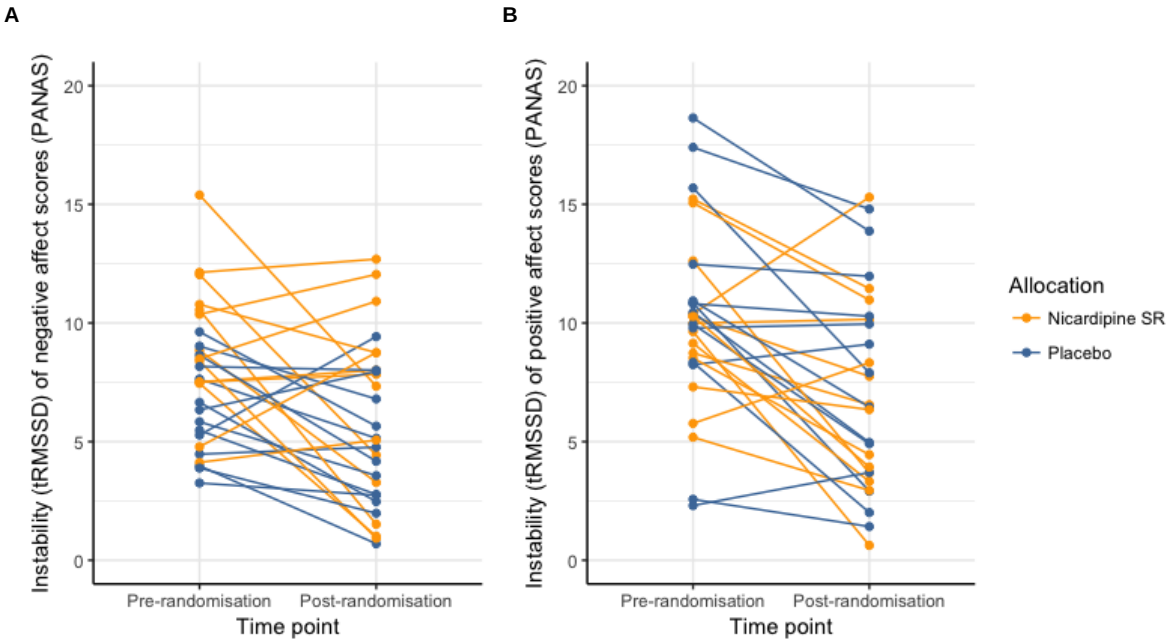


Figure 6.7. A. Individual participant data shown for instability in negative and **B.** positive mood scores on the PANAS-SF pre- and post-randomisation, for nicardipine SR (orange) and placebo (blue).

6.3.4.2 *ANCOVA*

The nicardipine SR had, by chance, statistically higher negative affect scores, and higher negative instability scores in the pre-randomisation phase compared to the control group (statistical analysis not presented here, but observable in Table 6.3). To control for this baseline imbalance, an ANCOVA was used to covary for baseline negative affect.

Negative instability (tRMSSD) change scores were included in the model as the dependent variable, with treatment group as the independent variable and pre-randomisation tRMSSD negative affect as the covariate. There was no statistically significant difference in negative tRMSSD change scores between nicardipine SR and placebo groups, once their means had been adjusted for pre-randomisation tRMSSD negative affect ($F(1,25)=.14$, $p=.71$, $\eta p_2=.006$).

The above analysis was repeated for instability in positive affect. An ANCOVA did not reveal a statistically significant difference in positive tRMSSD change scores between nicardipine SR and

placebo groups, once their means had been adjusted for pre-randomisation tRMSSD positive affect ($F(1,25)=.00$, $p=.99$, $\eta_{p^2}=.00$). Results of these analyses were identical when including post-randomisation tRMSSD negative/positive affect as the dependent variable, instead of change scores.

6.3.5 Correlations between baseline measures and mood instability

Mood instability in negative affect measured during the pre-randomisation phase significantly positively correlated with MDQ scores at baseline ($r=.38$, $n=28$, $p=.05$), total score on the AIM ($r=.43$, $n=28$, $p=.02$), total score on the ALS ($r=.42$, $n=28$, $p=.03$), the anxiety/depression subscale of the ALS ($r=.49$, $n=28$, $p<.01$), and total BIS score ($r=.44$, $n=28$, $p=.02$). Mood instability in positive affect measured during the pre-randomisation phase was only correlated with total score on the AIM ($r=.47$, $n=28$, $p=.01$).

6.3.6 Maintenance of blinding

At the end of the study, participants were asked to guess their treatment allocation using one of three responses 'nicardipine SR', 'placebo' or 'unsure'. Data are missing for one participant in the placebo group who did not complete the endpoint questionnaire. The maintenance of blinding was therefore tested for 14 individuals randomised to nicardipine SR and 13 randomised to placebo. The data are presented in Table 6.4.

Table 6.4. Actual and guessed allocations

	Guess, *n*			
Allocation	**Nicardipine SR**	**Placebo**	**Unsure**	**Total**
Nicardipine SR	4	4	6	14
Placebo	5	6	2	13
Total	9	10	8	27

Bang's blinding index (BI) was used to statistically assess the success of blinding. For the nicardipine SR group, Bang's BI = 0 [-0.39 – 0.39] and for the placebo group, Bang's BI = 0.08 [-0.40 – 0.56] signifying that guesses of allocation were not significantly different than those that would be obtained by chance and blinding was maintained during the study.

Of 4 individuals who correctly guessed they has been allocated nicardipine, 1 reported side-effects (dizziness, nausea, headaches, stomach cramps and fatigue), 1 observed decreases in blood pressure, and 1 reported that their mood seemed more stable and that they experienced side-effects (headaches and palpitations). Of 5 individuals randomised to placebo, who believed they were allocated to nicardipine SR, 3 individuals experienced side effects (swollen ankles, difficulty concentrating), 1 observed decreases in systolic blood pressure and 1 reported that their mood seemed more stable.

6.4 Discussion

OxCaMS is the first exploratory, experimental study to assess the effect of LTCC antagonism in individuals with mood instability. This chapter primarily focused on assessing whether 14-days administration of LTCC antagonist nicardipine SR had any effect on reducing mean affect or mood instability when compared with placebo. Nicardipine SR did not reduce overall mean negative and positive affect ratings on the PANAS-SF. Whilst reductions in both negative and positive mood instability were observed after the administration of nicardipine SR, the magnitude of these reductions were not significantly different to reductions observed in the placebo group. The analyses therefore did not demonstrate benefits of LTCCs in reducing mood instability.

Complicating the interpretation, participant numbers were lower than originally planned and individuals randomised to the nicardipine SR group demonstrated higher levels of mean negative affect and negative mood instability than the placebo group during the pre-randomisation phase of the study. This is thought to reflect baseline differences in negative affect, also reflected on the ALS-SF anxiety/depression subscale, in which the nicardipine SR group scored more highly than the placebo group. Such imbalances at baseline are due to chance in the randomisation procedure and are an unfortunate outcome. Indeed, it is more likely that differences between groups exist at baseline when the number of participants being randomised is relatively small (Herbert, 2005), such as in this study. In future, randomisation algorithms could be used that also take into account baseline mood scores. In any case, as appropriate randomisation procedures were adhered to, and blinding was shown to be maintained, previous literature has suggested that no adjustments need be applied to the analyses (Senn, 2013; Twisk et al., 2018; Van Breukelen & Van Dijk, 2007).

Nevertheless, when adjustments were made for baseline differences in mood instability using an ANCOVA, this did not change the interpretation of the null finding. ANCOVA is an accepted statistical approach for RCT data. The choice of covariate is not without its own issues, though here the pre-randomisation measure was used as is often used in the literature. It is acknowledged that there are a number of other ways in which this data could be analysed, including linear mixed modelling (LMM). However, ANCOVA methods have been demonstrated to be most effective in analysing pre-post data (Connell et al., 2017). More recent methods have suggested correcting for 'regression to the mean' (Verhulst et al., 2013) and could be used to further explore this data.

Instability in negative and positive affect was seen to be lower post-randomisation than pre-randomisation in both nicardipine SR and placebo groups. These reductions in mood instability

can therefore not be attributed to the pharmacological intervention. Participants were not taking any other psychotropic medications which might otherwise explain this. Similar observations were made from mood data in the COMET study in which positive mood instability only was found to decrease over the 10 weeks. As previously suggested in Chapter 2, it could be that regular self-monitoring draws attention to and allows individuals to be more aware of their mood states, which they are subsequently better able to self-regulate (increased emotional self-awareness) (Bakker & Rickard, 2018). Alternatively, subjective judgements of mood may change over time or participants may fall into learned/habitual ratings on the scales. This is a potential limitation in relying on participant self-assessments, which were not clinically validated. Mood scales could be developed that assess varied items at each response time to avoid possible habitual responses. Nevertheless, the observed decline in mood instability across both groups reduces power to detect a treatment effect. The number of participants would have to be increased if planning further studies in which mood instability were used as the primary outcome.

Only one other double-blind, placebo-controlled study has assessed LTCC antagonist nimodipine as a treatment for 'affective dysregulation' in BD (Pazzaglia et al., 1993). Nimodipine was reported to decrease the amplitude of self-reported mood fluctuations, although these results were only based on eight patients who completed the study. Another study has proposed to assess the efficacy of lithium, of which the mechanism of action is thought to involve Ca^{2+} homeostasis, in reducing mood instability in individuals with BD (Saunders et al., 2016). However, the outcome data for this study are not yet available. It is clinically important for further studies to test the effect of possible interventions for mood instability as studies such as the STEP-BD trial have shown that, in BD patients experiencing a depressive episode and who are treated with different medications and intensities of psychotherapy, mood instability in both

depressive and manic symptoms predicts both a lower likelihood and longer time course of recovery from a depressive episode (Stange et al., 2016).

It is possible that the 2-week post randomisation period of OxCaMS was not long enough to observe effects of LTCC antagonism and increasing the period of treatment may demonstrate effect. For example, antidepressant medications can exhibit delayed therapeutic effects, 2-6 weeks after initiation, but can demonstrate almost immediate cognitive or neural effects (Harmer et al., 2009). Chapter 7 of this thesis goes on to investigate whether there were any neural effects of LTCC antagonism which might suggest a 'delayed' psychiatric signal. Alternatively, the dose of nicardipine SR used in this study (30 mg bd) may have been insufficient to produce an effect and further studies may benefit from using the standard full dose of 45 mg bd.

The original recruitment target for OxCaMS was not met. This is largely due to the time taken to recruit this specific participant population (just over 2 years) and time restrictions of the DPhil. Many individuals were screened to take part in the study, a small proportion of whom met all inclusion criteria according to the MDQ. The majority of those who were identified as experiencing high mood instability, were often found to already be taking medication to treat their symptoms, meaning they could not take part in the study. In addition, OxCaMS was an intensive study, requiring between 3-5 visits and longitudinal monitoring of mood, cognition and activity over a 4-week period. Indeed, two recruited participants withdrew post-randomisation due to not being able to comply with all of these procedures. The reality is that this it is hard to recruit this population, and future studies should allow longer for recruitment of a large sample. Despite these challenges, this study has resulted in a rich and detailed dataset with which to explore LTCC antagonism on a range of outcomes.

Unlike previous studies of mood disorder which have usually used LTCC antagonists with poor BBB permeability and/or low specificity, the current study used a newer and LTCC-selective antagonist, from the dihydropyridine class, that is known to permeate the BBB (Uchida et al., 1997). Only one other open-label pilot study has shown potential efficacy of a dihydropyridine LTCC, Isradipine, in improving depressive symptoms in a very small number of BD patients (Ostacher et al., 2013). Despite this, there are still limitations to using LTCC antagonists more generally in their current form. Due to the abundance of LTCCs in the cardiovascular system compared to the brain, they have a high risk of side effects, though few were reported in the current study. If further studies show evidence of their therapeutic potential, it will provide the impetus to develop more selective LTCC antagonists that target isoforms more highly expressed in the brain than the periphery (Clark et al., 2020; Zamponi et al., 2015).

6.5 Conclusion

This is the first experimental medicine study of LTCC antagonism for a psychiatric indication. In a randomised, double-blind study, LTCC antagonism was not found to affect negative or positive mood instability over a two-week intervention period. Although no benefit for LTCC antagonism is immediately evident from the findings of this data, behavioural mood changes may be delayed and it is important to assess potential neural signals of LTCC antagonism.

Chapter 7. Neural effects of calcium channel antagonism

7.1 Introduction

In addition to providing important insights into differences in resting-state oscillatory power, functional networks, and dynamics of brain activity between healthy individuals and those with psychiatric disorders, MEG has more recently been used as a valuable tool to observe medication-related changes in neural activity (Kähkönen, 2006; Martín-Buro, Garcés, & Maestú, 2016; Muthukumaraswamy, 2014). Such investigations are termed pharmaco-MEG studies (Hall et al., 2010; Muthukumaraswamy, 2014).

Pharmaco-MEG is a useful tool to non-invasively assess target engagement, investigate the mechanism of action of drugs, and to identify biomarkers that might underlie disease mechanisms and treatment efficacy (Muthukumaraswamy, 2014; Palmer, 2014). Table 7.1 provides an overview of resting-state pharmaco-MEG studies in both healthy participants and in patients (previous reviews have also highlighted task-based pharmaco-MEG studies, see Kähkönen, 2006; Muthukumaraswamy, 2014). Approaches to study design, outcome measures, and analyses have been summarised in order to provide an overview of the most commonly used methods. This has been useful in informing analysis methods for the present investigation of the effect of calcium-channel antagonism on resting-state MEG activity.

Only one MEG study to date has assessed the effect of calcium channel antagonism in the human brain, specifically a T-type calcium channel (TTCC) antagonist, 1-octonal (Walton et al., 2017). In a sample of 32 healthy participants, MEG was recorded at baseline and at 5 intervals (15, 30, 60, 90 and 120 minutes) after oral delivery of 1-octanol. In a subset of participants whose baseline power spectra was dominated by an alpha peak, 1-octonol-induced changes included increases in theta and low alpha power (4.5-8.5 Hz). In another subset of participants,

with strong low frequency activity at baseline, 1-octonol-induced changes included decreases in delta and theta power (2.5-6.5 Hz), which the authors interpreted as consistent with the role of voltage-gated T-type calcium channels in generating low frequency oscillations. However, no placebo control was included to ensure changes in low frequency power were not a result of regression toward the mean (Walton et al., 2017).

Few studies have experimentally assessed the effect of LTCC antagonists in the human brain. Potential changes in MEG signal associated with LTCC antagonism are therefore of interest, given investigations into its therapeutic potential in mood disorders. Of the two LTCC proteins expressed in the brain, $Ca_v1.2$ is predominantly expressed in the forebrain, and accounts for 90% of brain LTCCs, while $Ca_v1.3$ is predominantly expressed in the midbrain (Hell et al., 1993; Kabir et al., 2016). The role of LTCCs in brain function has been widely reviewed (Berger & Bartsch, 2014; Bhat et al., 2012; Kabir et al., 2016; Kabir, Martínez-Rivera, & Rajadhyaksha, 2017; Striessnig et al., 2014; Zamponi et al., 2015). Not only do LTCCs shape neuronal firing at the postsynaptic membrane (Striessnig, Ortner, & Pinggera, 2015), they regulate Ca^{2+} signalling pathways involved in excitation-transcription coupling, such as phosphorylation of cAMP response element-binding protein (CREB), with such properties providing support for synaptic plasticity, learning, and memory in normal brain development (Kabir et al., 2017; Striessnig et al., 2014; Zamponi et al., 2015). In addition, LTCCS have been implicated in modulating dopaminergic and glutamatergic signalling pathways (Berger & Bartsch, 2014; Kabir et al., 2017) further demonstrating their possible significance in psychiatric phenotypes.

The ways in which LTCCs contribute to neural circuits, brain networks, and behaviours has been explored in rodent and human studies. In rodents with genetic modifications causing loss of function to LTCC isoforms, disruptions are observed in synaptic plasticity, cognitive processing such as spatial memory (e.g Moosmang, 2005), and mood such as increases in depressive and

anxious behaviours. Similar findings have been observed with administration of LTCC antagonists to non-genetically modified rodents (Degoulet et al., 2016). In humans, therapeutic doses of LTCC antagonist nimodipine have been shown to disrupt metaplasticity (Wankerl et al., 2010). Using fMRI, differences in brain activity have been shown between carriers of the *CACNA1C* risk allele and to non-carriers. Notably, differences have been shown in the PFC, striatum, ACC, and hippocampus during executive function, memory, and emotion processing tasks (Bhat et al., 2012; Bigos et al., 2010; Ou et al., 2015). In more recent evidence, using neurons derived from human induced pluripotent stem cells, LTCC antagonists were found to produce a dose-dependent effect on synchronous firing patterns of small-scale neuronal networks (Plumbly et al., 2019). Although the above findings implicate LTCCs in a range of neural functions relevant to normal brain function and psychiatric phenotypes (Harrison, Tunbridge, et al., 2019), the effects of LTCC antagonism in humans are not well documented or understood.

In a sub-sample of individuals with high mood instability recruited to the OxCaMS study, the present chapter explores the effect of the LTCC antagonist, nicardipine SR, on resting-state neural activity measured using MEG. MEG signals are of particular interest because they are primarily generated by temporally coordinated postsynaptic currents of cortical pyramidal neurons. Further, LTCC $Ca_v1.2$, the most sensitive to inhibition with dihydropyridine antagonists, is primarily located on the dendrites and soma of postsynaptic neurons (Bhat et al., 2012; Hell et al., 1993). If LTCC antagonism with nicardipine SR leads to a change in MEG signal, this might indicate functional occupancy of LTCCs and provide a marker of target engagement (Atkinson et al., 2019).

The aim of the present chapter was to examine changes in MEG spectral power in both sensor- and source-space, pre-and post-randomisation for nicardipine SR and placebo groups. Further,

alpha peak frequency was compared between participants. Such methods have been applied in previous pharmaco-MEG studies (Table 7.1). Additionally, the dynamics of resting-state oscillatory brain activity were characterised using a TDE-HMM for both pre- and post-randomisation MEG scans. Indication of target engagement in the brain would be demonstrated by post-randomisation changes in spectral power or in state dynamics in individuals receiving nicardipine SR, compared to those receiving placebo. Confirmation of target engagement would also open doors to investigate the biology of LTCCs, for example by identifying what brain areas and spectral signatures are affected. These analyses were exploratory, and no hypotheses were made as to the nature or direction of possible nicardipine-induced changes in MEG signal.

Table 7.1. Characteristics of resting-state pharmaco-MEG studies

Study	Participants	Age (yrs) Mean/Range	Medication	Randomised? Double blind?	MEG scanner	Design	Outcome measures/analysis	Findings
Healthy participants								
Osipova et al., 2003	Healthy participants *n=8*, 2 males; 6 females	59-80	Scopolamine hydrobromide (0.3 mg) or glycopyrrolate placebo (0.2 mg)	Randomised, double-blind cross-over study (7-day wash-out)	122-channel whole-head Neuromag scanner	• Eyes-open, 3 minutes • Eyes closed, 3 minutes • One scan each visit. MEG recorded 1 hour after administration of scopolamine hydrobromide or glycopyrrolate	• Sensor-level frequency analysis (Fast Fourier Transform (FFT)) • Spectral power and coherence were computed over 7 brain regions in 3 frequency bands (theta, alpha and beta)	Scopolamine significantly increased theta power in eyes open and eyes closed conditions and also reduced interhemispheric and left intrahemispheric coherence in the theta band (4-8 Hz). In addition, scopolamine led to a significantly reduced eyes closed/open ratio in all 3 frequency bands but most prominently in the alpha band.
Fingelkurts et al., 2004	Healthy participants *n=8*, 4 males; 4 females	20-29	Lorazepam (30 μg/kg) or placebo	Randomised, double-blind cross-over study (7-day wash-out)	306-channel Vectorview Neuromag scanner	• Eyes-open, 5 minutes • Eyes closed, 5 minutes • Conditions counterbalanced • One scan each visit. MEG recorded 5 minutes after lorazepam infusion	• Sensor-level frequency analysis (Hanning taper) • Dynamics of temporal characteristics of spectral patterns evaluated by computing the average number of successive MEG epochs of the same spectral pattern	Lorazepam significantly increased percentage of epochs in delta and theta activity (2.5-4 Hz) and beta activity, but reduced percentage of epochs characterised by fast-theta alpha activity (5.5-11.5 Hz).
Jensen et al., 2005	Healthy participants *n=8, 3* males; 5 females	26-35	Diazepam (80 μg/kg)	Not randomised	306-channel Vectorview Neuromag scanner	• Eyes-closed, 3 minutes • Two scans in one visit. Baseline MEG recording followed by repeated MEG recording 60 minutes after administration of Diazepam	• Sensor-level frequency analysis (Hanning taper) • Source-level estimation of beta peak frequency	Diazepam significantly increased beta power which was associated with decreased beta frequency. Source-level estimation showed primary sensorimotor cortex most sensitive to effects of benzodiazepines.
Hall et al., 2010	Healthy participants *n=8*, male	37	Diazepam (5 mg)	Not randomised	275-channel CTF scanner	• Eyes-open, 60-minutes • One scan with drug administration at start of recording, with peak levels after 10-15 minutes • First 5-minute period considered baseline, followed by 5 drug-active rest periods	• Source-level spectral power changes across drug active-rest periods using ROIs determined by Synthetic Aperture Magnetometry (SAM) Analysis	Significant decreases in frontal theta power and increases in alpha, beta and gamma power across frontal, temporal, precentral, postcentral, and occipital areas observed 20-40-minutes after diazepam administration.
Muthukumaraswamy et al., 2013	Healthy participants *n*=15, male	34.5	Psilocybin (2 mg) or placebo	Single-blind	275-channel CTF scanner	• Eyes-open, 5-minutes • Two scans in one visit. Baseline MEG recording	• Source-level analysis of power spectra using SAM Analysis	Decreased oscillatory power after psilocybin infusion across

(Data also included in secondary analyses in Barnett et al., 2020; Pallavicini et al., 2019; Schartner et al., 2017)						during placebo-infusion followed by a repeated MEG recording immediately after infusion of psilocybin or placebo	• Changes in resting-state networks identified through independent component analysis.	posterior areas from 1-50 Hz and in prefrontal cortices from 8-100 Hz. Of 11 identified functional brain networks, 7 showed significant reductions in oscillatory power after administration of psilocybin.
Muthukumaraswamy et al., 2015 (Data also included in secondary analyses in Barnett et al., 2020; Pallavicini et al., 2019; Schartner et al., 2017)	Exp 1 Healthy participants *n*=19, male	Exp 1 - 25.8	Ketamine (0.375 mg/kg/h) or placebo	Not randomised	275-channel CTF scanner	• Eyes-open, 15-minutes • Two scans on separate visits, one using a placebo saline infusion and one using a ketamine infusion. • Each visit, baseline MEG was recorded for 5 minutes, followed by a 10-minute MEG recording after infusion	• Sensor-level frequency analysis (Hanning taper) • Pre-infusion baseline spectra were subtracted from post-infusion spectra across frequency bands. • Source-level analysis of power spectra using SAM Analysis • Effective connectivity analysis using Dynamic Causal Modelling (DCM)	In both sensor- and source-space, ketamine associated with decreases in delta (1–4 Hz), posterior theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz) frequency bands and increases in anterior theta (4–8 Hz) and gamma (30–99 Hz). DCM showed decreases in frontoparietal effective connectivity with ketamine.
	Exp 2 Healthy participants *n*=6, male	Exp 2 - 27.2	Ketamine (0.375 mg/kg/h)	Not randomised		• Eyes-open, 80-minutes • One scan with baseline MEG recorded for 10 minutes followed by a 50-minute MEG recording after infusion	• Source-level analysis of power spectra using Synthetic Aperture Magnetometry Analysis • Effective connectivity analysis using DCM	Sustained and reduced alpha power was observed with ketamine as well as decreases in frontoparietal effective connectivity, similar to Exp 1.
Nutt et al., 2015 (Data also included in secondary analyses in Barnett et al., 2020)	Exp 1 Healthy participants *n*=12 male	Exp 1 - 27.7	Exp 1 - Zolpidem 10 mg, gaboxadol 15 mg or placebo	Randomised, single-blind cross-over study (7-day wash-out)	275-channel CTF scanner	• Exp 1 eyes open, 5-minutes • Three scans each visit. Baseline MEG recording and two further recordings obtained 60 and 160 minutes after oral administration of either placebo, zolpidem or gaboxadol	• Sensor-level frequency analysis (Hanning taper) • Baseline power spectra subtracted from each post-randomisation power spectra • Differences in frequency power between drugs and placebo examined at each post-randomisation time-point	After zolpidem administration, there were significant increases in delta power and reduced alpha power at both 60- and 160-min time-points. Increased beta and low gamma activity were seen at 60 min. After gaboxadol there were significant increases in low frequency power up to beta (1-30Hz).
	Exp 2 Healthy participants *n*=15, 14 males; 1 female	Exp 2 - 25.5	Exp 2 - Tiagabine 15 mg or placebo	Randomised, single-blind cross-over study (7-day wash-out)		• Exp 2 eyes closed, 5-minutes • Four scans each visit. Baseline MEG recording and three further recordings obtained 60 180 and 300 minutes after oral administration of either placebo or tiagabine	• As above	After tiagabine there were significant increases in low frequency power up to beta (1-30Hz) across all time-points. Additionally, decreases in gamma power (30-100 Hz) over parietal areas were seen at 180-min post-randomisation.

Carhart-Harris et al., 2016 (Data also included in secondary analyses in Shartner et al., 2017; Pallavicini et al., 2019 & Barnett et al., 2020)	Healthy participants *n*=14, 11 males; 3 females	32.1	LSD (75 µg) and placebo	Single-blind Within-participant design	275-channel CTF scanner	• Eyes closed, 14 minutes • Conditions counterbalanced • Two study visits during which participants received either LSD or placebo, separated by at least 14 days • Two MEG recordings (7 mins each) were made approximately 3.5 hours after LSD or placebo administered	• Sensor-level frequency analysis (Hanning taper) • Source modelling of spectral power • Between-condition differences in frequency-specific spectral power	LSD showed widespread decreases in spectral power from 1-30 Hz. Further, specific decreases in alpha power were associated with the experience of visual hallucinations.
Routley et al., 2017	Healthy participants *n*=20, male	22.9	Perampanel (6 mg) or placebo	Single-blind cross-over study (14-day wash-out)	275-channel CTF scanner	• Eyes open, 10-minutes • Two scans each visit. Baseline MEG recording and a further recording 120 minutes after oral administration of perampanel	• Sensor-level frequency analysis (Hanning taper) • Source-space functional connectivity analyses	Perampanel increased low frequency power (1-30 Hz) in posterior sensors but decreased high gamma power (50-90 Hz) over central parietal sensors. Functional connectivity analyses showed increases mainly over parietal regions in alpha and beta band.
Major Depressive Disorder								
Nugent et al., 2016	Patients with MDD *n*=13, 11 males; 2 females Healthy participants *n*=18, 12 males; 6 females	MDD = 45 Healthy participants = 39	Ketamine (0.5mg/kg) (MDD group only)	Not randomised Open label	275-channel CTF scanner	• Eyes closed, 4 minutes • Two scans in one visit. Baseline MEG recording followed by repeated MEG recording approx. 6-7 hours post-ketamine infusion.	• Source-level analysis using SAM Analysis in beta band (14-30Hz) • ICA with a priori regions of interest including the left and right amygdala and the subgenual anterior cingulate cortex (sgACC). • Percent change in connectivity pre- post-ketamine was correlated with percent change in depression ratings for significant ROIs	Ketamine significantly reduced increased connectivity between the left insulo-temporal IC and right amygdala in MDD participants found at baseline, to a level comparable with healthy controls. Further, post-ketamine, MDD participants demonstrated significantly lower connectivity between the bilateral precentral gyrus IC and the sgACC than healthy participants.
Park et al., 2018	Patients with MDD *n*=23, 11 males; 12 females	36.8	Scopolamine 4 µg/kg or placebo	Randomised, single-blind cross-over study (14-day wash-out)	275-channel CTF scanner	• Eyes-closed, 250 seconds • Three sessions in total; baseline, placebo and scopolamine • Two scans each session. First MEG recording obtained 60-120 minutes after administration of	• Source-level analysis of power spectra using SAM Analysis • Comparison of gamma power (30-50 Hz) change	No significant change in gamma power following administration of scopolamine versus placebo.

						scopolamine or placebo and a further recording obtained 30-60 minutes later		
Nugent et al., 2019	Patients with MDD *n*=35, 14 males; 21 females Healthy participants *n*=26, 10 males; 16 females	MDD = 35.5 Healthy participants = 33.9	Ketamine (0.5mg/kg) or placebo	Randomised, double-blind cross-over study	275-channel CTF scanner	• Eyes-closed, 250 seconds • Three sessions in total; baseline, day of infusion and 11-13 days post-infusion • Two scans each session. First MEG recording obtained 6-9 hours post-infusion and a further recording obtained 30-60 minutes later	• Source-level analysis using SAM Analysis • Comparison of gamma power (30-50 Hz) change between groups and sessions • Exploratory analysis of gamma power and antidepressant response	Six-nine hours after ketamine infusion, regions involving the central executive network (CEN), the salience network (SN) and the DMN showed increases in gamma power compared to placebo in healthy control and MDD participants. MDD participants with lower baseline gamma power who showed greatest increases in gamma power post-ketamine infusion, demonstrated better antidepressant response.
ADHD								
Wienbruch et al., 2005	ADHD children *n*=35, 29 males; 6 females	11.7	Methylphenidate (0.1–0.5 mg/kg)	Not randomised Single-blind	148-channel magnetometer MAGNES scanner	• Eyes open, 5-minutes • Two scans in one visit. MEG recording 1.5 hours after administration of placebo, followed by repeated MEG recording 1.5 hours after administration of methylphenidate	• Sensor-level frequency analysis (Fast Fourier Transform (FFT)) • Average power values after placebo were subtracted from power values after methylphenidate across frequency and region	Methylphenidate resulted in higher global power (1.5 – 25 Hz) in frontal channels and higher relative theta power but lower relative alpha power. A positive correlation was found between increases in theta power and improved behavioural measures of attention after methylphenidate.
Wilson et al., 2013	Patients with ADHD *n*=12, 8 males; 4 females Healthy participants *n*=12, 4 males; 8 females	ADHD = 40.6 Healthy participants = 40.1	Dextroamphetamine	Not randomised	306-channel Vectorview Neuromag scanner	• Eyes closed, 6-minutes • Two scans in one visit. Baseline MEG recording followed by repeated MEG recording for ADHD participants, 75 minutes after administration of their normal dose of dextroamphetamine	• Source-level frequency analysis (Fast Fourier Transform (FFT)) • Cross-frequency coupling (CFC) analyses • Focus on regions of the DMN	Before administration of dextroamphetamine, unmedicated ADHD adults showed reduced activity in the medial prefrontal cortex (MPFC) across all frequencies, aberrant activation within the default mode network (DMN) and abnormal CFC between the MPFC and posterior cortices in the gamma range compared to healthy controls. Increases in alpha activity in the MPFC and gamma CFC correlations were observed with dextroamphetamine

								administration in ADHD patients.
Parkinson's disease								
Stoffers et al., 2007 (Data also included in secondary analyses in Stoffers et al., 2008)	Patients with Parkinson's *n*=70 Levodopa treated patients *n*=37, 19 males; 18 females *de novo* patients n=18, 6 males; 12 females Healthy participants *n*=21, 10 males; 11 females	Patients with Parkinson's = 62.1 Levodopa treated patients = 63.5 *de novo* patients = 59.4 Healthy participants = 59.4	Levodopa (mean total dose in levodopa treated patients = 729 mg)	No	151-channel whole-head CTF scanner	• Eyes closed, 3 3.1 second epochs • Two scans in one visit. MEG recording before patients' first morning dose of levodopa ('OFF' state), followed by repeated MEG recording 1 hour after patients' normal dose of levodopa ('ON' state)	• Sensor-level frequency analysis (Fast Fourier Transform (FFT)) • Mean relative spectral power calculated in ROIs (frontal, central, temporal, parietal and occipital)	Analyses of clinical features showed that patients with *de novo* Parkinson's disease had greater theta and low alpha power than controls, but decreased beta power. Analyses of the effect of levodopa showed slight modulations of relative spectral power. Specifically, in the 'ON' state, levodopa increased right parietal gamma power and decreased right frontal theta, left occipital beta and left temporal gamma.

*Exp = Experiment, ROI = region of interest, SAM = Synthetic aperture magnetometry, FFT= Fast Fourier Transform, DCM= Dynamic causal modelling, CFC=Cross frequency coupling, DMN= Default model network, MPFC= Medial prefrontal cortex.

7.2 Methods

7.2.1 Experimental Design

The current MEG dataset was acquired as part of the OxCaMS study. Participants underwent two resting-state scans; one during the baseline pre-randomisation phase (day 14), and one at least 7 days after being randomised to nicardipine SR or placebo (day 21-28) (for study timeline see Chapter 6, section 6.2.2, Figure 6.1). This design allows both within- and between-participant comparisons of neural measures. T1-weighted structural MRI scans were collected at the same time points (after MEG scans to avoid magnetization effects) and were used in conjunction with MEG data during pre-processing (section 7.2.4).

7.2.2 Participants

Of 28 participants who were recruited to the OxCaMS study, 22 underwent MEG scanning protocols pre- and post-randomisation (six did not undergo scanning due to technical failures of the MEG scanner). Due to contraindications, only 20 out of 22 participants also underwent structural MRI scanning, necessary to enable source localisation of MEG data during analyses. Of these, 10 were randomised to nicardipine SR and 10 to placebo (see Table 7.2).

Table 7.2. Demographics of OxCaMS MEG sample	**Nicardipine SR (n=10)**	**Placebo (n=10)**
Age (mean; SD)	23 (4)*	29 (6)*
Female (*n*; %)	6 (60%)	5 (50%)
MDQ score (mean; SD)	10 (2)	10 (1)
Affect Intensity Measure (AIM) (mean; SD)	161.4 (18.56)	147.30 (23.22)
Affect Lability Scale (ALS) (mean; SD)	54 (8.94)	44.2 (12.7)

* denotes significant differences between groups in independent samples t-tests at $p<.05$.

7.2.3 Data acquisition

MEG data were acquired at OHBA using an identical scan protocol to that described in Chapter 5 section 5.2.3. For each MEG recording, participants were seated in the scanner and instructed to keep their eyes open and fixated on a white circle (7cm diameter) presented on a grey projector screen located 1 meter away, whilst blinking normally. MEG was recorded for 10 minutes. Eye-tracking data were also recorded to ensure participants remained awake for the duration of the scan (data not included in this thesis).

On the same day, or as close as possible after the MEG scan, T1-weighted structural whole-brain MR images, including ears and nose, were acquired for co-registration of MEG data during pre-processing (see section 7.2.4). The structural scan specification was as follows: TR = 1900 ms, TE = 3.96 ms, flip angle = 8o, FoV = 256mm, voxel dimension = 1mm isotropic, acquisition time = 7 mins 21s. Scans were acquired on a Siemens Prisma 3T scanner at OHBA.

7.2.4 Data pre-processing

MEG data were pre-processed in Matlab R2017a using freely available tools. Pre-processing was performed using OSL. Data pre-processing followed almost identical procedures to those detailed in Chapter 5 section 5.2.4. The only difference in pre-processing steps between the COMET and OxCaMS datasets were during the application of MaxFilter version 2.2 (Elekta Neuromag), whereby interference from external and internal noise sources in OxCaMS were separated from the MEG signal using a temporally extended signal space separation (tSSS) algorithm (Taulu & Simola, 2006). A benefit of using tSSS is in the removal of strong participant artefacts, for example from dental material (Hillebrand et al., 2013), which were present in some OxCaMS participants. All processing steps were subsequently applied to maxfiltered data including co-registration, down sampling, filtering, bad-segment and artefact detection, ICA, sensor normalisation, beamforming for source localisation, parcellation, and correction for spatial leakage.

7.2.5 Data analysis

7.2.5.1 *Sensor-space frequency analysis*

Frequency analysis was conducted by applying Welch's method (Welch, 1967) to pre-processed resting-state MEG data recorded from 204 planar gradiometers (method previously described in Chapter 5, section 5.2.5.1). Consistent with other pharmaco-MEG studies, the resulting power spectra were averaged across frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13Hz), beta (13-30 Hz). The pre-randomisation spectra were subtracted from the post-randomisation spectra. These measures were entered into an OLS GLM (as described in Chapter 5, section 5.2.5.1) with a parametric regressor for age and three categorical regressors including pre-post change in the nicardipine SR group, pre-post change in the placebo group, and gender (male or female). Both gender and age were z-transformed. A differential contrast was computed between nicardipine SR and placebo groups (nicardipine SR<placebo) to obtain a measure of nicardipine SR-induced power changes. To account for variance in the differential contrast, group-level statistics were performed on the t-statistic rather than the COPE values. Statistical significance was determined using non-parametric permutations (as described in Chapter 5, section 5.2.5.1). Significant effects both before and after controlling for multiple comparisons are reported.

7.2.5.2 *Associations between change in frequency power and change in mood instability*

Associations between change in frequency power and change in mood instability (negative and positive) were explored in all participants. Spearman's correlations were used due to changes in theta and alpha power being non-normally distributed according to tests of normality.

7.2.5.3 *Sensor-space alpha peak frequency analysis*

For each participant, pre- and post-randomisation, the peak of the dominant alpha frequency across all sensors was identified. Differences in alpha peak frequency between groups and time-point were normally distributed and compared using a repeated-measures ANOVA.

7.2.5.4 *Source-space frequency analysis*

Sensor-space frequency analyses were repeated with source-localised MEG data following the same methods outlined in section 7.2.5.1.

7.2.5.5 *Intraclass correlations between pre- and post-randomisation spectral measures*

The test-re-test reliability of sensor-space spectral measures pre- and post-randomisation, in both groups was assessed using intraclass correlations (ICC) (McGraw & Wong, 1996). ICCs and 95% confidence intervals were calculated in Matlab R2017a using the ICC function (Salarian, 2020), with a two-way mixed-effects model, with absolute agreement and single measurement (Koo & Li, 2016; McGraw & Wong, 1996). Resulting ICC values could range from 0 - 1, with 0 indicating no reliability and 1 perfect reliability (Koo & Li, 2016).

7.2.5.6 *TDE-HMM analyses*

A TDE-HMM with 8 states was applied to pre-processed pre- and post-randomisation scans from nicardipine SR and placebo groups in order to obtain states common to all participants. Model implementation followed the exact procedure previously outlined in Chapter 5, sections 5.2.5.4 – 5.2.5.7. For temporal characteristics estimated by the model, change scores were computed for each participant (post minus pre), and for each state (in the case of FO, LT and IT). Independent sample t-tests were used to test for differences in pre-/post-randomisation change in FO, LTs, ITs and SR between nicardipine SR and placebo groups. Analyses were undertaken in Matlab R2017a.

7.3 Results

7.3.1 Mood data

Analyses of change scores in pre- vs. post-randomisation mood instability from the subsample of OxCaMS participants who completed MEG scanning (n=20) showed a similar pattern to that observed when the full cohort had been analysed (n=28) (see Appendix 3).

7.3.2 Sensor-space time-frequency analysis

The mean topographies for each frequency are shown in Figure 7.1. Figure 7.2 shows mean power spectra over all sensors for nicardipine SR and placebo groups, pre-and post-randomisation. All participants showed declines in spectral power with increasing frequency, with the exception of alpha peaks at approximately 8-10 Hz.

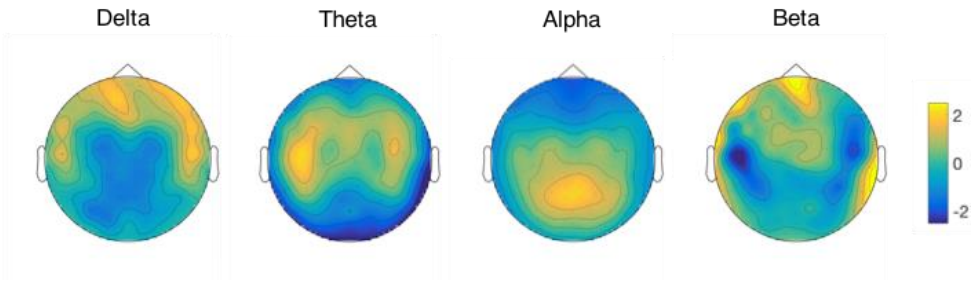


Figure 7.1. Topographical plots represent mean power spectral density (PSD) across all participants, modulated by frequency. Units shown are z-scored PSD. For visualisation, planar gradiometers were combined to obtain a single value under each sensor.

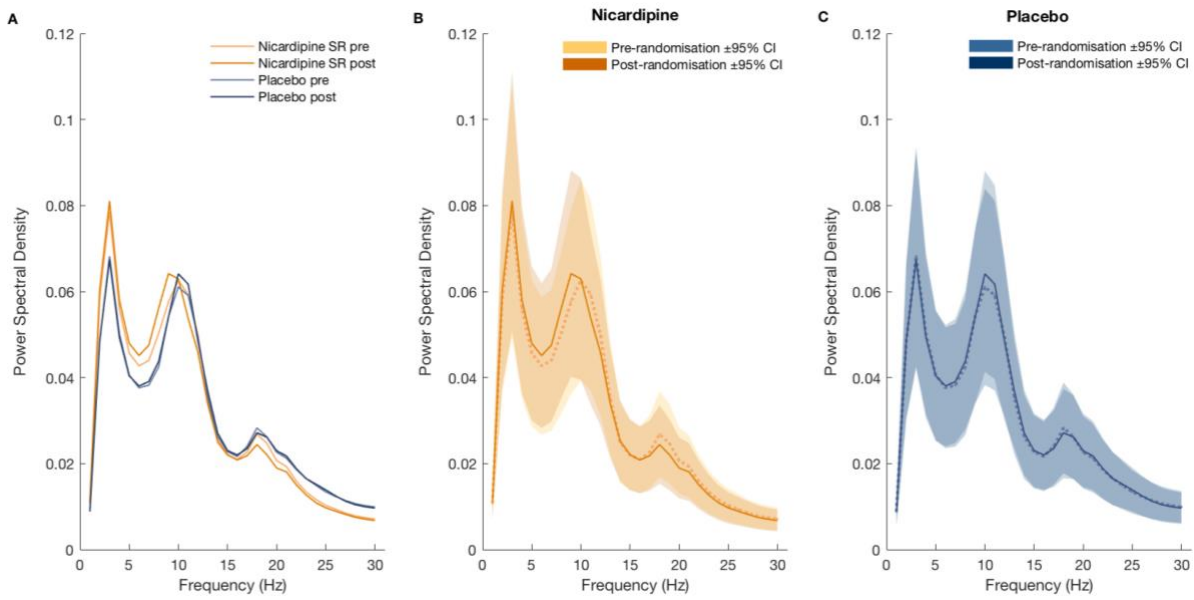


Figure 7.2. A. Mean power spectra averaged over all sensors for nicardipine SR and placebo groups, pre-and post-randomisation. **B.** Mean power spectra shown separately for the nicardipine SR group and **C.** placebo group, pre- and post-randomisation with 95% confidence intervals (CI).

Changes in spectral power between nicardipine SR and placebo groups (shown in Figure 7.3), were examined in sensor-space. Nicardipine SR-induced changes showed increases in delta and theta power across frontal and parietal sensors. Compared to the placebo group, the nicardipine SR group also showed decreases in alpha power across frontal and parietal sensors and decreases in beta power in frontal and temporal sensors. However, these changes in power did not survive correction for multiple comparisons over sensors (Figure 7.4).

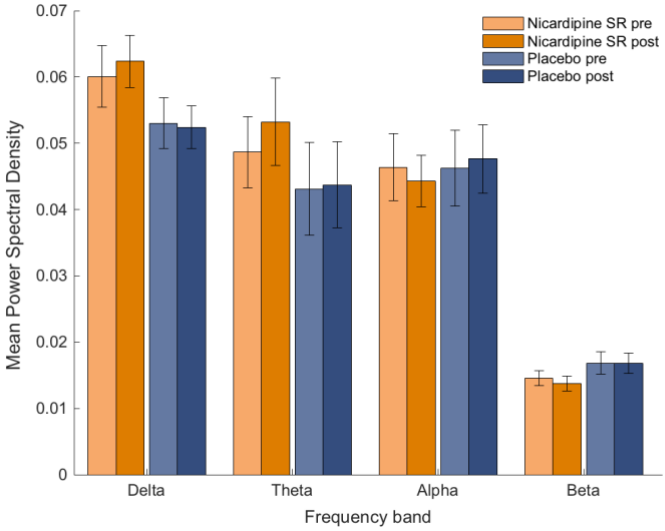


Figure 7.3. Mean power spectral density (PSD) within each frequency band, estimated from frequency analysis in sensor-space. Values shown for drug and placebo groups, pre- and post-randomisation within each frequency band. Error bars represent ±SE of mean.

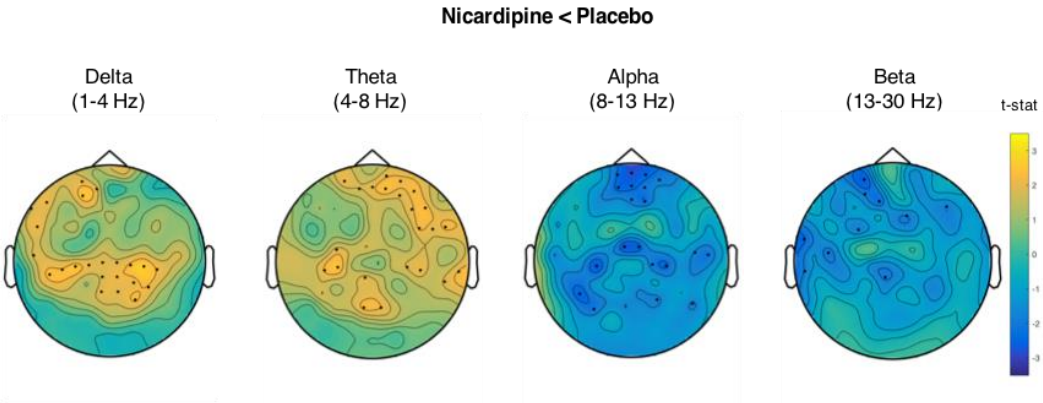


Figure 7.4. Statistical analysis of sensor-space MEG data. Contrast of nicardipine SR-induced changes compared to placebo across delta, theta, alpha and beta frequency bands, shown topographically. Yellow indicates increases in power, and blue indicates decreases in power. Marked sensors indicate those showing significant increases or decrease after permutation testing, but before correction for multiple comparisons across all sensors. Units displayed are t-statistics. For visualisation, planar gradiometers were combined to obtain a single value under each sensor.

7.3.3 Associations between change in frequency power and change in mood instability

No significant associations were observed between changes in PSD in each frequency and changes in negative or positive mood instability from pre-post randomisation in all participants (Table 7.3).

Table 7.3. Correlations between change in PSD and change in mood instability		Change in delta PSD	Change in theta PSD	Change in alpha PSD	Change in beta PSD
Change in negative mood instability (tRMSSD)	Spearman's rho	-.16	-.13	.20	.13
	p-value	.49	.58	.39	.58
Change in positive mood instability (tRMSSD)	Spearman's rho	-.10	-.24	.05	.42
	p-value	.67	.30	.83	.07

7.3.4 Alpha peak frequency

Observing spectral power in Figure 7.2 suggested potential shifts in alpha peak frequency in the nicardipine SR group post-randomisation. However, a repeated-measures ANOVA revealed no significant interaction between time and group ($F(1,18)=.51$, $p=.48$, $\eta p^2=.03$), and no main effect of group ($F(1,18)=.40$, $p=.54$, $\eta p^2=.02$), or time ($F(1,18)=2.06$, $p=.17$, $\eta p^2=.10$).

7.3.5 Source-space time-frequency analysis

The sensor-space power analysis was repeated for source-parcellated MEG data. The mean spectral power for each frequency across all participants is shown in Figure 7.5. Figure 7.6 shows mean power spectra over all parcels for nicardipine SR and placebo groups, pre-and post-randomisation. These demonstrated similar spectral patterns pre-and post-randomisation across groups, to those observed in sensor-space.

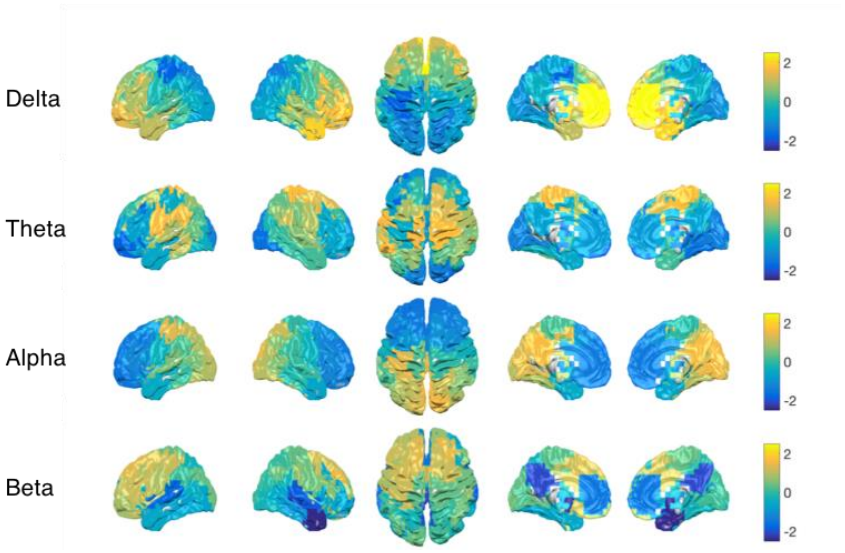


Figure 7.5. Source-space mean power spectral density (PSD) across all participants, modulated by frequency. Units shown are z-scored PSD.

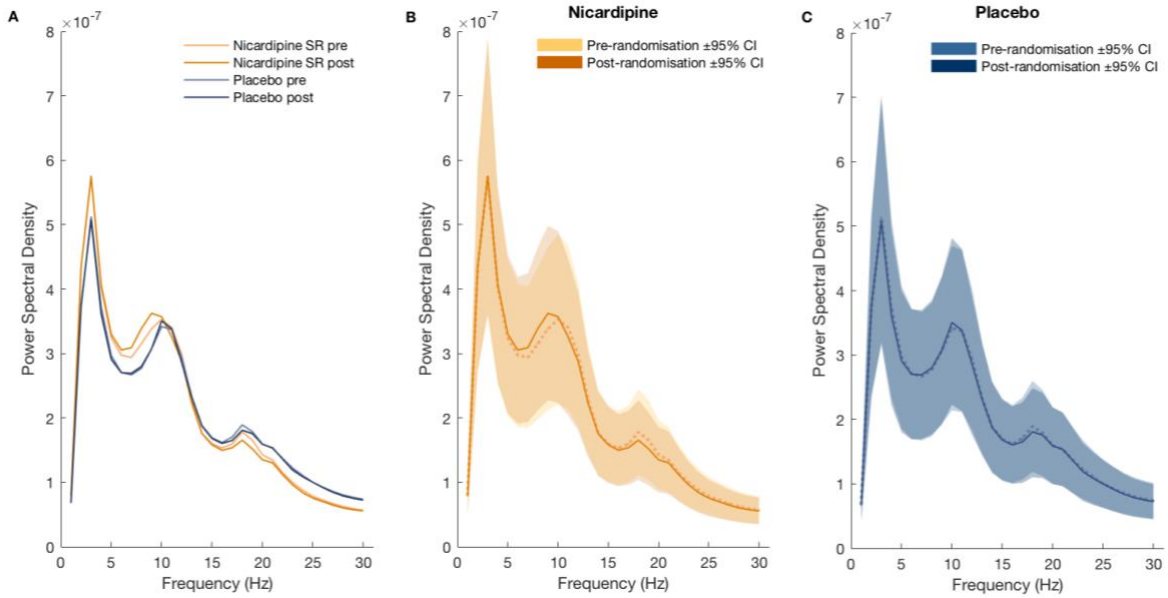


Figure 7.6. A. Mean power spectra averaged over all parcels for nicardipine SR and placebo groups, pre-and post-randomisation. **B.** Mean power spectra shown separately for the nicardipine SR group and **C.** placebo group, pre- and post-randomisation with 95% confidence intervals (CI).

Changes in source-localised spectral power were examined between nicardipine SR and placebo groups (shown in Figure 7.7). Nicardipine SR-induced changes demonstrated increases in delta

and theta power. In the delta band, increases in power were observed in five parcels; one in the temporal lobe, two in the parietal lobe including the angular gyrus, precuneus and cingular cortex and two located in the lateral occipital cortex. In the theta band, increases in power were observed in seven parcels; three parcels in regions of the frontal lobe including the insula, two parcels in the parietal lobe including the precuneus, and two in the occipital lobe. Further, alpha power was found to be increased in one parcel located in the frontal lobe including the insula, and beta power was found to be increased in one other parcel in the frontal lobe. None of these changes survived correction for multiple comparisons across parcels (Figure 7.8).

Compared to the placebo group, the nicardipine SR group also showed decreases in delta power in one parcel in the frontal lobe and decreases in beta power in two parcels; one in the temporal lobe and one in the parietal lobe including the precuneus. Again, none of these changes survived correction for multiple comparisons across parcels (Figure 7.8).

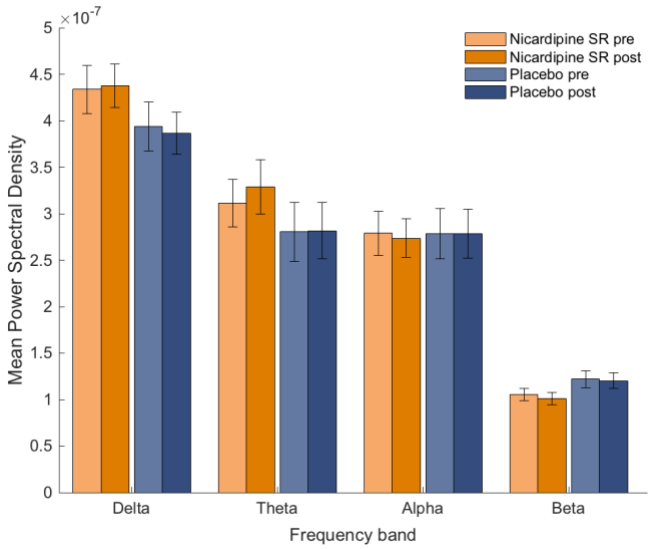


Figure 7.7. Mean power spectral density (PSD) estimated from frequency analysis in source-localised MEG data. Values shown for drug and placebo groups, pre- and post-randomisation within each frequency band. Error bars represent ±SE of mean.

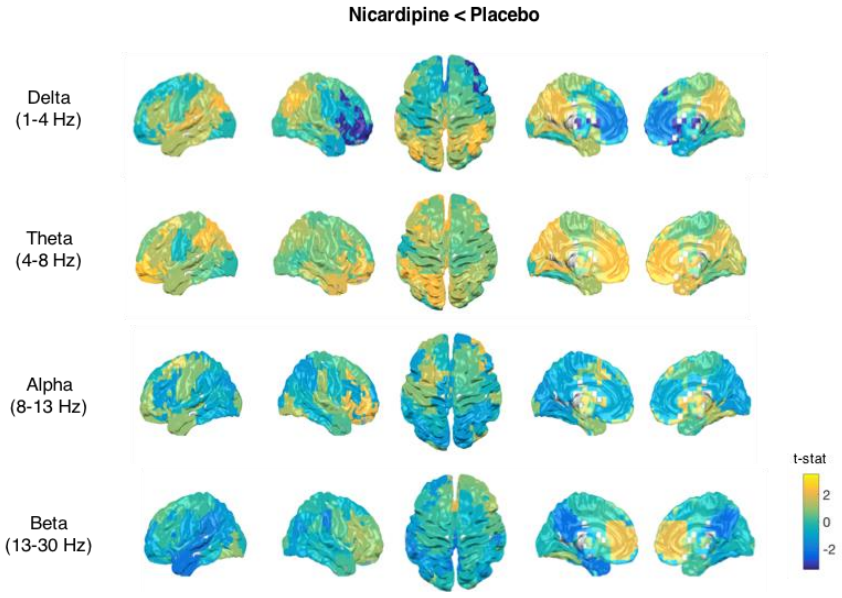


Figure 7.8. Statistical analysis of source-parcellated MEG data. Contrast of nicardipine SR-induced changes compared to placebo across delta, theta, alpha and beta frequency bands. Yellow indicates absolute increases in power, and blue indicates absolute decreases in power. No parcels were significant after correction for multiple comparisons across parcels. Units are t-statistics.

7.3.6 Intraclass correlations between pre- and post-randomisation spectral measures

Resting-state measures of mean PSD at each frequency, computed pre- and post-randomisation, demonstrated high test-retest reliability estimates in both participant groups (Table 7.4). Test-re-test-reliability was similar between sensor- and source-space, though slightly higher in source-space in most cases. The placebo group showed higher ICCs and narrower confidence intervals across theta, alpha and beta frequency bands, in both sensor- and source-space. This suggests less variability between scan visits. However, estimates of reliability in the delta band were higher in the nicardipine SR group than the placebo in sensor- and source-space.

Table 7.4. ICC between pre- and post-randomisation mean PSD	**Delta** ICC (CI)	**Theta** ICC (CI)	**Alpha** ICC (CI)	**Beta** ICC (CI)
Sensor-space				
Nicardipine SR	.91 (.69-.98)	.89 (.61-.97)	.90 (.66-.97)	.91 (.66-.98)
Placebo	.84 (.48-.96)	.97 (.90-.99)	.97 (.90-.99)	.97 (.87-.99)
Source-space				
Nicardipine SR	.94 (.79-.99)	.89 (.64-.97)	.96 (.86-.99)	.95 (.73-.99)
Placebo	.87 (.57-.97)	.95 (.81-.99)	.97 (.88-.99)	.96 (.85-.99)

ICC = intraclass correlation, CI = confidence intervals

7.3.7 TDE-HMM analyses

7.3.7.1 *State power and connectivity*

The TDE-HMM was inferred with 8 states to the raw time courses of resting-state MEG data of all participants, and scans. Figure 7.9 shows the mean broadband activation maps (PSD) and coherence networks of all 8 states observable after applying the state-wise multi-taper. Distinct networks can be observed including frontal, visual and sensorimotor networks.

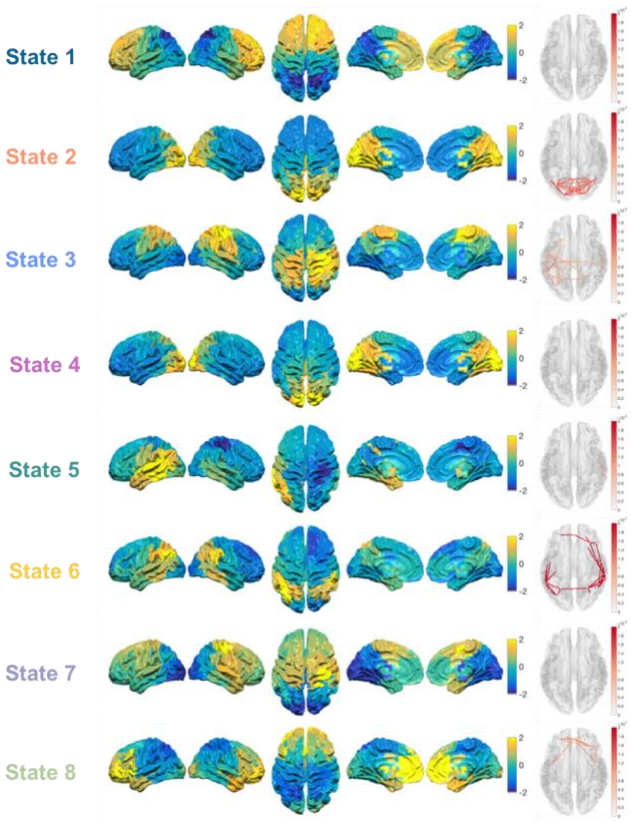


Figure 7.9. Mean broadband activation maps and coherence networks of each 8 states. These were computed from the state-wise multi-taper, applied after the TDE-HMM inference. Mean activation is z-scored across parcels. In the mean activation maps, yellow represents brain parcels in which the mean activation was found to be increased, and blue represents brain parcels in which the mean activation was found to be decreased, in a particular state.

Figure 7.10A shows the probabilistic state time course depicting the probability that each state was active at a certain time point in the data. The accompanying Viterbi path (Figure 7.10B) shows the most likely sequence of states. As shown in the example segment of data, one state did not dominate the time-course. Instead, the probability of a state occurring varied across time e.g. State 4 was more likely to be active in the first 700 ms, and then was less likely to be active in the following 300 ms. In addition, the probability of state-to-state transitions are shown in Figure 10C. The most probable transition at a certain time point (t) to the next (t+1) was from State 1 to State 7.

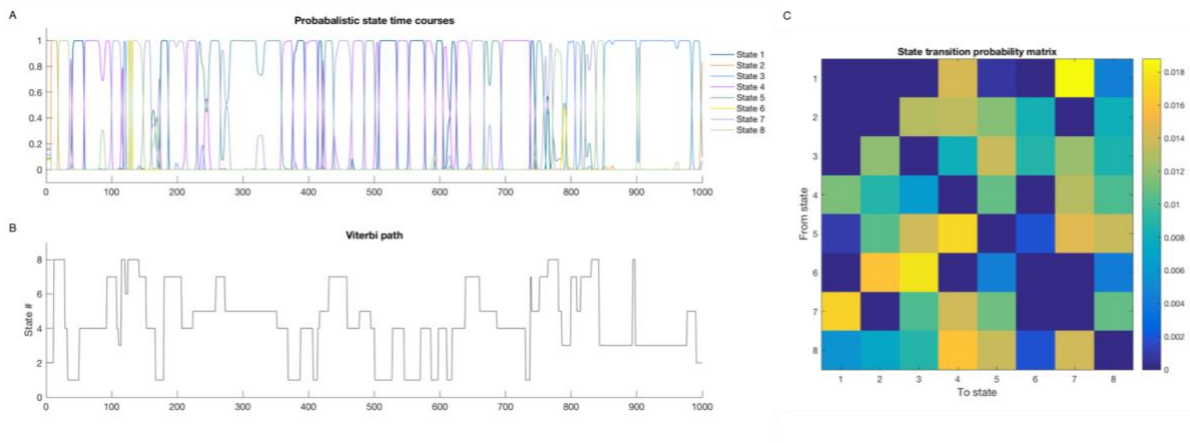


Figure 7.10. A. The probabilistic state time course of each 8 states shown for 1000 ms of OxCaMS MEG data. The probability of being in a state is shown by the y axis (0 being not probable and 1 being highly probable). Only one state is probable at a certain moment in time. **B.** The Viterbi path displaying the most likely sequence of states during the 1000 ms of MEG data shown. **C.** The state transition probability matrix depicting the probability of moving from a state (y axis) to another state (x axis).

7.3.7.2 *Temporal Characteristics*

Temporal characteristics of each of the 8 states estimated from the Gamma time course are shown in Figure 11 and Table 5. States 1-5 and 7-8 exhibited fractional occupancies of between 10-20%, however State 6 demonstrated a lower fractional occupancy of around 5%. Average state life times were approximately 50-100 ms and average interval times were approximately 300-900 ms, with the exception of State 6, which exhibited much longer interval times of approximately 1.7 seconds, in line with its reduced fractional occupancy (Figure 7.11A and 7.11C). This pattern of results is in keeping with previous implementations of the TDE-HMM. All participants visited each of the 8 states at some point during the resting-state scan.

Independent sample t-tests tested for differences in pre-/post-randomisation change in fractional occupancy, life times, and intervals times for each state between nicardipine SR and placebo groups. There was a group difference in the pre-post change of fractional occupancy in

State 2 (occipito-temporal state) ($t(1,18)=-2.08$, $p=.05$). The nicardipine SR group showed decreases in fractional occupancy after treatment (M=-.01, SE=.01) and the placebo group showed increases in fractional occupancy post-randomisation (M=+.01, SE=.01) (mean difference=.02, SE=.01). However, this difference was no longer significant after Bonferroni adjustment for multiple comparisons. No further significant differences were found between groups in pre-/post-randomisation change of any of the temporal characteristics (Table 7.5).

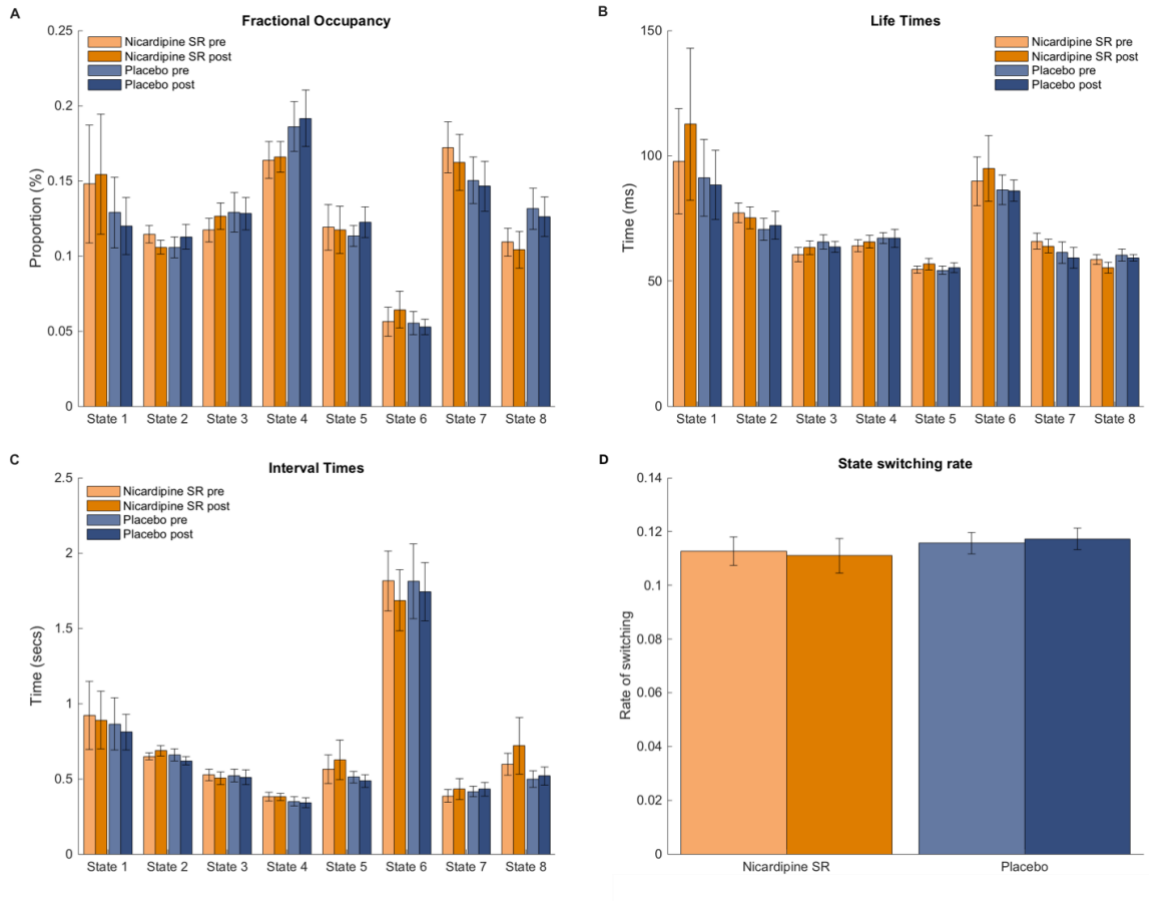


Figure 7.11. The global temporal statistics describing **A.** the fractional occupancy, **B.** life times, **C.** interval times and **D.** state switching rate, for nicardipine SR and placebo, pre-and post-randomisation. Error bars represent the ±SE of the mean.

Table 7.5. State temporal characteristics by group			FO (mean, SD)	LTs (mean, SD)	ITs (mean, SD)
State 1	**Pre**	**Nicardipine SR**	.15 (.12)	97.72 (66.40)	.92 (.72)
		Placebo	.13 (.07)	91.19 (48.27)	.86 (.55)
	Post	**Nicardipine SR**	.15 (.13)	112.59 (95.66)	.89 (.61)
		Placebo	.12 (.06)	88.40 (43.81)	.81 (.38)
State 2	**Pre**	**Nicardipine SR**	.11 (.02)	77.18 (12.30)	.65 (.07)
		Placebo	.11 (.02)	70.54 (13.83)	.66 (.13)
	Post	**Nicardipine SR**	.11 (.01)	75.19 (13.61)	.69 (.11)
		Placebo	.11 (.03)	72.26 (17.36)	.62 (.09)
State 3	**Pre**	**Nicardipine SR**	.12 (.02)	60.53 (8.85)	.53 (.12)
		Placebo	.13 (.04)	65.58 (9.26)	.52 (.13)
	Post	**Nicardipine SR**	.13 (.03)	63.34 (8.56)	.50 (.13)
		Placebo	.13 (.03)	63.57 (7.09)	.51 (.16)
State 4	**Pre**	**Nicardipine SR**	.16 (.04)	64.04 (7.77)	.38 (.09)
		Placebo	.19 (.05)	67.17 (7.03)	.35 (.10)
	Post	**Nicardipine SR**	.17 (.03)	65.66 (8.00)	.38 (.07)
		Placebo	.19 (.06)	67.05 (11.37)	.34 (.10)
State 5	**Pre**	**Nicardipine SR**	.12 (.05)	54.56 (4.27)	.56 (.30)
		Placebo	.11 (.02)	54.29 (5.06)	.51 (.12)
	Post	**Nicardipine SR**	.12 (.05)	56.80 (7.24)	.63 (.42)
		Placebo	.12 (.03)	55.26 (6.03)	.49 (.13)
State 6	**Pre**	**Nicardipine SR**	.06 (.03)	89.79 (30.76)	1.82 (.63)
		Placebo	.06 (.02)	86.35 (18.67)	1.81 (.78)
	Post	**Nicardipine SR**	.06 (.04)	94.94 (41.65)	1.68 (.64)
		Placebo	.05 (.02)	86.05 (13.32)	1.74 (.61)
State 7	**Pre**	**Nicardipine SR**	.17 (.05)	65.86 (10.11)	.37 (.13)
		Placebo	.15 (.05)	61.34 (13.46)	.42 (.11)
	Post	**Nicardipine SR**	.16 (.06)	63.90 (8.82)	.43 (.22)
		Placebo	.15 (.05)	59.23 (13.01)	.43 (.15)
State 8	**Pre**	**Nicardipine SR**	.11 (.03)	58.58 (5.91)	.60 (.23)
		Placebo	.13 (.04)	60.30 (7.77)	.50 (.17)
	Post	**Nicardipine SR**	.10 (.04)	55.31 (6.81)	.72 (.60)
		Placebo	.13 (.04)	59.32 (4.22)	.52 (.19)

7.3.7.3 *Spectral modes*

The frequency content of each state was examined by applying a NNMF, as described in Chapter 5, section 5.2.5.6, which decomposed the data into unimodal frequency bands. The resulting spectral modes broadly corresponded to delta/theta, alpha and beta frequency bands. The estimated power maps and phase coherence networks for each spectral mode are shown in Figure 7.12.

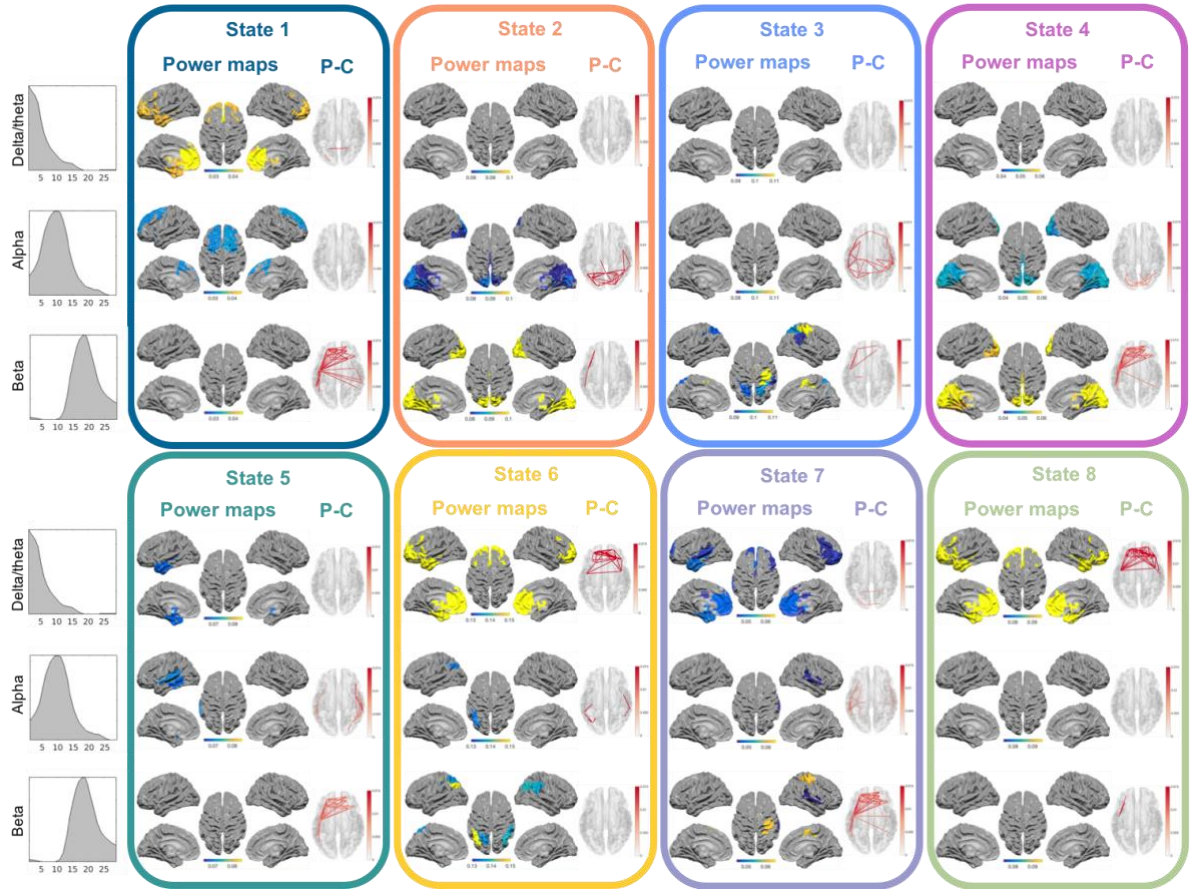


Figure 7.12. Spectrally resolved state power maps and coherence networks for all 8 states inferred by the TDE-HMM for combined UKMP and COMET data. The output of the NNMF, used to decompose the data in more data driven frequency bands, is shown on the left-hand side. The top, middle and bottom rows within each state description represent delta/theta, alpha, and beta power. Power maps show the top 15% of parcels. PC=phase-coupling.

7.4 Discussion

The OxCaMS experimental medicine study provides the first dataset in which MEG has been used to explore the effect of LTCC antagonism on human neuronal activity. A tendency toward increases of power at delta and theta frequencies in frontal, parietal and temporal regions and decreases in power at alpha and beta frequencies in frontal and temporal regions in the nicardipine SR group were observed in both sensor-level and source-localised analyses. However, there was no statistically significant evidence of nicardipine SR-induced power changes after correction for multiple comparisons. Change in power, in any frequency, was not correlated with behavioral change in negative or positive mood instability, from pre- to post-randomisation in sensor-space. Although visualisation of the data hinted at potential shifts in alpha peak frequency after nicardipine SR administration, no significant differences were observed between groups. Further, the effect of nicardipine SR was investigated on the characteristics of fast transient brain states estimated by the TDE-HMM. Again, nicardipine SR was not found to have any significant effects on state dynamics.

The relatively low number of participants combined with excessive corrections required for the exploratory analyses compromised statistical power in these analyses. However, given the novelty of the study, it is still worth looking at non-significant trends to direct future research. The general pattern of observations revealed through analyses of sensor- and source-space PSD showed that nicardipine SR increased PSD in delta/theta bands and decreased PSD in alpha/beta bands. It is possible this pattern is reflective of alterations in the state of excitability in the brain (Routley et al., 2017). However, as this is the first human neuroimaging study of the effect of LTCCs antagonists for a psychiatric indication, there are no directly comparable studies with which to compare these results. Despite this possibility, the lack of significant findings across multiple analyses suggest target engagement was not achieved. This is in line with suggestions that antihypertensive doses of dihydropyridine LTCC antagonists (similar to the one

used in this study) do not cause any long-term changes in neural function in healthy individuals using them for high blood pressure and angina indications (Striessnig et al., 2014; Zamponi et al., 2015). In addition, it is thought that doses over and above those of approved LTCC antagonists may be needed to observe effects on the brain (Zamponi et al., 2015; Cipriani et al., 2016).

Alternatively, it could be that resting-state MEG is not sensitive to target engagement in this case. Effects of LTCC antagonism might be observed measuring neural activity during ongoing cognitive processing rather than observing whole-brain spontaneous activity. Such tasks might include executive function, working memory or emotional processing where the effect of the *CACNA1C* risk allelle and the role of LTCCs have already been indicated (as briefly outlined in the introduction to Chapter 7). The OxCaMS MEG protocol was developed to include a precision working-memory task for this reason. Preliminary analysis of these data does not show any behavioural differences between groups in WM memory recall or precision. However, MEG data are yet to be analysed and ongoing work may provide insights into target engagement and the effect of LTCC antagonism on more specific neural processes.

This chapter explored a number of frequency domain and dynamic measures of resting-state activity as outlined in the study protocol (Atkinson et al., 2019) and in line with previous pharmaco-MEG studies (Table 7.1). The study required participants to undergo two MEG scans, pre- and post-randomisation allowing for a within- and between-participants design. An important consideration was therefore the test-re-test reliability of resting-state spectral measures in the same participants, as if they varied considerably between time-points, this would reduce power in observing any effect of nicardipine SR (Deuker et al., 2009). The current data confirm high estimates of ICCs across frequency bands in both nicardipine SR and placebo groups, though estimates were very slightly higher in the placebo group across theta, alpha and beta bands. In the placebo group only, ICCs in the delta band were not as high as other frequency

bands. These observations are in line with previous estimates of ICCs reported across eyes-open, resting-state MEG scans in both healthy controls (ICC>0.75) (Martín-Buro, Garcés & Maestú, 2015) and schizophrenia patients (mean ICC=0.87) (Candelaria-Cook et al., 2020). It is encouraging that global spectral measures were reliable in a population demonstrating high mood instability and demonstrates the feasibility of repeated scanning to determine drug changes in this study design.

There are a number of limitations to this dataset. It is possible that no significant group differences in spectral power remained after correction for multiple comparisons across sensors and parcels due to a lack of power. No formal power calculations were undertaken for this study due to its novelty. Sample size was based on a similar experimental medicine studies that also aimed to assess imaging outcomes (e.g Saunders et al., 2016), but not all participants underwent MEG scanning. Perhaps if all recruited OxCaMS participants had undergone scanning, the sample may have been sufficiently powered to observe any potential effects. Nevertheless, the current sample is similar to sample sizes of previous pharmaco-MEG studies (Table 7.1). Despite considerations to select a LTCC antagonist that is known to cross the BBB, it is possible that the dose of nicardipine SR used in this study (30 mg bd) was insufficient to produce the occupancy of LTCCs required to observe a strong neural signal.

7.5 Conclusion

These analyses do not provide strong statistical evidence that nicardipine SR had any effect on resting-state MEG measures including PSD in sensor- and source-localised data, alpha peak frequency, and dynamics of network activity. This suggests a sub-optimal functional occupancy of brain LTCCs by nicardipine SR (in the regimen used in OxCaMS), though alternative explanations may also exist for the lack of effect on MEG signal. Nevertheless, the current work

demonstrates high test-re-test reliability of PSD, highlighting the feasibility of repeated MEG sessions to assess drug-related effects in experimental medicine studies.

Chapter 8. General Discussion

There were two overarching goals of this thesis. Firstly, it aimed to characterise the dynamics of mood instability and explore its cognitive and neural correlates in healthy individuals with high and low levels of mood instability. Secondly, it aimed to explore the candidacy of L-type calcium channel (LTCC) antagonism as a potential treatment for mood instability and assess its effects on neural activity.

8.1 Summary of results - COMET

The COMET study utilised digital technologies in order to facilitate the remote collection of simultaneous mood and cognitive data over 50 days, in addition to assessing neural activity using MEG. Chapter 2 demonstrated the utility of the MDQ as a screening tool to identify and recruit individuals to the COMET study. Individuals recruited on the basis of high MDQ scores (7 or above) revealed consistently higher negative mood instability, variability, and mean levels of negative affect as measured by the PANAS-SF, compared to individuals with low MDQ scores (<5). However, the groups did not show such striking differences in positive mood instability or mean positive affect. Further, instability, particularly negative mood instability, was shown to be highly correlated with trait measures of affect lability and intensity on the ALS-SF and AIM. These two well characterised low and high MDQ groups were then used to investigate how differences in mood instability might relate to cognitive and neural measures.

Chapter 3 investigated whether low and high MDQ participants exhibited baseline differences in selective attention tested in a lab-based task, prior to exploring measures of attentional processing measured longitudinally in Chapter 4. A CombiTVA task was adapted with the aim of establishing sensitive measures of visual and attentional processing in the absence and presence of emotional distractors. Selective attention was not disrupted to a greater extent in the context of emotional, particularly fearful, distractors in the high MDQ compared to the low MDQ

group. Further, model parameters estimating VSTM capacity and speed of processing were not different between groups. High MDQ participants required higher minimum exposure duration for targets to be consciously perceived, though this did not correlate with levels of mood instability. The findings did not point to any significant low-level deficits in selective attention in the high MDQ group that would in principle compromise performance on learning-related longitudinal tasks.

In Chapter 4, learning-based attention was assessed both within days and across days, to test whether mood instability may affect cognitive performance over different time frames. Within days, low and high MDQ participants showed comparable RT facilitation for identifying targets in repeated contexts versus novel contexts. Instability in learning slopes for repeated contexts each day was also not correlated with negative or positive mood instability. However, when these contexts were repeated across days, high MDQ participants were slower at detecting and using contextual regularities to guide recognition of targets, revealing subtle impairments in learning regularities and integration of outcomes in the environment.

Chapter 5 explored whether instability at the level of behaviour was also reflected in instability at the neural level. A TDE-HMM was applied to resting-state MEG data to reveal transient brain states and their associated networks. Higher levels of negative mood instability in high MDQ participants was associated with decreased overall state switching, reduced proportion of time spent in a fronto-limbic state, and increased time between visits to this state. These correlations were replicated in a larger dataset which confirmed the integrity of dynamic networks observed in COMET. These associations were not present in the low MDQ group.

8.2 Summary of results - OxCaMS

Insights from COMET informed the design and methodology of OxCaMS. Participants with high MDQ scores were recruited to a randomised, double-blind assessment of the LTCC antagonist nicardipine SR or placebo for 14 days to evaluate its effects on mood, cognition, and neural activity. Chapter 6 did not reveal a significantly greater pre-post-randomisation change in mood instability after the administration of nicardipine SR compared to placebo. However, general reductions in mood instability were observed in both nicardipine SR and placebo groups, similar to that observed in Chapter 2.

Chapter 7 investigated whether there was any resting-state MEG signal of LTCC antagonism. Importantly, high test-re-test reliability of spectral measures was observed; however, compared to placebo, nicardipine SR did not significantly affect measures of spectral power, alpha peak frequency, or characteristics of fast transient brain states estimated by the TDE-HMM. Reasons for these findings are briefly discussed below.

8.3 Implications and future work

Observations from the COMET study, in Chapter 2, suggest that instability in negative affect might be of particular importance in this sample. Significant differences in low and high MDQ groups were observed more consistently across measures of negative mood instability than positive mood instability. In addition, higher MDQ scores at baseline were significantly associated with increased levels of negative mood instability whilst associations with increased positive mood instability did not quite reach significance. Higher scores on the MDQ, when used as a screening tool for BD, reflect higher probability for detecting BD, or a 'bipolar phenotype' (Hirschfeld et al., 2000; Rock et al., 2013, 2010). The presence of negative mood instability may therefore confer particular risk for developing BD in healthy individuals.

In line with this, very recent research from Sperry, Walsh and Kwapil (2020) has shown that instability (measured using the MSSD) in negative affect at baseline was more strongly associated with the development of *new* bipolar spectrum diagnoses at three-year follow-up than instability in positive mood at baseline. The increased presence of negative mood instability identified through longitudinal monitoring may therefore provide a particular opportunity for early intervention. The same authors found that the presence of both negative and positive mood instability at baseline and three-year follow-up was associated with *existing* bipolar spectrum diagnoses (Sperry, Walsh, & Kwapil, 2020). Whilst other studies observe overall increased negative and positive mood instability in diagnosed BD samples compared to controls (Crowe et al., 2019; Hofmann & Meyer, 2006; Tsanas et al., 2016), an increasing number report greater variability or instability in negative affect in participants with mood disorders compared to controls (Houben et al., 2015; Lamers et al., 2018; Nelson et al., 2018; Peeters et al., 2006; Schoevers et al., 2020; Servaas et al., 2017; Sperry et al., 2020; Thompson et al., 2012). Notably, instability and variability in negative affect is also found to be a stronger predictor of poorer psychological well-being than instability and variability in positive affect (Houben et al., 2015). These findings together support the value of examining the dynamics of negative and positive mood independently, rather than assessing overall mood instability.

Interestingly, negative mood instability in the high MDQ group was associated with alterations in neural dynamics identified using the TDE-HMM. In particular, the overall rate of state switching, and proportion of time spent in the fronto-limbic network was reduced. This may suggest mechanisms via which regulation of mood is disrupted. As suggested in Chapter 5, dynamic transitions between functional networks (or states) are observed at rest (Deco et al., 2011), allowing the brain to reconfigure flexibly to the optimal functional network as and when required (Taghia et al., 2018). Reduced switching between brain states might reflect less flexible

exploration between certain networks, notably those that support mood regulation and cognition. Future work on these data will benefit from detailed interrogation of the state transition matrix probabilities fitted by the TDE-HMM for the low and high MDQ group independently (rather than all participants) to observe whether probabilities of transitioning between certain states, and their directionality are more likely in one group than another. Recent work applying the HMM to resting-state fMRI data in schizophrenia patients, a population who also experience mood instability and impaired cognition, has also shown reduced dynamism of brain networks compared to controls, particularly in the DMN (Kottaram et al., 2019).

In line with reductions in state switching, higher negative mood instability was also associated with decreased proportion of time spent in a fronto-limbic state and increases in time between visits to this state. Fronto-limbic regions are particularly important in mood regulation and are engaged during cognitive re-appraisal and self-regulation strategies, particularly in the presence of negative stimuli or affect (Goldin et al., 2008; Ochsner et al., 2002; Phillips, Ladouceur, & Drevets, 2008; Quirk & Beer, 2006; Schaefer et al., 2002). In addition, the strength of fronto-limbic connectivity measured with fMRI was found to predict successful regulation of negative affect (Banks et al., 2007). Reduced time spent in this state might therefore reflect a failure to regulate negative mood adequately, leading to heightened instability. Further fronto-limbic disruptions are implicated in psychiatric disorders characterised by mood dysregulation (e.g Servaas et al., 2017).

Despite promising insights into potential mechanisms underlying mood instability discovered with MEG, these findings should be interpreted with caution. Given that there is no 'optimal' rate of state switching, the extent of the functional consequences of reductions in overall state

switching is not clear, even though it may correlate with behaviour. More normative data will be essential to study the nature of such deficits in psychiatric populations.

The COMET study did not find correlations between mood instability and cognitive instability directly. However, at the group level, participants in the high MDQ group did display deficits in implicit learning of regularities presented across days, rather than within days. The lack of learning regularities can be seen as a form of instability itself. The inability to detect and integrate regularities over longer periods, such as across days, could point to more general deficits that interfere with the regulation of adaptive behaviour. Although speculative, failure to learn and utilise predictive patterns and outcomes may ultimately also contribute to mood instability if the deficits also apply to learning and utilising regularities in situations with affective or reward-related consequences. Whilst this DPhil cannot confirm such mechanisms, it has revealed interesting group differences for which to generate further hypotheses. Importantly, this subtle difference between groups existed in the absence of differences in general measures of attentional processing such as RT or VSTM. This highlights the importance of developing more sensitive tasks than those measuring global attentional performance.

An experimental medicine model provided a useful way to assess the treatment potential (Harmer, Cowen, & Goodwin, 2011) and underlying mechanisms of LTCC antagonism in healthy individuals with high mood instability. However, the non-significant effects of LTCC antagonism on indices of mood instability and MEG were particularly disappointing given increasing evidence that LTCC genes contribute to the aetiology of psychiatric disorders and phenotypes. Consequently, from these data, it was not possible to elucidate mechanisms by which LTCCs may affect psychiatric phenotypes. In Chapter 7, nicardipine SR did show a tendency toward post-randomisation increases in delta and theta power in frontal, parietal and temporal regions and decreases in alpha and beta power in frontal and temporal regions,

compared to placebo. However stringent thresholding methods meant that these did not remain significant after correction for multiple comparisons across regions. These suggestive findings nevertheless encourage further, more directed investigations.

Although at first glance the null MEG results may suggest lack of target engagement by LTCCs in the brain, there are many other possibilities. From a physiological point of view these might include: compensatory mechanisms activated to overcome reductions in neuronal Ca^{2+}, specific factors limiting the MEG signal such as LTCCs present on inhibitory as well as excitatory neurons such that signals cancel out (Geier et al., 2011; Rubi et al., 2013), or LTCCs not clustered on sufficient suitably oriented pyramidal neuron dendrites for a measurable change in signal. Alternatively, as discussed in Chapter 7, effects of LTCC antagonism may be more apparent for cognitive domains impacted by the *CACNA1C* risk allele, such as attention and WM (Cosgrove et al., 2017; Heck et al., 2014; Thimm et al., 2011), reward processing (Lancaster et al., 2014), and emotion processing/recognition (Nieratschker, Brückmann, & Plewnia, 2015; Tesli et al., 2013). Ongoing work is investigating this possibility using a WM task.

Lastly, longitudinal monitoring of mood in both COMET and OxCaMS has revealed that measures of mood instability reduce over time in the absence of any other intervention. This has important implications for its use as an outcome measure in experimental medicine studies or clinical trials within psychiatry. Sample sizes will have to be larger, in order to increase power to observe any effects of a drug over and above the effects that regular mood monitoring might have, in addition to accounting for regression toward the mean.

8.4 Limitations

Specific limitations of each dataset have been highlighted in the relevant chapters. However, there are some overarching limitations to the studies in this DPhil. Firstly, participants in the

COMET study were recruited to high and low MDQ groups based on cut-offs (≥7 and <5, respectively). Whilst this method was successful in identifying groups experiencing high and low levels of mood instability and allowed specific group comparisons, it may be interesting to observe changes among participants on a more continuous level to enable more sensitive, regression-based/parametric analyses. Secondly, MEG datasets were smaller than the mood and cognitive datasets, reducing power to detect potential neural differences between groups. Future work could combine high MDQ samples from COMET and OxCaMS (baseline MEG recordings only) allowing a larger sample for exploratory analyses. Nevertheless, replications in larger, independent samples will be necessary to establish the robustness of these findings.

8.5 Conclusion

Through the investigation of self-reports, cognitive testing, and neural activity, this work provides novel insights into mood instability and its cognitive and neural correlates, with a particular focus on the possible role of LTCCs. Instability in negative mood might be of particular significance in individuals scoring highly on the MDQ. Not only did these individuals show deficits in learning task regularities across days, but higher levels of negative mood instability were also associated with changes in resting-state neural activity, measured using MEG, such as reduced switching of brain states and reduced time spent in a fronto-limbic state thought to be relevant for the regulation of mood. This thesis did not find evidence to support LTCC antagonism as a potential treatment to reduce mood instability. Despite also not observing changes in resting-state MEG signal, future work will consider the effects of LTCC antagonism on task-based MEG given evidence that the *CACNA1C* risk allele contributes to cognitive phenotypes affected in psychiatric disorders exhibiting mood instability. Finally, this work has demonstrated the feasibility of multimodal, high-intensity studies to investigate transdiagnostic constructs and the potential of new treatments.

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Appendix 1

Such large multi-modal studies are not possible without the collaborative effort of a number of individuals. In addition, the varying outputs from such studies are numerous. The following sections outline the contributions from a number of individuals involved in both COMET and OxCaMS studies, that are relevant to this DPhil, and acknowledge where data included in this thesis has also been used as part of other Masters/DPhil theses in independent analyses, alongside other datasets.

Contributions to the COMET study

Professor Kia Nobre, Professor Catherine Harmer, Professor Matthew Rushworth, Professor Kate Saunders, Dr Jacqueline Scholl, Dr Nahid Zokaei, and Dr Marco Wittman were involved in the design of the COMET study and the design of the novel cognitive tasks described in this thesis. Professor Kate Saunders underwent detailed screening of all participants who entered the study. Dr Natalie Neilson and Priyanka Panchal, another DPhil Psychiatry student, collected the mood, cognitive and fMRI data for the COMET study. My contributions to the study included the collection of MEG data. The COMET demographic and mood data is being included in the DPhil thesis of Priyanka Panchal to use alongside other cognitive, physiological and imaging measures. The COMET data included in this thesis has been analysed independently and is the result of my own work.

Contributions to the OxCaMS study

The initial idea for the OxCaMS study was that of my supervisor, Professor Paul Harrison. The protocol was developed with Professor John Geddes, Professor Catherine Harmer, Professor Kia Nobre, Professor Kate Saunders, Professor Andrea Cipriani, Dr Elizabeth Tunbridge, Dr Arne Mould, Dr Lucy Potter, and me. Dr Lucy Potter, Dr Alexander Smith and I underwent detailed screening of all participants who entered the study. Mood, cognitive and neural data

were collected by me, Dr Lucy Potter, Dr Alexander Smith and Icy Sui Ping Yeung. Mood and demographic data from the pre-randomisation phase of the OxCaMS study has been included in the submitted thesis of Icy Sui Ping Yeung toward a Masters in Experimental Psychology, Oxford. Mood and demographic data will also be used alongside cognitive and neural measures in the DPhil thesis of Dr Lucy Potter. The OxCaMS data included in this thesis has been analysed independently and is the result of my own work.

Appendix 2 – Mood instability outcomes in COMET MEG subsample

Analysis of mood instability data in the subsample of participants who underwent MEG scanning in the COMET study (14 high MDQ; 12 low MDQ). Independent samples t-test were used to assess group differences in overall negative and positive mood instability (tRMSSD), variability (SD) and mean affect scores.

The high MDQ group demonstrated marginally greater overall instability in negative affect, as measured by tRMSSD, compared to the low MDQ group (2.47 ± .98 vs 1.53 ± 1.59, $t(24)=-1.86$, $p=.07$). There were no significant differences in instability of positive affect (3.47 ± 1.30 vs 3.18 ± 1.61, $t(24)=-.52$, $p=.61$).

High MDQ participants further demonstrated significantly greater variability as measured by SD in negative affect (2.12 ± .84 vs 1.15 ± 1.07, $t(24)=-2.60$, $p=.02$) but not positive affect (2.94 ± .73 vs 2.55 ± 1.37, $t(24)=-.92$, $p=.37$) compared to low MDQ participants.

The high MDQ group experienced greater mean negative affect scores (7.54 ± 1.59) than the low MDQ group (6.03 ± 1.40) ($t(24)=-2.56$, $p=.02$). However, the high and low MDQ groups did not differ in mean positive affect scores (11.29 ± 2.53 vs 11.45 ± 4.66 respectively, $t(24)=.11$, $p=.92$) (see Figure 9.1 below).

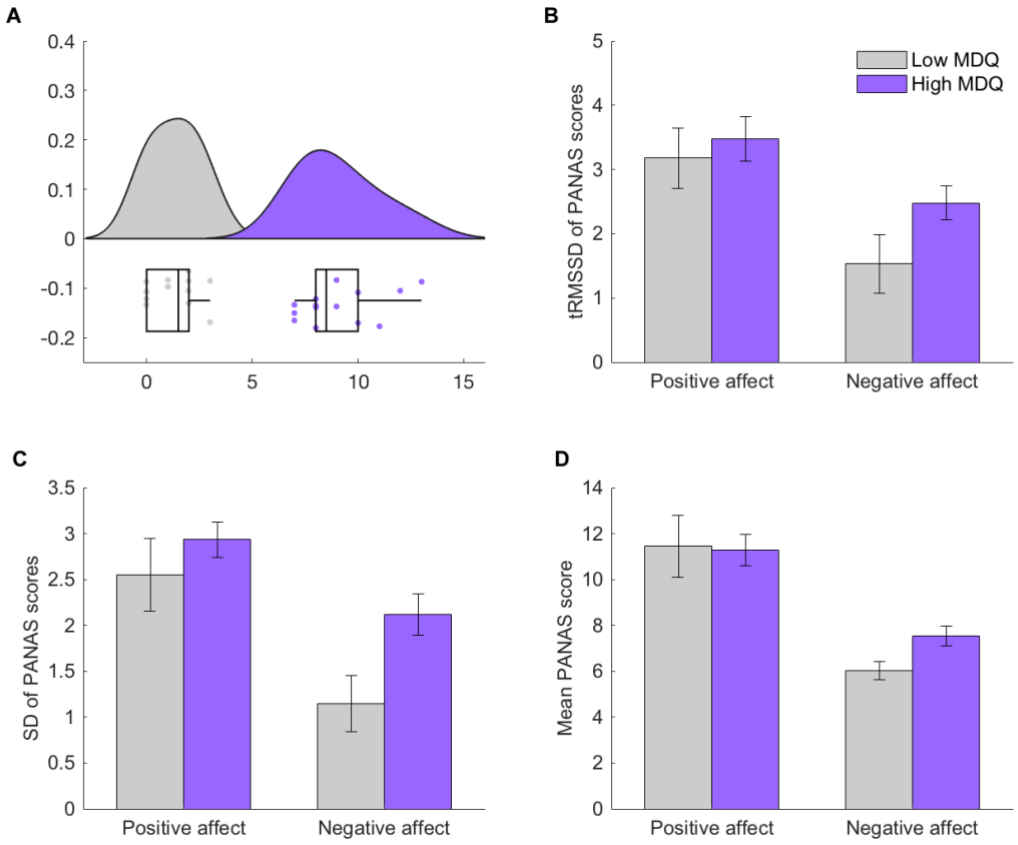


Figure 9.1. **A.** Distribution of MDQ scores in low (grey) and high (purple) MDQ groups. **B.** Group mean instability of negative and positive PANAS-SF scores. Individual participant instability quantified using time adjusted Root Mean Square of Successive Differences (tRMSSD). **C.** Group mean variability of negative and positive PANAS-SF scores. Individual participant variability quantified using SD. **D.** Group mean of negative and positive PANAS-SF scores. Error bars represent ±SE of mean.

Appendix 3 – Mood instability outcomes in OxCaMS MEG subsample

Analysis of mood instability data in the subsample of participants who underwent MEG scanning in the OxCaMS study (10 nicardipine SR; 10 placebo). An ANCOVA was used to assess change scores (post-pre randomisation) in negative and positive mood instability (tRMSSD), adjusting for pre-randomisation mood differences between groups.

When assessing group differences in change scores of negative instability pre- and post-randomisation, an ANCOVA did not demonstrate any differences between nicardipine SR and placebo groups, once their means had been adjusted for pre-randomisation tRMSSD of negative affect ($F(1,17)=.11$, $p=.74$, $\eta_{p^2}=.007$).

Similarly, when assessing group differences in change scores of positive instability pre- and post-randomisation, an ANCOVA did not demonstrate any differences between nicardipine SR and placebo groups, once their means had been adjusted for pre-randomisation tRMSSD of positive affect ($F(1,17)=.07$, $p=.79$, $\eta_{p^2}=.004$).