Characterising mood instability: clinical, behavioural, and neural implications for mood disorders

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Abstract

Mood instability is a core characteristic of, and risk factor for, mood disorders including bipolar disorder (BD) and major depressive disorder (MDD). However, little is currently understood of the wider, clinical, behavioural, and cognitive correlates of mood instability, and the neural mechanisms that may underlie it. It is hoped that a more thorough understanding of this pathophysiological basis may aid in better distinguishing between disorders, in predicting the onset and severity of symptoms, and in developing better suited targets for therapeutic intervention. Therefore, the current thesis aims to explore the profile of mood instability using a translational neuroscience approach combining remote technology, wearable devices, and neuroimaging techniques, in order to investigate the temporal dynamics of this relationship.

Throughout this thesis data is presented from the Cognition and Mood Evolution across Time (COMET) study. The COMET study is a prospective, between-subjects experimental cohort study conducted over 10 weeks. Seventy-four participants took part, 37 of whom screened in for risk of BD using the Mood Disorder Questionnaire (MDQ) (MDQ≥7; high MDQ group), and 37 who did not (MDQ≤5; low MDQ group). All participants underwent a battery of multi-modal investigations, including remote monitoring of mood and activity, as well as cognitive testing and functional magnetic resonance imaging (fMRI). Clinical assessments revealed that 9 out of 37 high MDQ participants met criteria for one or more DSM-IV axis I psychiatric disorder (*chapter 2*).

Given the emergence of new technologies and the ubiquity of internet access, I first explored whether prospective monitoring of daily mood could capture longitudinal mood instability in the high MDQ group (*chapter 3*). High MDQ individuals showed greater variability in daily mood ratings compared to low MDQ individuals, and reported significantly greater absolute negative affect across time. They also had significantly greater clinical symptoms of mania, depression, and anxiety, and reported greater variability across these measures. Additionally, increased levels of negative affect were reported in high MDQ participants who met criteria for an axis I disorder,

regardless of classification, compared to those without a diagnosis. Therefore, analyses showed that daily mood monitoring could capture dynamic mood instability in individuals who screen in for BD. Despite screening in on a tool that targets manic and hypomanic symptoms, mood instability seemed to be more strongly associated with experiences of negative affect.

While confirming the presence of mood instability in the high MDQ group, these results also paved the way for a closer examination of the related behavioural dynamics, a common symptom of mood disorders often manifesting in the form of circadian rest-activity disruptions. The subsequent study aimed to explore whether longitudinal actigraphy monitoring could distinguish between high MDQ participants and low MDQ participants, and also examined the influence of concurrent mood instability (*chapter 4*). High MDQ individuals showed significantly lower circadian relative amplitude, a marker of differentiation between daytime and night-time activity, driven by reduced levels of daytime activity. Relative amplitude was also differentially associated with mood instability and absolute negative mood in high MDQ participants and low MDQ participants, who also showed significant association with both night-time and daytime activity and mood instability. Together, these findings suggest that disruptions in circadian rhythms in mood disorders persist outside of the effects of clinical diagnosis and functional impairment, and are significantly impacted by the experience of mood instability.

Subsequently, the second part of my thesis aimed to determine whether an overarching disruption in neural homeostatic mechanisms may be responsible for both regulating mood and circadian rhythms. Thus, resting-state fMRI was carried out at two time points during the COMET study, and analyses explored both static and dynamic patterns of functional connectivity, so as to more accurately capture the temporally dynamic experience of mood instability. Firstly (*chapter 5*), whole-brain analyses using the ICA method did not demonstrate network variability between groups and across time. Similarly, and using a seed-based approach, there was no difference in specific connectivity with the emotion processing and regulation regions of the amygdala and insula between groups or across time. This paved the way for more nuanced analyses of the dynamic patterns of functional connectivity that may be present. Therefore, subsequent analyses (*chapter 6*) aimed to build on this by

exploring whether mood instability is reflected in altered patterns of dynamic neural connectivity, representing an overarching disruption in neural homeostatic mechanisms.

A sliding-window approach was employed in order to characterise dynamic functional connectivity. Results revealed a comparative level of activation within four distinct meta-states (namely, highly interconnected, DMN, sensorimotor, and low connectivity) across all participants and scan sessions. When assessing dynamic properties, high MDQ individuals were found to occupy a greater number of meta-states and change more frequently across states than those in the low MDQ group. This pattern of instability was found to persist across sessions in the high MDQ group, whilst the low MDQ group showed a pattern of habituation or regulation across these metrics over time. Analyses of the relationship between dynamic properties with mood measures revealed a pattern of lowered variability in functional connectivity as a function of mood instability, as well as a potentially protective association between dynamic properties and circadian rest-activity patterns. Together, these findings uncover more dynamically nuanced details of the pathophysiology of mood and related instabilities.

Led by the need to better understand the wide-ranging correlates of fluctuating mood and to improve clinical outcomes for patients with mood disorders, the aim of this thesis was to build a profile of the translational neuroscientific nature of mood instability. As the first study to do this, I was able to uncover the beginnings of an overarching disruption in neural homeostatic mechanisms that are responsible for regulating mood and related clinical and behavioural outcomes. It is hoped that the doctoral research presented here will encourage continued investigation of this transdiagnostic marker employing further novel and sophisticated methods, in order to capture the temporally dynamic nature of mood instability. Ultimately, such research will prove valuable in transforming our understanding of mood disorders and in the search for better-targeted therapeutic interventions.

This thesis contains approximately 48 500 words.

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List of Abbreviations

ACC	anterior cingulate cortex
ADHD	attention deficit hyperactivity disorder
AIM	Affect Intensity Measure
ALS-SF	Affective Lability Scale - short form
ANOVA	analysis of variance
APA	American Psychiatric Association
ASRM	Altman Self-Reporting Mania scale
BD	bipolar disorder
BD NOS	bipolar disorder, not otherwise specified
BET	FSL's Brain Extraction Tool
BIS-II	Barratt Impulsiveness Scale
BOLD	blood oxygenation level dependant
BPD	borderline personality disorder
BST	British Summer Time
CBT	cognitive behavioural therapy
COMET	Cognition and Mood Evolution across Time
CONBRIO	Collaborative Oxford Network for Bipolar Research to Improve Outcomes
CSF	cerebrospinal fluid
dFNC	dynamic functional network connectivity
DMN	default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	diffusion tensor imaging
emoTVA	Theory of visual attention task - emotional version
ENMO	Euclidean Norm Minus One
EPI	echo planar imaging
EQ-5D	EuroQol Group, quality of life measure
EV	explanatory variable
FEAT	FMRI expert analysis tool
FIX	FMRIB's ICA-based Xnoisefier
FLAIR	Fluid-attenuated Inversion Recovery
FLAME	FMRIB's Local Analysis of Mixed Effects
FLIRT	FMRIB's linear image registration tool
fMRI	functional magnetic resonance imaging
FNIRT	FMRIB's non-linear image registration tool
FOV	field of view
FPN	fronto-parietal network
FSL	FMRIB Software Library
FWHM	full width at half maximum
GAD	generalised anxiety disorder
GAD-7	Generalised Anxiety Disorder questionnaire
GICA	group independent components analysis
GIFT	Group ICA of fMRI Toolbox
GLM	general linear model
GMT	Greenwich Mean Time
GUI	graphical user interface
HDRS	Hamilton Depression Rating Scale
I-PANAS-SF	International Positive and Negative Affect Scale - short form
ICA	independent components analysis
IS	interdaily stability
IV	intradaily variability
LECN	left executive control network
LEQ	Life Events Questionnaire
LMM	Linear mixed-effects model
MATLAB	Matrix Laboratory, software by MathWorks
McFLIRT	FMRIB's Linear Image Registration Tool
MDD	major depressive disorder
MDQ	Mood Disorder Questionnaire
MEG	magnetoencephalography
MELODIC	Multivariate Exploratory Linear Decomposition into Independent Components
MNI	Montreal Neurological Institute
MONARCA	MONitoring, treAtment and pRediCtion of bipolAr disorder episodes
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
MSCD	meta-state composition differences
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIMH	National Institute of Mental Health
NPCRA	non-parametric circadian rhythm analysis
OCMR	Oxford Centre for Clinical Magnetic Resonance Research
OFC	orbitofrontal cortex
OHBA	Oxford Centre for Human Brain Activity
OMPFC	orbital and medial prefrontal cortex
OxLeq	Oxford Life Events Questionnaire
OxLith	Oxford Lithium Trial
PCA	principal component analysis
PCC	posterior cingulate cortex
PFC	prefrontal cortex
PTSD	post-traumatic stress disorder
QIDS	Quick Inventory of Depressive Symptomatology
RA	relative amplitude
RDoC	Research Domain Criteria
RECN	right executive control network
RMSSD	root mean square of successive differences
ROI	region of interest
RSN	resting-state network
SAD	seasonal affective disorder
SCI-R	Sleep Condition Indicator - revised
SCID	Structured Clinical Interview for DSM disorders
SCN	suprachiasmatic nucleus
SD	standard deviation
SEM	standard error of the mean
SN	salience network
SPSS	Statistical Package for the Social Sciences
TE	echo time
TFCE	threshold-free cluster enhancement
TR	repetition time
***t*RMSSD**	*timed* root mean square of successive differences
wFNC	windowed functional network connectivity
WHO	World Health Organisation
WM	white matter
WoF	wheel of fortune

Chapter 1 | Introduction

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1.1 From mood disorders to mood instability

Traditionally, illness prognosis and consensus for treatment decisions have led to the need for distinct diagnostic categories in order to direct clinical care. However, owing to the frequent overlap in clinical presentations, a growing body of evidence has revealed that these distinctions are not necessarily biologically valid or conducive to symptom management (Akil et al., 2010; Nesse & Stein, 2012; van Praag, 1999). Therefore, modern psychiatric research has shifted from considering only distinct diagnostic categories based on clinical consensus to capturing fundamental underlying mechanisms of dysfunction. This shift has occurred in part as a response to developments in neuroscience and related methods such as functional neuroimaging, electrophysiology, and techniques for quantifying neural connections *in vivo*, and also address the vital need for the development of new treatments targeted at more accurately improving the often heterogenous nature of clinical outcomes. Thus, and in line with Research Domain Criteria (RDoC) set out by the National Institute of Mental Health (NIMH) (Insel et al., 2010), there is a move towards conducting research that aims to understand the nature of psychiatric illness in terms of varying degrees of dysfunction in general psychological and biological systems.

The study of mood disorders, incorporating both major depressive disorder (MDD) and bipolar disorder (BD), is particularly strengthened when employing this framework for its ability to address both the similarities and differences in clinical presentation. In particular however, and something that has become increasingly apparent given advances in assessment techniques, is the need for the identification and use of biomarkers to direct distinct clinical care and treatment. The discovery of mood instability, or rapid oscillations of intense affect with difficulty in regulating these oscillations or their behavioural consequences (Marwaha, Parsons, Flanagan, & Broome, 2013), aims to do just this. Therefore, its standing as a potential transdiagnostic marker across mood disorders can aid in capturing the temporally dynamic nuances underlying the pathophysiology of such disorders, in order for more accurate predictions of clinical outcomes to be made.

1.2 Aims and objectives

In the spirit of the RDoC framework, the current thesis aims to explore the pathophysiological circuits which may underlie mood instability, by considering both neural systems and behavioural dimensions. As such, the clinical, behavioural, and neural correlates of mood instability, as measured first by risk propensity to BD and then temporally using longitudinal objective and subjective measures, will be explored in order to inform us of both the process by which mood disorders develop, and the dynamics by which they are maintained over time. Ultimately, it is hoped that a clearer investigation of the underlying mechanisms of this phenomenon will aid in refining our understanding of mood stabilising drug treatments such as lithium, and also in identifying new and better tolerated targets for treatment development.

1.3 Mood disorders: major depressive disorder (MDD) and bipolar disorder (BD)

1.3.1 Clinical presentation

Mood disorders, including MDD and BD, are a major cause of disability worldwide, affecting social and occupational functioning, quality of life, and mortality rates (World Health Organisation (WHO), 2017). It is estimated that 21% of adults in the US will experience a mood disorder at some point in their lives (National Comorbidity Survey, 2007), and the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association (APA), 2013) has further expanded the guidelines for mood disorders in order to account for the complexities in their symptomatic profiles.

Clinically, MDD and BD are predominantly characterised by subjective emotional symptoms – such as lowered mood and anhedonia in the case of MDD, and lowered mood and mania in the case of BD. Contrasts in their core cognitive profiles are also often emphasised, with BD being more closely associated with impairments in decision-making and impulsivity, resulting in changes in reward processing (Christodoulou, Lewis, Ploubidis, & Frangou, 2006). However, MDD and BD share many symptomatic similarities, the clearest of which is the presence of depressive episodes. This contributes to clinical overlap, whereby BD is often misdiagnosed for MDD (Ghaemi, Sachs, Chiou, Pandurangi, & Goodwin, 1999). Depressive episodes usually present initially in the course of BD and are often experienced more saliently

than manic or hypomanic episodes (Hirschfeld, 2010). They are also both highly heritable, such that first-degree relatives of those with BD also have an increased risk of developing MDD (McGuffin & Katz, 1989).

Additionally, this more complex intertwined nature of the disorders, especially in the shared case of depressive episodes, is reflected in some of their downstream cognitive symptoms, for instance, in consistent findings of impairments in working memory and attention in MDD and BD (Harvey, 2007) related to the depressive symptom of a "diminished ability to think or concentrate" (American Psychiatric Association (APA), 2013). A breadth of recent research, aided by developments in neuroscience, has particularly begun to elucidate these cognitive underpinnings of mood disorders. It is the presence of these symptoms, ranging from difficulties in sustained attention, learning, and memory, to decision-making and reward processing, together with the recurring nature of such disorders, that likely magnify its wider effect on quality of life and economic burden.

1.3.2 Cognitive emotional processing

Before building a profile of mood instability and its underlying neurobiological mechanisms, it is important to first consider the similarities and differences of the mood disorders, BD and MDD, for which it is characteristic. This will aid in determining the shared mechanistic underpinnings of the disorders, and also in predicting symptomatic progression across the course of illness. Thus, the current chapter will introduce a consideration of cognitive affective processing across BD and MDD, an area of research which has garnered much attention for its ability to inform us of related clinical, behavioural, and neural functioning. A consideration of how this processing

uncovers the temporal dynamics of mood disorders will also be presented, paving the way for subsequent analyses of mood instability in this thesis.

Owing to the widespread prevalence of cognitive impairments in mood disorders, recent research has emphasised the importance of interactions between cognitive and emotional systems (Pessoa & Adolphs, 2010; Roiser & Sahakian, 2016), and proposed that these interactions are implicated in both the prodrome and maintenance of MDD and BD. Thus, cognitive emotional processing works as a cyclic system: cognitive factors, such as our interactions with the environment and the process by which we make decisions, are influenced by emotional context, or our emotional state, and vice-versa. This system is key to human behaviour and experience (Elliott, Zahn, Deakin, & Anderson, 2011) and aids us in forming appropriate responses to our environment, some of which have a strong evolutionary basis (for example, stress and fear). This processing is also fundamental in guiding our behavioural actions, as well in forming social responses, be it in terms of determining how we interact with our loved ones or in allowing us to behave altruistically with strangers. It then follows that impairments in such a processing style can lead not only to the clinical and cognitive symptom profile of mood disorders, but also the behavioural disruptions and social difficulties that patients often experience. By viewing these patterns in a related manner, we are also able to hypothesise on the putative neural mechanisms which may underlie BD and MDD.

While we all interact with our environment in a way that blends cognition and emotion, the varying degrees with which we do so and the consequences that can arise from distortions in such processing are vital to understand. Mood disorders are at the core

of this. Owing to the shared mood and cognitive symptom profile of MDD and BD, researchers have begun to investigate trait-related cognitive effects across the disorders. These trait effects of cognitive processing during periods of remission or euthymia, and even prior to the onset of illness, rather than specific state effects that are manifested specifically during periods of depression or mania, are in line with the RDoC movement towards focusing on the transdiagnostic and translational mechanisms that span such related mental disorders, involving both objective behavioural and neuroimaging methods (Insel et al., 2010). Such methods enable us to better capture the complex nature of MDD and BD, which is often hindered by a strict focus on distinct clinical diagnostic classifications, and allows us to fully consider and appreciate the phenomenon of mood instability in contributing to cognitive affective processing across mood disorders.

1.3.2.1 Attentional biases

Owing to the fact that individuals with depression experience major difficulties in their social interactions, tests involving facial expressions of emotion are some of the most powerful and ecologically valid ways of investigating attentional biases in cognitive processing (Gross & John, 2003). Across a range of experimental studies using six basic facial expressions (happy, sad, fearful, angry, disgusted, and surprised) (Ekman & Friesen, 1971), MDD patients have been consistently shown to exhibit a negative bias (King, 2002), such that they tend to recognise and focus significantly more on negative emotional expressions (e.g. sadness or anger) or less on positive facial expressions (e.g. happiness). In line with the clinical symptoms of rumination and in combination with a tendency to hold negative schemas and expectations, Bradley, Mogg and Lee (1997) suggest that individuals with MDD are both biased towards

perceptually recognising negative information, especially that of facial expressions, and have greater difficulties in disengaging once this information has become the focus of their attention.

In line with this, Gotlib and colleagues (Gotlib, Krasnoperova, Yue, & Joormann, 2004) demonstrated a depression-relevant negative attentional bias in a sample of MDD patients and healthy controls. When presented with a dot probe task incorporating happy, sad, and neutral faces, individuals with MDD selectively attended to the sad faces above and beyond controls and participants diagnosed with generalised anxiety disorder (GAD). The authors particularly noted here that the negative attentional biases observed were specific to sadness, an emotion specific to depression, and not other types of negative stimuli, explaining this bias in cognitive affective processing as a characteristic of MDD. Similar results have also been reported by other studies of facial expressions by Gotlib and colleagues (Gotlib, Kasch, et al., 2004; Gotlib, Krasnoperova, et al., 2004; Joormann & Gotlib, 2007), and in comparisons of MDD depressed individuals with those recovered from a depressive episode, as well as individuals with a diagnosis of other axis I disorders (e.g. social phobia).

Whilst a breadth of behavioural studies have found evidence for this negative attentional bias towards mood congruent sad faces in MDD, studies of the particular attentional mechanisms involved have been less consistent. Duque and Vázquez (Duque & Vázquez, 2015) aimed to clarify these mechanisms further by testing to see if such a negative bias is observed in both the orienting and maintenance of attention, using an eye-tracking technique to complement their face processing task. Whilst further confirming the presence of a negative attentional bias to mood congruent sad

faces, the authors also reported a bias in the maintenance of gaze or attention, over orientation. This finding lends further empirical support to the idea that once individuals with MDD focus on negative information, they experience particular difficulties in disengaging from it (Bradley et al., 1997).

This consistent finding of negative attentional biases in MDD towards sad facial expressions leads us to question whether the same mechanism is also in play in BD, and whether such bias is modulated by specific mood episodes. Whilst this area of enquiry has been less researched in BD, some studies have found evidence for a similar mood congruent bias. For example, Lembke and Ketter (2002) found that participants with BD mania were significantly impaired at recognising negative facial expressions, including fear, sadness, anger and disgust, and that the recognition of sad faces inversely correlated with their mania symptom severity, such that their ability to recognise sadness became more impaired as they experienced more manic symptoms. Whilst this positive bias seems to follow on from the idea of mood congruent cognitive processing of emotional faces in mood disorders, results in mania have not always been so consistent. Gray and colleagues (2006) found a result similar to MDD in that BD depressed participants showed a decreased sensitivity to happy faces and increased bias towards sadness. They did not, however, find evidence of a mood congruent positive bias in the perception of emotional faces in their sample of manic patients.

Drawing from evidence of mixed results in BD mood episodes, an investigation of cognitive processing of facial expressions during periods of euthymia may help to elucidate the particular trait-related mechanisms at play. In a study by Harmer and

colleagues (2002), euthymic BD participants were reported to show preferential recognition and perception of facial expressions of disgust, with no other differences in processing of other facial expressions reported. Whilst this can also be viewed as adding to the premise of negative attentional biases in mood disorders, other results in euthymia have not been so consistent. For instance, whilst Venn et al. (2004) reported a statistical trend towards lower recognition of fear in their patients, they and Vaskinn and colleagues (2007) more generally found no significant difference between BD patients and controls in their measures of sensitivity to facial expressions of emotion, suggesting the absence of a specific trait-like bias in emotional perception and attention in BD. Martino et al. (2011), however, furthered the trend reported earlier (Venn et al., 2004) by confirming a lowered recognition of fearful facial expressions in their larger sample of BD I and II euthymic patients.

Whilst the differing nature of facial expression paradigms – such as a simple recognition task, a dot-probe task, or a facial morphing task – is often provided as an explanation for inconsistent findings; it is important to note that many of the participants included in these studies, as with most studies investigating euthymia, were medicated. As lithium is known to influence cognition and cognitive processing more generally, it is both difficult to control for this in face processing tasks during euthymia, and to interpret the results as being a characteristic trait marker of cognitive affective processing in BD. Nevertheless, in Bilderbeck and colleagues' (2017) study of medicated BD patients, a mood stabilising effect of both lithium and dopamine antagonist (antipsychotic) medication was found whereby medicated patients showed reduced recognition of angry facial expressions compared to those who were mediation-free, as well as an inverse modulation of happy face recognition by

increasing depressive symptoms. Therefore, this study is of particular value in highlighting the complexities of studying medicated euthymia considering the cognitive implications of such therapeutic agents.

As with the results from tasks of facial expressions of emotion, Murphy and colleagues (1999) reported that MDD patients were impaired in their ability to shift attention between differentially valenced information when completing the Affective Go/No Go task, such that they were slower in responding to happy but not sad stimuli. Whilst this further confirmed the presence of negative attentional biases in MDD, it is important to note that the majority of participants were again medicated. However, Erickson et al. (2005) confirmed this in their sample of unmedicated MDD patients by finding that their participants responded more quickly to sad words than happy words, and also made more emission errors when responding to happy words.

The evidence in BD, again, has not been so conclusive. Murphy and colleagues (1999) also employed the same Affective Go/No Go task in a sample of BD manic patients and found that they were faster at responding to positive words compared to negative words, supporting the notion of a mood congruent attentional bias. Rubinsztein et al. (2000), however, found no such bias to happy or sad words in their sample of remitted or euthymic BD patients. In García-Blanco and colleagues' (2013) study of mood congruent attentional biases across the different episodes of BD, they found support for a negative attentional bias during depressive episodes, a positive attentional bias during manic episodes, and no mood congruent bias during euthymia. Whilst this supports the idea of mood congruent biases in mood disorders, the presence of conflicting results in other tasks of attention, especially in the case of BD, leads us to

question whether more robust methods, utilising complimentary behavioural paradigms (for example, face processing tasks) and neuroimaging techniques can help to clarify the particular mechanisms by which cognitive affective processing in relation to attention in mood disorders operate.

1.3.2.2 Memory biases

Building on the literature for mood congruent biases in attentional processing, research has also looked into the effect of emotional stimuli in tests of memory, particularly of verbal memory recall and retention. Tests using more “cold” forms of memory processing, that represent processing in the absence of emotionally salient responses or stimuli, have found impairments in the recall of information, but not in retrieval and retention, in MDD (Kizilbash, Vanderploeg, & Curtiss, 2002). The picture has not been so clear in BD, with a range of studies and meta-analyses reporting heterogeneous results (Bourne et al., 2015), with differing profiles of impairments in individuals with a diagnosis of BD I and BD II (Sole et al., 2012), suggesting a modulation of impairment by symptomatology and illness severity. Whilst the participants in these studies are usually in the euthymic phase of the disorder, they are also more likely to be medicated. Nevertheless, impairments in verbal recall memory have also been found in first-degree relatives of participants with BD (Bora, Yucel, & Pantelis, 2009), suggesting that this impairment could form part of a core trait-related cognitive profile of the disorder.

Delving into this further, BD depressed individuals are known to show a greater degree of impairment in learning and memory recall than individuals with MDD (Burt, Prudic, Peyser, Clark, & Sackeim, 2000; Wolfe, Granholm, Butters, Saunders, & Janowsky,

1987). Combining this with the idea of mood congruent biases in the recognition of, and attention towards, information – especially emotionally-valenced information – suggests that the disorder may involve disruptions in the encoding and consolidation of memory, attenuated by the presence of affective biases and current mood state. Support for this is also provided by evidence of persistent memory impairments in BD euthymic individuals (Martínez-Arán et al., 2004). Whilst further research is needed to fully elucidate the mechanisms of cognitive emotional processing in relation to memory in BD in order to understand whether the mood congruent biases that are present during attention are applicable over the memory impairments reported outside of emotional stimuli, contributions from the MDD literature can help.

As with negative attentional biases, depressed individuals are reported to have a tendency towards remembering more negative-valenced information compared to controls (Mogg, Bradley, & Williams, 1995). This was further demonstrated in a study by Harmer and colleagues (2009), which looked at the presence of negative affective biases in antidepressant-administered MDD patients across facial recognition, attention, and memory. Not only did those in the placebo group show reduced recognition of positive facial expressions of emotion, as well as a negative attentional bias, they also had significantly reduced memory for positive self-relevant personality adjectives. Providing support for the neuropsychological model of antidepressant action, this study also showed a reversal in these biases towards negative information, over and above any subjective change in mood, in their sample of MDD patients administered the antidepressant agent reboxetine. Thus, whilst providing support for the presence of emotional biases in memory in MDD, this study also points to the

importance of cognitive affective processing in being a core target for treatment in mood disorders.

1.3.2.3 Reward processing

Compared to the research into emotional biases in attention and memory in mood disorders, reward processing is a relatively understudied area of cognitive emotional processing. Nonetheless, it is an area that is garnering precedence due to its close association with many of the clinical symptoms of both MDD and BD, and the potential for sophisticated neuroscientific and computational methods to be applied. For instance, anhedonia, or "markedly diminished interest or pleasure…in activities", is a core clinical symptom of MDD and suggests an impairment or dampening in reward processing. Similarly, elevated mood and impulsivity associated with manic symptoms and episodes in BD also points to disruptions in reward processing, albeit perhaps in a differing direction and to varying degrees. The mechanisms by which reward processing differs in mood disorders is important to understand as disturbed reward processing can lead to harmful social consequences (for example, excessive impulsivity and irrational decision-making, particularly in BD) and also predicts response to treatment (Uher & Rutter, 2012).

In line with the presence of negative affective biases in other cognitive domains in MDD, depressed individuals are often reported to show a hypersensitivity towards negative feedback, for example punishment (Elliott, Sahakian, Herrod, Robbins, & Paykel, 1997), and hyposensitivity towards positive feedback, for example responses to reward (Admon & Pizzagalli, 2015). This maladaptive response to punishment is thought to be reflected in a blunted ability to respond to feedback information (Steele,

Kumar, & Ebmeier, 2007). For instance, in Holmes and Pizzagalli's (2011) study, individuals with high levels of depressive symptoms were less able to adjust their performance and increase their accuracy following negative performance feedback on a range of cognitive tasks. Murphy et al. (2003) furthered this by attempting to elucidate the mechanisms of feedback that may hinder cognitive performance for those with MDD. In their probability reversal and spatial working memory tasks, they found that individuals with MDD showed impaired performance after negative, but misleading, feedback but that their performance was no more disrupted compared to controls following negative, but accurate, feedback. Whilst these findings stress the importance of context in mediating maladaptive responses to feedback, the hypersensitivity to negative feedback and disrupted ability to modify behaviour in such cases reflects a perceived lack of control or motivation in MDD.

Pizzagalli and colleagues have also shown that individuals with both an increased vulnerability to MDD (Holmes & Pizzagalli, 2011) and those with a diagnosis (Admon & Pizzagalli, 2015) were less able to learn about rewarding stimuli, and thus were less able to use this information to guide their subsequent behaviour in their reward processing task. This impairment, along with those of maladaptive responses to negative feedback, are also reported to correlate positively with symptom severity, as well as present in first-degree relatives and recovered individuals (Eshel & Roiser, 2010), suggesting that such disruptions in reward processing are a core and pervasive feature of cognitive affective processing in MDD.

A more recent systematic review and meta-analysis has further shed light on the mechanisms of reward processing in MDD. Across 48 studies, Halahakoon and

colleagues (2020) reported a small to medium level of impairment in MDD patients compared to healthy controls. Delving into this further, the authors reported the largest degree of impairment in the reward bias domain, part of the decision-making process, whereby individuals tend to choose more frequently rewarded stimuli, regardless of perceptual accuracy, reflecting weaker reward biases (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008). They also showed smaller impairments in the option valuation domain of decision-making, reflecting the process by which an individual assesses the explicit information provided for reward-related options (for example, probability, reward, and cost), such that depressed individuals were less able to effectively evaluate cost-benefit decisions (Treadway & Zald, 2011). Similar impairments were also reported in the reinforcement learning domain, reflecting the process by which individuals use feedback to guide their subsequent decision-making. Despite the confounding influence of "cold" cognition, such as working memory impairments, on this domain, a number of studies have reported impairments such that individuals with MDD use feedback less effectively to adapt subsequent behaviour compared to healthy controls (Admon & Pizzagalli, 2015; Holmes & Pizzagalli, 2011; Thoma, Norra, Juckel, Suchan, & Bellebaum, 2015).

Taken together, these studies have highlighted the importance of specific reward processing domain when assessing impairments related to depression. The majority of research points to a mechanism of "decisional anhedonia" (Halahakoon et al., 2020) such that symptomatic difficulties in feeling pleasure and experiencing normally pleasurable activities result in impaired cost-benefit decision making, or vice-versa (Treadway & Zald, 2011). Whilst this offers an interesting interpretation of the reward processing difficulties often observed in MDD, placing it in the wider context of mood

symptoms experienced and thus, providing potential avenues and hypotheses for the relationship in BD depressive and manic episodes; further research is warranted in order to tease apart the effect of anhedonia on such decision-making, and the directionality of this relationship, made feasible through controlled experimental and neuroimaging studies.

Quite unusually for the area of cognitive emotional processing in mood disorders, which has often favoured the study of MDD, reward processing is a cognitive domain that has been studied more so from a BD perspective. In line with findings of greater impulsivity in individuals with BD during manic phases, researchers have found a strong connection between manic patients and responsiveness to rewarding stimuli, which can then go on and influence decision-making. Following on from the literature in MDD, BD depressed individuals are also shown to have a hypersensitivity towards negative feedback, such that they made a disproportionate number of errors following an incorrect response and resulting negative task feedback compared to controls (Roiser et al., 2009). A similar response to negative feedback has also been reported in manic BD patients (Minassian, Paulus, & Perry, 2004), lending support to the hypothesis that impairments in cognitive affective processing in mood disorders may be directly linked to a “catastrophic response to perceived failure” (Beats, Sahakian, & Levy, 1996).

Further research has attempted to clarify the distinct processes that may contribute to altered decision-making and reward processing in BD. In their comparison of BD manic and MDD patients, Murphy et al. (2001) found that the two groups were markedly slower at making choices on a probabilistic reward processing task and also

earned significantly fewer points based on the reward learning information provided in the task. They suggest that these first line results provide further support for cognitive emotional processing impairments in mood disorders, particularly in the executive functioning domain of set-shifting. However, when delving into the decision-making process further, the researchers also noted how manic patients were more likely to make detrimental choices leading to early termination of blocks, or “losing the game”, compared to MDD depressed patients, as well as having a tendency to select the choice associated with a lower probability of reward, indicating an impairment in learning about optimal reward information. Thus, it seemed that not only were manic patients poorer at making optimal decisions, they were also more willing to engage in risk-taking behaviour when making these decisions, compared to both MDD patients and controls.

Again, whilst these results begin to highlight some of the cognitive impairments reported in mood disorders in the domain of reward processing, the fact that such impairments are modulated by mood episode and symptom severity points to the idea that these may be state-like characteristics of the disorders. A closer examination of the mechanisms at play during euthymic phases of BD should therefore aid us in understanding the trait-related features of the disorder, with the hope of describing the clinical symptoms of anhedonia during depression, and hyperhedonia, or excessive pleasure-seeking behaviour, during mania and their relation to cognitive affective processing in further detail. Pizzagalli et al. (2008) set out to study this in their sample of euthymic BD patients by testing whether BD is characterised by an impairment in the ability to adapt behaviour in response to changing reward, accounting for trait-related features that can be applicable across distinct mood episodes. In their

probabilistic reward task, they found that euthymic patients were slower at selecting, and less likely to select, the more frequently rewarding stimuli, suggesting an impairment in response bias towards rewarding information, as well as decreased ability to learn and integrate information about reward over time. Whilst this impairment was exacerbated by residual anhedonic symptoms in the sample, alluding to a similar pattern of diminished learning and negative attentional biases, the suggestion of impairments in learning over time, again, highlights underlying difficulties in executive function. Taken together with the interesting, yet inconclusive, evidence of cognitive emotional processing in other domains such as attention and memory, particularly in BD but also across mood disorders, such findings lead us to examine the neural mechanisms that may modulate and underpin these disorders.

1.3.3 Neural underpinnings

A discussion of the neural underpinnings of cognitive affective processing, via neuroimaging techniques such as magnetic resonance imaging (MRI), may help us to better understand the shared and distinct features of mood disorders. Generally, abnormalities are usually found in limbic structures, including the amygdala and hypothalamus, and in regions of the prefrontal cortex (PFC), including the orbital and medial prefrontal cortex (OMPFC), as well as various connections between the two (Price & Drevets, 2012) across both MDD and BD, accounting for most major mood-related symptoms.

In MDD, patients are reported to have increased activation in the amygdala, orbitofrontal cortex (OFC) and prefrontal cortex (PFC) when showing an attentional bias towards negative facial expressions (Wagner, Muller, Sommer, Klein, & Hajak,

2004). As well as being involved in emotional processing and executive functions such as attention – linking the two together – disruptions in these regions and circuits are also thought to increase the risk of developing the disorder (Price & Drevets, 2010). Other researchers have also reported increased activation in limbic areas, such as the hippocampus, insula and anterior cingulate cortex (ACC), during the processing of negative facial expressions (Anand et al., 2005; Elliott et al., 2011; Lee et al., 2008), modulated by symptom severity, emphasising how the emotional component of the information is intrinsically related to cognitive processing in MDD. However, results in MDD have not always been so conclusive, with some studies failing to see increased amygdala responses to facial expressions (e.g. Gotlib et al., 2005), whilst others have found differing patterns of activation in tasks engaging both attention and memory of facial expressions (Hamilton & Gotlib, 2008; Roberson-Nay et al., 2006). Methodological differences, including task instructions and the cognitive domains required, have been proposed as potential explanations for such differing results, and also suggest the need for more stringent investigations.

Increased activation in limbic regions during face processing tasks have also been reported in BD. In their systematic review and meta-analysis of the neural correlates of emotional processing in BD and MDD, Delvecchio and colleagues (2012) argued that increased limbic engagement, particularly involving the parahippocampal gyrus and amygdala, formed part of the core phenotype of cognitive affective processing of facial expressions in mood disorders, but that clear distinctions in other regions existed. For instance, BD, but not MDD, was associated with reduced activation in the ventrolateral PFC, an area known to be implicated in inhibitory control. As difficulties with inhibition, particularly within manic episodes, is a core feature of the disorder, this

suggests that processing in this region and its associated circuits is specific to the experience of BD (Cerullo, Adler, Delbello, & Strakowski, 2009; Chen et al., 2006). In a similar fashion, increased activation in the thalamus, particularly the pulvinar, was found to be associated with BD rather than MDD, while processing negative facial expressions. As this particular "higher order" region is known to have various cortical connections (Pessoa & Adolphs, 2010), it has been proposed that overamplification towards emotionally salient information helps to explain the difficulties in fluctuating mood in BD, whilst the suppression of activation in the same region during the processing of positive facial expressions in MDD points to the dampening of reactivity towards positive information associated with depression (Rottenberg, Gross, & Gotlib, 2005).

A combination of connections between these cortical, striatal and thalamic regions are thought to be intrinsically related to reward processing in mood disorders. According to research in MDD, patients show a decrease in activation in the ventral striatum in response to rewarding stimuli, compared to healthy controls, and this deactivation is known to be modulated by an increase in anhedonic symptoms (Treadway & Zald, 2011). Increased activation in the caudate nucleus, a structure of the striatum, is reported in BD when processing rewarding stimuli, including happy facial expressions during manic episodes (Abler, Greenhouse, Ongur, Walter, & Heckers, 2008; Giuseppe Delvecchio et al., 2012). This is in line with research that has shown distinct abnormalities in the function, size and shape of the basal ganglia (Abler et al., 2008; Hwang et al., 2006; Strakowski, Delbello, & Adler, 2005; Strakowski, Adler, & DelBello, 2002), a region comprising the striatum, pallidum, the substantia nigra, and the subthalamic nucleus, and known to be particularly implicated in reward processing,

with connectivity to PFC regions and the amygdala. Taken together, reward learning and processing is known to involve cortico-striatal learning systems, such as those discussed here, in combination with prefrontal regions of executive control. Whilst there is still a need for further neuroimaging research in this area in order to parse out the particular neural contributions, findings of disruptions in these areas across the domains of perception, attention and memory of affective information combine to further inform us of the behavioural impairments noted in reward processing across mood disorders, and the distinct mood-related mechanisms which may modulate the severity and direction of impairment within the disorders.

These neurobiological patterns, suggesting an overarching pathophysiological marker, have also been reported in resting-state fMRI studies in both MDD and BD, implicating connectivity within a variety of neural circuits outside of task demands. Wang and colleagues (2012) commented on the robust nature of findings involving cortico-limbic structures in MDD, such that abnormal connectivity in regions such as the thalamus and amygdala were thought to represent the persistent and core feature of negative biases and maladaptive emotional perception in depressed patients. Further, the consistent finding of abnormal connectivity in the default mode network (DMN) in these patients, including within the regions of the PFC and cingulate cortex, also begins to highlight a differential marker of functional connectivity associated with mood disorders. When contrasting these findings with those seen in patients with BD, researchers have again reported overall markers of functional connectivity disruption in BD, and have highlighted differential patterns in such connectivity that may distinguish between BD and MDD. For instance, Marchand et al. (2013) found increased connectivity between the posterior cingulate cortex (PCC) and regions

involving the insula in BD patients compared to MDD, and this association was modulated by severity of depressive symptoms and current suicidal ideation. In a similar fashion, Anand et al. (2009) reported overall abnormalities in cortico-limbic functional connectivity in BD patients that was in line with that seen in MDD, but that the severity of this association seemed to distinguish BD from MDD. These studies suggest that such functional neuroimaging techniques are able to characterise the similarities and differences between neural connectivity and pathophysiology in mood disorders and could thus, lead to the development of diagnostic procedures that may aid us in differentiating between their clinical presentations.

In their systematic review of resting state functional MRI studies in BD, Vargas and colleagues (2013) found a similar pattern of connectivity to that found in task-dependent data. For instance, BD patients were consistently reported to show differential patterns of functional connectivity in the PFC with the ACC and limbic areas including the amygdala, insula, and thalamus (Anand et al., 2009; Chepenik et al., 2010) compared to healthy controls. However, variations in the nature of connectivity was also reported, such that some studies found increased connectivity between these regions (Anticevic et al., 2013), whilst others instead found it to be decreased (Anand et al., 2009). Further, differences in the patterns of connectivity were often noted within patients, such that patients in a depressive episode differed from those in a manic episode, who in turn differed from those currently euthymic; and it was this pattern of differential connectivity depending on mood state that has been suggested as the reason for such heterogenous results.

Investigation of these functional connectivity patterns during euthymia can thus aid us in teasing apart the core underlying patterns of brain connectivity in BD (Blumberg et al., 2003) and also in elucidating the distinct pathophysiological differences between BD and MDD (Vargas et al., 2013). When focusing on these euthymic patients, Syan and collegues (2018) found a consistent pattern of functional connectivity in the DMN, fronto-parietal network (FPN) and salience network (SN) which was comparable to that found in healthy controls, but that patients who had a history of significant mood episodes involving psychosis often reported hyperconnectivity in the DMN. Again, when assessing connectivity with specific limbic and striatal regions, they found consistent atypical functional connectivity patterns with the amygdala, PFC, and cingulate cortex. Together, whilst these results suggest a pattern of general stability in broad resting state networks during euthymia, the consistent presence of differences in connectivity between regions such as the amygdala, insula, and PFC, areas known to be involved with cognitive and emotional processing, may reflect patterns of overall BD pathophysiology.

However, it should be noted that the majority of neuroimaging studies here, across both task-based and resting-state fMRI, include small sample sizes, thus compromising the statistical power of results. This limitation has been suggested to contribute to the often inconclusive or inconsistent nature of results across studies, and is further complicated when considering the heterogeneous nature of illness studied and the complex nature of interaction between neuroanatomy and function, and clinical characteristics. ENIGMA, an international consortium with the goal of combining neuroimaging, genetic, and clinical data so as to better understand brain structure and function across a range of psychiatric and neurological diseases (Hibar

et al., 2015; Thompson et al., 2014), has begun to address this limitation in both MDD and BD. For instance, a large meta-analysis by the group across 1728 MDD patients found significantly lower hippocampal volumes in patients compared to controls (Schmaal et al., 2016). Whilst this region has long been associated with depression (Sheline, 2011), helping to explain some of the well-documented cognitive symptoms that accompany it (Sapolsky, 2001), Schmaal and colleagues (2016) also noted that the recurrent nature of illness contributed significantly to this structural brain alteration, shedding light on the dynamic nature of neuroanatomical impairment across disorder. Importantly, this relationship with the recurrent nature of episodes further emphasises the need to better understand contributing factors for the development and maintenance of depression, such as early life stressors, genetic predisposition, and risk factors such as mood instability.

In a similar manner, the ENIGMA consortium has been used to identify consistent brain alterations associated with BD. In their sample of over 2000 BD patients, Hibar and colleagues (2018) reported widespread cortical thinning in regions of the inferior frontal gyrus, left fusiform gyrus, and left rostral middle frontal cortex. While these regions are known to be further involved in cognitive functioning, particularly in the domains of emotional face processing and attention (Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015; Perlman et al., 2013), they again showed significant association with duration of illness. For instance, the rostral ACC and right cuneus – known to be involved in manic and impulsive symptoms (Fornito et al., 2008; Matsuo et al., 2009) and attentional and emotional processing (Delvecchio, Sugranyes, & Frangou, 2013; Haldane, Cunningham, Androutsos, & Frangou, 2008) – showed a pattern of reduced cortical thickness with illness progression, yet the right entorhinal gyrus – known to be

involved with affective lability and symptoms of irritability (Bertocci et al., 2019) – showed increased thickness as a function of illness progression. Interestingly, the authors also reported significant effects of age in BD, such that adolescents and young adults had additional thinning beyond that explained by age or diagnosis alone, further implicating the importance of understanding risk factors for the development and maintenance of mood disorders, facilitated by the identification of biomarkers.

1.3.4 Behavioural outcomes

Along with the mood and cognitive symptoms that characterise the course of mood disorders, behavioural changes are also often reported. For instance, depression is associated with a reduction in physical movement as well as fatigue or loss of energy, while BD mania is characterised by psychomotor agitation and the engagement of purposeless movements, such as pacing (American Psychiatric Association (APA), 2013). In a similar vein, both are associated with disruptions in sleep, be it insomnia or hypersomnia, and together highlight the involvement of circadian rhythms in mood disorders.

When assessing these symptoms experimentally, researchers have often noted changes in the sleep-wake cycle in MDD such that depressed patients experience disrupted and fragmented sleep (Souetre et al., 1988) and lower levels of activity during the day (Burton et al., 2013), thought to be caused by disruptions within the suprachiasmatic nucleus (SCN), or the molecular circadian clock (McClung, 2007). Evidence from BD patients furthers this by also showing an association with a delayed onset of sleep-wake phase, highlighting overall fragmentation of circadian patterns (Nurnberger et al., 2000; Robillard et al., 2014, 2013). While *chapter 4, section 1*

discusses the interplay between mood disorders and circadian rest-activity patterns in more detail, the dynamic nature by which mood disruptions develop across the disorders, particularly in BD marked by changeability in depression and mania, suggests a shared pathophysiological basis. Thus, employing RDoC framework, we are able to hypothesise that disruptions in a neural homeostatic mechanism may be responsible for underlying mood instability and its projections to circadian rest-activity networks.

1.4 Mood instability

1.4.1 Clinical presentation

Mood instability is a significant feature of, and risk factor for, a variety of psychiatric illnesses, particularly mood disorders. Owing to its increased prevalence in psychiatric populations, DSM criteria across a range of disorders have been updated to include this symptom. Whilst the presentation and course of mood instability is discussed in more detail in *chapter 3*, a number of recent studies have begun to explore the prevalence and implications of this phenomenon in clinical populations. Due to the fact that mood instability infers a time-based or temporal course, particular emphasis is often given to its dynamic nature across time. Thus, the importance of mood instability in BD, a disorder characterised by distinct episodic changes in mood, is increasingly noted.

In a study of patients engaging with mental healthcare services over a period of 7 years, Patel and colleagues (2015) reported a mood instability prevalence rate of

12.1%. It was found to be most frequently documented in individuals with BD, but was also common in those with MDD (Thompson, Berenbaum, & Bredemeier, 2011), personality disorders, and schizophrenia. Whilst this is in line with clinical observations and overall prevalence rates reported in other studies (e.g. 13.9% in Marwaha et al., 2013), the empirical assessment of clinician-identified, rather than self-reported, mood instability was also shown to predict worse functional outcomes as measured by a greater number of days spent in hospital, greater frequency of hospitalisation, greater likelihood of compulsory admission, and an increased likelihood of mood stabilising drug treatment. Interestingly, when assessing this relationship with treatment, much of the increased risk of antipsychotic mood stabiliser prescriptions occurred within the first year of follow-up, while the cumulative risk of non-antipsychotic prescriptions increased steadily over the 5-year follow-up period, suggesting the increased need for rapid stabilisation of mood instability. Together, this study provided a formative account of the nature of mood instability in clinical populations, and particularly highlighted the wide-ranging and longitudinal implications it can cause.

Building on this, mood instability is often described as a multi-faceted construct composed of frequent and intense fluctuations in emotion in response to both pleasant and unpleasant events or the interpretation of events (Thompson et al., 2011). This multi-faceted nature allows us to consider its mechanistic value in contributing to illness severity, as is the case in Patel et al. (2015)'s study, as well as its associations with other affective symptoms and thus, its predictive ability to determine the course of illness and potential treatment response. For instance, mood instability is known to be associated with many of the symptoms of depression, including negative affect (Miller, Vachon, & Lynam, 2009) and neuroticism (Miller & Pilkonis, 2006). Given that

depression, and mood disorders more generally, are associated with negative affective biases, it follows then that the symptom of mood instability may be closely linked to this cognitive emotional processing style, and may work to both maintain this bias and present as a consequence of this bias, across time (Kircanski, Joormann, & Gotlib, 2012; Thompson et al., 2011). That is, mood instability may additionally distort the way individuals interact with their environment and make choices, often leading to negative outcomes and stressful life events, further perpetuating overall negative affect and instabilities in mood. This is especially pertinent in conditions such as borderline personality disorder (BPD) which is known to be both characterised by mood instability and associated with interpersonal impairment (Nica & Links, 2009).

When considering mood instability in the context of MDD, it has further been shown to be a marker of illness severity. For example, by assessing mood instability using a measure of affect variability, not only have positive associations between instability and depressive symptoms been reported (Kuppens, Van Mechelen, Nezlek, Dossche, & Timmermans, 2007; McConville & Cooper, 1996), but also that increased levels in changeability in mood were the strongest predictor of MDD diagnosis (Angst, Gamma, & Endrass, 2003). Thompson and colleagues (2011) extended this by showing that in addition to a relationship between mood instability and depressive symptoms, instability significantly predicted anhedonic depression above differences in subjective levels of affect intensity. This is particularly interesting given that affect intensity, or the disposition to experience high levels of both pleasant and unpleasant emotions (Diener, Larsen, Levine, & Emmons, 1985; Larsen & Diener, 1987), has often been associated with depressive symptoms, albeit with small effect sizes and low predictive value (e.g. Mennin, Heimberg, Turk, & Fresco, 2005; Mennin, Holaway, Fresco,

Moore, & Heimberg, 2007; Thorberg & Lyvers, 2006), to a greater degree than mood instability.

However, other studies of mood instability in depression have revealed mixed results, often attributed to differences in the conceptualisation of the phenomenon and thus, in measurement techniques. For instance Golier et al. (2001) found that MDD patients did not show differences in variability between measures of “sad” and “happy”, but instead between items assessing “anxious” and “relaxed”, compared to healthy controls. One particular reason for this is the tendency towards measuring mood instability in a static manner, using an individual construct of positive and negative mood (for example, only between “happy” and “sad”) and thus, losing temporal sensitivity and capturing only a single facet of the wide-ranging experience of mood. Recent developments in longitudinal assessments have been suggested as a method of overcoming these inconsistencies, and to also improve the validity of measures in capturing the temporally changeable, or dynamic, nature of mood instability.

1.4.1.1 Longitudinal remote monitoring of mood

The MONARCA trials (Bardram, Frost, Szántó, & Marcu, 2012; Faurholt-Jepsen et al., 2013, 2014) were developed to do just this, by using objective and subjective smartphone measures of mood and related activity to measure the day-to-day or week-to-week mood instability that is more characteristic of BD than full-blown episodes (Bonsall, Wallace-Hadrill, Geddes, Goodwin, & Holmes, 2012). In their initial study of BD patients in the MONARCA I trial, Faurholt-Jepsen and colleagues (2014) found a significant association between daily electronic self-rated depressive symptoms and scores on the Hamilton Depression Rating Scale (HDRS-17)

(Hamilton, 1967) over a period of three months. This was complemented by preliminary findings of an association between decreasing movement, as measured by the objective number of daily cell tower ID changes made by a device, and depressive symptoms. Whilst no associations between daily self-rated manic symptoms and clinically validated scores were found, the researchers particularly commented on the ability for such a remote and longitudinally monitoring methodology to measure finer-grained mood fluctuations, as is the case in mood instability, and related behavioural patterns which not only characterise changeability in mood, but may also act as both predictors of illness and targets for therapeutic intervention.

Following on from this, the researchers also reported differences in mood instability between BD diagnoses in their larger follow-up trial, MONARCA II (Faurholt-Jepsen et al., 2019). Patients with BD II – known to be associated with frequent episodes of depression and less frequent periods of hypomania – were found to experience greater levels of mood instability during periods of depression, compared to those with BD I – known to be characterised by more significant episodes of mania. Over the course of nine months, daily smartphone self-rated measures of mood were also able to distinguish patients based on manic symptoms, such that those with BD II experienced a lower intensity of these symptoms across time. Whilst no differences in overall mood or intensity of depressive symptoms were found, again indicating that instability in mood may be a more sensitive characteristic of the longitudinal course of mood disorders with characteristic depression, the ability for smartphone devices to collect large-scale, fine-grained, and real-time data reflects an advantageous shift in the study of mood instability.

Given the ubiquity of internet access and remote technologies, as well as the perceived tolerability and compliance with these measurement techniques in patient groups (Bardram et al., 2013), the current thesis presents data collected as part of a longitudinal remote monitoring study of mood and related symptoms using objective and subjective measures (see *chapter 2*). By aiming to more accurately capture the temporally dynamic nature of mood instability, it is hoped that a translational neuroscience model of the related behavioural outcomes and underlying neural mechanisms will be uncovered.

1.4.2 Cognitive affective processing

Little has yet been researched into the relationship between mood instability and the cognitive domains of perception, attention and memory; however, the relationship between mood instability and reward processing has gained recent attention. Owing to the fact that reward-processing differences are particularly noticeable across mood disorders and employ learning, memory and executive functions across time, its relationship with mood instability is of value for the similar reason that mood instability reflects fluctuations in affect across a longitudinal temporal scale. Recent research by Eldar and Niv (2015), for example, has shown a bidirectional relationship between emotional state and the perception and valuation of rewards and outcomes. In their task involving slot machines and an emotion-impacting wheel of fortune (WoF) draw, the researchers found that a large, unexpected outcome in the draw affected both emotional state and subsequent reward perception in the same direction in their group of individuals showing high levels of mood instability. This positive feedback loop, whereby unexpectedly winning a relatively large sum at chance on the WoF draw resulted in a positive bias in mood and subsequent decision-making was not observed

in control participants who otherwise showed stable mood. Utilising computational modelling techniques, the researchers noted how such biasing also worked to result in mood destabilisation, thus proposing mood instability as a result of a disruption in the relationship between emotional state and perception of reward.

Eldar and colleagues (2016) furthered this idea of a bidirectional relationship between mood and reward by proposing that mood is both affected by discrepancies in reward outcomes and expectations, and that mood works to bias the way we perceive outcomes and learn to make decisions based on these outcomes. Therefore, mood is proposed to reflect the "overall momentum of recent outcomes" such that biases work to account for environmental contingencies (Eldar et al., 2016). As demonstrated by Eldar and Niv (2015) above, this interaction can become dysfunctional in the case of mood instability, contributing to the development and maintenance of mood disorders. While the presence of a similar pattern of cognitive and affective processes employing computational modelling techniques has yet to be fully elucidated in MDD and BD, mood instability's standing as a prominent feature of the disorders and the clinical symptoms of anhedonia, hyperhedonia, and mania – implicating changes in reward processing – suggest the importance of this bidirectional relationship. By combining these methods of investigation in mood instability and cases of psychopathology, future research can begin to clarify the particular mechanisms at play that both cut across and differentiate between MDD and BD.

In a recent systematic review of mood instability, Broome et al. (2015) found impairments in cognitive processing reflecting increased distractibility, decreased recognition of and sensitivity to facial expressions, and increased attention towards

highly salient or intense negative facial expressions (e.g. anger and disgust). They also reported increased limbic engagement, particularly in the amygdala, suggesting a similar pattern of behavioural and neural activity to that often reported in MDD and BD. However, the researchers emphasised how the studies to date did not investigate mood instability in isolation, rather as a feature of a psychiatric diagnosis such as attention deficit hyperactivity disorder (ADHD), borderline personality disorder (BPD) or mood disorders, and so it becomes difficult to decipher whether the differences reported are diagnostically specific or relevant to the transdiagnostic phenomenon of mood instability. More recent research such as the study discussed in the current thesis aims to address this by considering mood instability in the prodrome of mood disorders, and should be further considered in combination with clinical groups and healthy controls, in order to fully elucidate the shared and distinct features of cognitive affective processing in mood instability.

1.4.3 Behavioural and neural correlates of mood instability

To my knowledge, there have been no direct empirical investigations of the various behavioural and neural correlates of mood instability. However, based on evidence from studies of mood disorders, mood instability is also expected to be reflected in specific disruptions in circadian rest-activity patterns and neural mechanisms. Whilst these components are discussed and investigated in more detail in *chapter 4*, and *chapters 5* and *6*, respectively, it is hoped that longitudinal remote monitoring of mood will shed light on the related mechanisms of circadian rest-activity behaviour thought to also characterise mood disorders. Similarly, it is then predicted that such a cyclic network of mood and circadian instabilities will be reflected in an underlying disruption in functional connectivity, both between regions known to be implicated in emotional

processing and regulation in MDD and BD, such as the amygdala and insula, and in dynamic mechanisms of whole brain connectivity. Together, it is expected that building such a translational model of mood instability will aid us in capturing the fundamental underlying mechanisms of dysfunction that characterise mood disorders.

1.5 Chapter aims

The current thesis aims to explore the emotional, behavioural, and neural correlates of mood instability, given its recent emergence as a core feature of BD and related mood disorders. Thus, it focuses on the data I collected and analysed from the longitudinal and multi-modal study, COMET (Cognition and Mood Evolution across Time), as part of the wider CONBRIO (Collaborative Oxford Network for Bipolar Research to Improve Outcomes) set of studies.

As highlighted thus far, little is currently understood of the nature of mood instability, outside of its clinical importance. Led by the need to improve clinical outcomes for patients with mood disorders, the overall objective of the current work is to begin to build a profile of the translational neuroscientific nature of mood instability. It is hoped that this advanced understanding will aid in better elucidating the method of action of lithium in BD characterised by persistent mood instability, as well as in developing new and better-tolerated targets for treatment.

In the process of building this profile of mood instability, a number of domains will be addressed: the dynamics of mood instability, behavioural correlates, and neural

underpinnings. By first presenting the COMET study methodology and clinical characteristics, subsequent analyses will target each domain in the following manner:

1.5.1 Identifying mood instability using daily remote monitoring and the Mood Disorder Questionnaire (MDQ): a modern phenotyping tool for mood disorders

(*Chapter 3*)

In order to conceptualise and monitor mood instability in a sub-clinical and medication-naïve sample, I first explore whether remote mood monitoring can capture mood instability longitudinally and in individuals who show dimensions of BD as measured by the Mood Disorder Questionnaire (MDQ).

1.5.2 Circadian rest-activity patterns in mood instability: an actigraph study

(*Chapter 4*)

Using circadian rhythms as a measure of behaviour[1], I aim to explore whether longitudinal actigraphy monitoring can distinguish between high MDQ participants with mood instability and low MDQ participants without mood instability. Additionally, I examine the influence of concurrent changeability in mood on these patterns, such that the dynamics of mood and related behaviours can be captured.

[1] "Behaviour" and "behavioural" is used throughout this thesis to refer to circadian rest-activity patterns (as a measure of behaviour).

1.5.3 Exploring resting-state functional connectivity patterns in mood instability

(*Chapter 5*)

By extending current findings of the neural basis of mood disorders, I am interested in examining the functional connectivity patterns of mood instability. To do this, I am first required to build a profile of whole-brain connectivity that may underlie the distinct mechanisms of mood instability, and its specific associations with emotional processing and regulation regions such as the amygdala and insula.

1.5.4 Dynamic resting-state functional connectivity in mood instability

(*Chapter 6*)

Building on the functional connectivity profile of mood instability established in the previous chapter, I now assess the particular dynamic mechanisms by which nuances in connectivity may be related to the temporally dynamic experience of mood instability. Together, such analyses aim to investigate whether the presence of dynamic functional connectivity patterns underlie the core pathophysiological basis of mood instability and its related behavioural outcomes.

Whilst I am unable to experimentally address the cognitive implications of mood instability in the current thesis, it is hoped that further research (particularly of the cognitive data collected as part of the current COMET study) combined with the review of cognitive affective processing through mood disorders and into mood instability presented thus far, will complement the pathophysiological profile established here.

Ultimately, and in line with RDoC framework, it is expected that mood instability will be reflected in an overarching disruption in neural homeostatic mechanisms that are responsible for regulating mood and related behavioural and cognitive outcomes.

Chapter 2 | Exploring the cognitive neuroscience of mood instability through the Cognition and Mood Evolution across Time (COMET) study: study methodology and sample characteristics

2.1 Background and Rationale

The Cognition and Mood Evolution across Time (COMET) study aimed to explore the potential interaction and neural underpinnings of mood instability and cognitive and behavioural function. Whilst mood instability is known to characterise a number of related mood disorders, this aim is based on a number of observations in BD. Firstly, that the current diagnostic view of the disorder as comprising distinct and discrete episodes of depression and mania, between which mood is normal (euthymia), is misleading. Secondly, that diagnosis is based on retrospective assessment of mood which carries the risk of limited reliability and poor delineation from other mood disorders. Thirdly, that there is evidence for impaired cognition and functioning during euthymia. And finally, that little is understood of the neural underpinnings of the disorder and how current mood stabilising medications such as lithium may work. The combination of these questions has led to a shift in research motivations and approaches to better understand BD, and has ultimately led to the discovery of mood instability as a core characteristic of the disorder.

However, whilst this ‘bottom up’ approach has provided an interesting and more valid understanding of the phenotypic nature of BD, research to date has failed to explore the complexities of this relationship over a longitudinal basis. The emergence of new

technologies and the ubiquity of internet access can address this issue by using high frequency and prospective monitoring. This is particularly important given the dynamic nature of mood instability (Solhan, Trull, Jahng, & Wood, 2009) and the expanding need to understand its underlying neural mechanisms in order to develop new and better-suited targets for treatment (Broome, Saunders, Harrison, & Marwaha, 2015).

Given that emotional and cognitive functions are known to interact continually during perception, decision-making, and memory, mood instability is thought to result as a consequence of disruption in neural homeostatic mechanisms. Additionally, the presence of distinct and cyclic variations in circadian rhythms, determining the nature and functioning of sleep and activity patterns, is thought to also share significant overlap with the oscillating nature of mood instability. Thus, the COMET study aims to investigate whether mood instability develops in response to disruption of these mechanisms to sustain and balance emotional, cognitive, and behavioural functions by giving particular attention to the temporal dynamics that underlie these functions. Identification of this relationship will aid the development of effective experimental medicine interventions to help redress the biases that contribute to mood instability. Using recent evidence that suggests that mood instability is a core predisposing factor in BD and also MDD, results ultimately aim to transform the current understanding and treatment of mood disorders.

Whilst the current chapter aims to outline the particular methods of investigation employed in the longitudinal and exploratory COMET study, as well as present results from screening and clinical assessments, subsequent chapters will further explore and unpack the distinct affective, behavioural, and neural data that are collected. By first

providing this methodological overview, it is hoped that a broad profile of mood instability is built in order to highlight both its translational importance across the fields of psychiatry and neuroscience, and to further support its placing as a transdiagnostic marker across mood disorders. Owing also to the novel nature of such temporally dynamic investigation, subsequent analyses and discussions will refer back to this broader picture so that a more conclusive evaluation of mood instability and its potential avenues for therapeutic intervention can be drawn.

2.2 Methods

2.2.1 Participants

Seventy-four participants completed the COMET study. Of these participants, 37 showed dimensions of BD by screening in on the Mood Disorder Questionnaire (MDQ) ("high MDQ" group) (MDQ≥7) and 37 were age and gender matched, but did not screen in on the MDQ ("low MDQ" group) (MDQ≤5). A further 7 participants screened out (*n*=2) or withdrew (*n*=5).

All participants gave their written informed consent and were compensated for their participation. The study was approved by the Central University Research Ethics Committee of the University of Oxford (MSD-IDREC-C2-2014-023).

2.2.1.1 The Mood Disorder Questionnaire (MDQ)

The MDQ[2] (Hirschfeld et al., 2000) has been identified as a sensitive and specific screening tool for BD in both outpatient populations (Hirschfeld et al., 2000) and in the general population (Hirschfeld et al., 2003). Answering "yes" to seven or more items assessing mood-related experiences in question 1 of the MDQ and indicating that a combination of these feelings and experiences had happened during the same period of time in question 2, identified participants in the high MDQ group. The cut-off used for the high MDQ group (MDQ≥7) is in line with the clinical use of the MDQ for

[2] A copy of the MDQ is included in *appendix 2.1*.

questions 1 and 2 only, in order to ensure a sensitivity rating of 0.73 and specificity of 0.90 (Hirschfeld et al., 2000). Participants who answered “yes” to five or fewer items in question 1 met criteria for the low MDQ group. Responses to the third, and final, question of the MDQ, assessing functional impact, were not included.

2.2.1.2 Inclusion/Exclusion Criteria

Participants were invited to take part in the study based on their MDQ score and subsequent group assignment. Participants were excluded if they had a contraindication to MRI or MEG, history of current axis I psychiatric illness (excluding BD I or II, major depressive disorder (MDD), and anxiety disorder in the high MDQ group), history or current neurological condition, and first degree relative with BD. Exclusion criteria also included currently using (or had done so in the past 6 weeks) lithium, antidepressant, antipsychotic, or anticonvulsant medication; and current substance abuse.

2.2.1.3 Recruitment

All participants were recruited by university or community-wide advertisements. After registering initial interest, they were directed to an online screening form (conducted using the Qualtrics platform (Qualtrics, Provo, UT, USA)), which included the MDQ, MRI screening questionnaire, and several questions pertaining to demographics and current or past psychiatric health. All individuals who completed the screening questionnaire then received an email from the researchers with one of four outcomes: (a) they were invited into the study as a member of the high MDQ group, (b) they were invited into the study as a member of the low MDQ group, (c) they had been placed

on the waiting list of low MDQ group participants, (d) they were ineligible for the study. All screening data collected at this point were kept on a secure database only accessible by the study researchers.

2.2.2 Design

The COMET study was a prospective, between-subjects experimental cohort study of the temporal relationship between mood instability and behavioural, neural, and cognitive functioning using a range of objective and subjective measures.

2.2.3 Equipment and Data Management

A range of technology was used in the study, including remote monitoring and wearable devices. All participants were provided with study Apple iPads (Apple, Cupertino, CA, USA) to be used throughout the 10-week study period. Participants were also required to wear wrist-worn GENEActiv accelerometers (www.activinsights.com/products/geneactiv; ActivInsights Ltd, Kimbolton, Cambridgeshire, UK).

Participants were required to complete daily iPad testing on a study specific website (www.comet.psych.ox.ac.uk/comet) that could only be accessed with a unique participant username and password. All data collected through this website were uploaded and stored on a secure university-housed server that only study researchers had access to. Actigraphy data collected on the GENEActiv watches were stored on the device when worn and extracted onto secure storage drives by the researchers upon their return.

2.2.4 Procedure

All participants took part in the study for a 10-week period. Within this period, they attended a number of research visits. This included an initial baseline visit, two MRI and (where possible) two MEG scans; two GENEActiv "watch swap" visits, and a final visit for the end of study and return of devices[3].

As well as these research visits, participants were asked to complete short cognitive and mood assessment tasks for 5 days per week during the 10-week study period. These tasks were accessed and completed on an iPad (provided at the baseline visit) using the specialised testing website and took no longer than 15 minutes to complete. They were also asked to wear the GENEActiv actigraph throughout this period.

In addition, participants were required to answer a set of four clinical self-monitoring questionnaires as part of the online True Colours (www.truecolours.nhs.uk; True Colours, Department of Psychiatry, University of Oxford, Oxford, UK) system, once a week for the 10-week study period.

2.2.4.1 Baseline Visit

Based on their responses on the online MDQ screening questionnaire, eligibility was determined and those that met criteria were invited in for a baseline visit. During this visit, participants had the opportunity to discuss the information sheet and ask further questions. Researchers then sought written informed consent. All participants took

[3] Study flow chart can be found in *appendix 2.2.*

part in an individual SCID I assessment, conducted either by the study psychiatrist if in the high MDQ group, or research assistant if in the low MDQ group. All participants also completed a number of self-report screening questionnaires assessing trait mood lability using the Affective Lability Scale (ALS-SF) (Oliver & Simons, 2004); mood intensity using the Affect Intensity Measure (AIM) (Larsen, 1984); impulsivity using the Barratt Impulsiveness Scale (BIS-II) (Patton, Stanford, & Barratt, 1995); sleep using the Sleep Condition Indicator (SCI-R) (Espie et al., 2014); and a screening tool for borderline personality disorder (BPD), the McLean Screening Instrument for BPD (Zanarini et al., 2003)[4].

During this visit, participants were also fitted with a GENEActiv accelerometer, and completed the emotional version of the Theory of Visual Attention (Bundesen, 1990, 1998) task (emoTVA) on a study computer. Participants were then set up with their own unique access credentials to the study website, and researchers ran a demo version of the iPad tasks for the participants to get accustomed to. Furthermore, all participants were signed up for an online True Colours account in order to complete weekly questionnaires.

Participants were then set to complete their daily and weekly tasks remotely.

2.2.4.2 Daily Mood Assessment

Before accessing their daily cognitive tasks, participants were asked to complete the International Positive and Negative Affect Scale, Short Form (I-PANAS-SF)

[4] A copy of the screening questionnaires can be found in *appendix 2.3*.

(Thompson, 2007). Here they were required to rate the extent to which they experienced 10 emotions on a 5- point likert scale ranging from “very slightly/not at all” to “extremely”. Participants were asked to answer this in relation to the last 24 hours, or since they had last completed the questionnaire. The I-PANAS-SF scale measured positive affect using the words “alert”, “attentive”, “active”, “determined” and “inspired”, and negative affect using “afraid”, “ashamed”, “hostile”, “nervous” and “upset”[5].

Participants also rated their current mood on a short happiness scale before and after each of the four cognitive tasks (i.e., 5 ratings per session). This was a 21-point scale ranging from unhappy (-10), through neutral (0), to happy (10)[6].

2.2.4.3 Daily Life Events Recording

Following the completion of the I-PANAS-SF scale, participants also completed a life events questionnaire using the Oxford Life Events Questionnaire (OxLeq) measure, adapted from the Life Events Questionnaire (LEQ) (Norbeck, 1984; Sarason, Johnson, & Siegel, 1978) by Dr. Amy Bilderbeck and Professor Guy Goodwin at the Department of Psychiatry, University of Oxford. This questionnaire allowed recording of both medical and non-medical life events. In the former category, participants were able to note changes in medical care including hospitalisations and medication alterations (not expected to be applicable in the COMET study but included for the joint use in a related clinical trial, OxLith (Saunders et al., 2016)). In the latter category, participants were able to record life events in a number of sub-categories (e.g., work, relationship, home) and indicate whether these had a positive or negative effect on their wellbeing,

[5] A screenshot of the I-PANAS-SF scale can be found in *appendix 2.4*.
[6] A screenshot of the happiness scale can be found in *appendix 2.5*.

as well as the strength of this effect. Completion of the OxLeq was voluntary on a day-to-day basis[7].

2.2.4.4 Weekly Mood Assessment

Participants were also required to answer a set of four self-monitoring questionnaires as part of the online True Colours system, once a week for the 10-week study period. These questionnaires assessed mood depression using the standardised clinical scale QIDS (Quick Inventory of Depressive Symptomatology) (Rush et al., 2003), mood elevation using the clinical scale ASRM (Altman Self-Reporting Mania scale) (Altman, Hedeker, Peterson, & Davis, 1997), quality of life using the EQ-5D measure (EuroQol Group, 1990), and anxiety using the GAD-7 measure (Generalised Anxiety Disorder questionnaire) (Spitzer, Kroenke, Williams, & Lo, 2006)[8].

Data collected through this system were stored on a secure sever created by the University of Oxford and Oxford Health NHS Foundation Trust. Researchers were able to access the data using a secure researcher account on the online system, and participants were able to track their weekly scores on the online interface.

2.2.4.5 Actigraphy Monitoring

Participants were requested to wear the GENEActiv accelerometers 24 hours per day for the duration of the study. These wrist-worn devices recorded body temperature, light levels, and activity at a 25hz recording rate. Due to the fact that each device only

[7] A copy of the OxLeq questionnaire can be found in *appendix 2.6*.
[8] A copy of the True Colours questionnaires can be found in *appendix 2.7*.

recorded data for 28 days at a time, participants attended two short “watch swap” visits in order to return the full device and be fitted with a new one. Devices were completely waterproof, and participants were asked to wear them continuously, including when bathing and sleeping.

2.2.4.6 Daily Cognitive Tasks

Following the mood assessment, participants completed four cognitive tasks, masked as mini-games and adapted for the iPad. These tasks measured a range of cognitive functions, including decision-making and reward processing (“Wheel of Fortune”), reward processing and environmental learning (“Fractals”), performance learning (“Guess the Gap”), and contextual cueing (“Whack-a-T”). All tasks were completed in a random order. As this data was not analysed in the current thesis, please see appendix 2.8 for further details of the cognitive tasks.

2.2.4.7 Neuroimaging Data

Where possible, Magnetic Resonance Imaging (MRI) and Magnetoencephalography (MEG) scans were conducted. Participants completed two sets of scans, typically between weeks 1 and 2, and again between weeks 9 and 10.

2.2.4.7.1 MRI

Scanning was performed at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR), John Radcliffe Hospital, University of Oxford, using a 3-Tesla Siemens TIM Trio Scanner (Siemens Medical Solutions, Bracknell, UK) with a 32-channel head-coil.

At both time points, structural and functional scans were conducted in the following order:

	Scan 1 (weeks 1-2)	Scan 2 (weeks 9-10)
1	Resting-state fMRI scan	Resting-state fMRI scan
2	Task fMRI: "Wheel of Fortune"	Task fMRI: "Guess the Gap"
3	Structural scan	Structural scan
4	Diffusion Tensor Imaging (DTI) scan	Task fMRI: "Fractals"
5	FLAIR (Fluid-Attenuated Inversion Recovery) scan	

Table 1: Scan procedure. Scan sequences conducted during both MRI (and MEG, excluding DTI and FLAIR) scans are shown. All tasks were adapted for scanner presentation.

Table 2 shows the neuroimaging protocol for each of the MRI sequences used.

Scan	Protocol
Structural	T1-weighted images, TR = 3000ms, TE = 4.71ms, flip angle = 8°, field of view = 256mm, voxel dimension = 1mm isotropic, acquisition time = 8 mins 48s.
Resting-state fMRI	Gradient-echo EPI sequence, TR = 2000ms, TE = 28ms, flip angle = 89°, field of view = 192mm, voxel dimension = 3.0 x 3.0 x 3.5mm, 180 volumes, acquisition time = 6 mins 04s.
Task fMRI	Deichman, TR = 3000ms, TE = 30ms, flip angle = 87°, field of view = 192mm, voxel dimension = 3mm isotropic, 2000 volumes, acquisition time: up to 1 hour 40 mins 06s.
Diffusion Tensor Imaging (DTI)	TR = 89000ms, TE = 94.8ms, field of view = 192mm, voxel dimension = 2mm isotropic, b-value = 1500 s/mm^2 (0 s/mm^2), acquisition time = 9 mins 56s (36s).
FLAIR (Fluid-Attenuated Inversion Recovery)	Axial T2-weighted images, TR = 9000ms, TE = 90ms, flip angle = 150°, field of view = 220mm, voxel dimension = 1.1 x 0.9 x 3.0mm, acquisition time = 5 mins 08s.

Table 2: MRI neuroimaging protocol.

This thesis includes analyses of the resting-state fMRI data collected. Please see *chapters 5 and 6* for further details of the resting-state fMRI and structural scans used.

2.2.4.7.2 MEG

MEG images were acquired using a passively shielded Elekta Neuromag 306-channel scanner (204 planar gradiometers and 102 magnetometers) (Elekta, Stockholm, Sweden) at the Oxford Centre for Human Brain Activity (OHBA), University of Oxford. A similar set of sequences were conducted to that of the MRI scans (excluding DTI and FLAIR) (see table 1). Due to MEG scanner downtime, only the first four participants and the latter twenty participants received MEG scans.

2.3 Results: Sample Characteristics

2.3.1 Demographic Data

Demographic data from all 74 participants are shown in table 3 below. All participants were age and gender matched and differed on their MDQ scores (fig. 1).

	High MDQ (*n*=37)	Low MDQ (*n*=37)	*p*
Age *[mean (SD)]*	24.65 (7.02)	25.00 (6.61)	.825
Age *[range]*	18-46	18-49	
Gender *[m:f]*	13:24	13:24	1.00
MDQ **[q.1]** *[mean (SD)]*	9.32 (1.65)	1.11 (1.31)	

Table 3: Demographic data. Means are shown for age and MDQ, with spread of data (standard deviation) in parentheses.

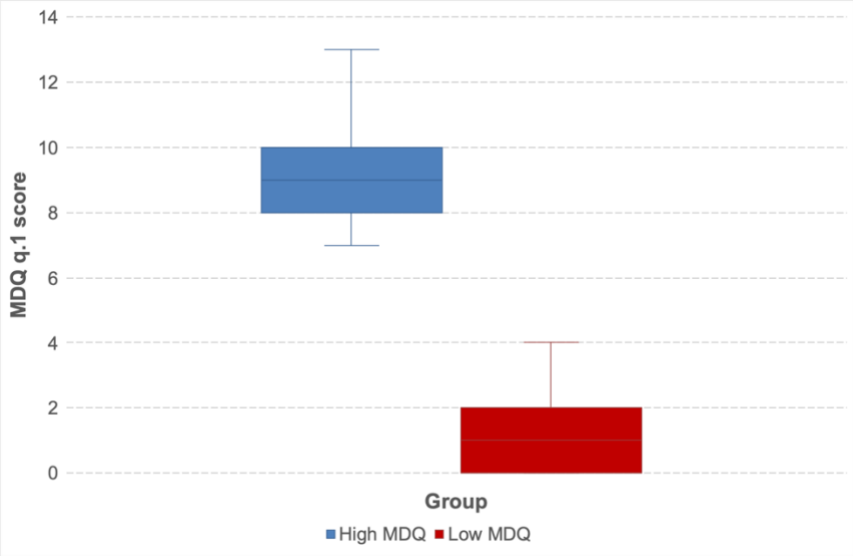


Figure 1: MDQ score. Responses to question 1, assessing mania and hypomania symptoms are shown.

2.3.2 SCID Assessment Results

Outcomes from the SCID I assessment in high MDQ participants are shown below in table 4. No participant in the low MDQ group met criteria for an axis I or II disorder as measured by the SCID.

BD NOS	BD II	MDD	Past Alcohol Dependence	Past Panic Disorder	PTSD
2	2	6	2	0	1

Table 4: SCID results in High MDQ group. Number of participants meeting diagnostic criteria are shown. BD NOS = bipolar disorder, not otherwise specified. MDD = major depressive disorder. PTSD = post-traumatic stress disorder.

A number of comorbidities were identified by the research psychiatrist. One participant with BD NOS also met criteria for past alcohol dependence, one participant with MDD met criteria for PTSD, another participant with BD II also met criteria for MDD, and one participant with MDD met criteria for past alcohol dependence.

2.3.3 Screening Measures

Results for all participants on the five screening questionnaires are presented in table 5, below.

		High MDQ	Low MDQ	*p*
AIM		148.19 (24.68)	134.08 (27.56)	.023*
ALS-SF	**Total**	40.54 (11.20)	22.41 (4.95)	<.001***
	Anxiety/Depression	11.41 (4.02)	6.11 (1.58)	<.001***
	Depression/Elation	20.38 (6.03)	10.90 (3.18)	<.001***
	Anger	8.76 (3.52)	5.41 (1.04)	<.001***
McLean Screen for BPD		3.59 (2.28)	0.27 (.61)	<.001***
SCI-R		6.28 (2.25)	8.12 (1.73)	<.001***
BIS-II	**Total**	110.19 (17.63)	94.11 (14.05)	<.001***
	Attentional	19.14 (4.28)	14.89 (3.78)	<.001***
	Motor	23.32 (4.04)	20.95 (3.19)	.006**
	Nonplanning	25.27 (5.55)	22.43 (3.98)	.014*

Table 5: Screening questionnaire results. Means are shown with spread of data (standard deviation) in parentheses. AIM = Affect Intensity Measure. ALS-SF = Affective Lability Scale, Short Form. SCI-R = Sleep Condition Indicator, Revised. BIS-II = Barratt Impulsiveness Scale. * $p < .05$, ** $p < .01$, *** $p < .001$

2.3.3.1 Affect Intensity

As demonstrated by table 5 and figure 2, participants in the high MDQ group had significantly more intense affect ($t(72) = 2.32$, $p = .023$).

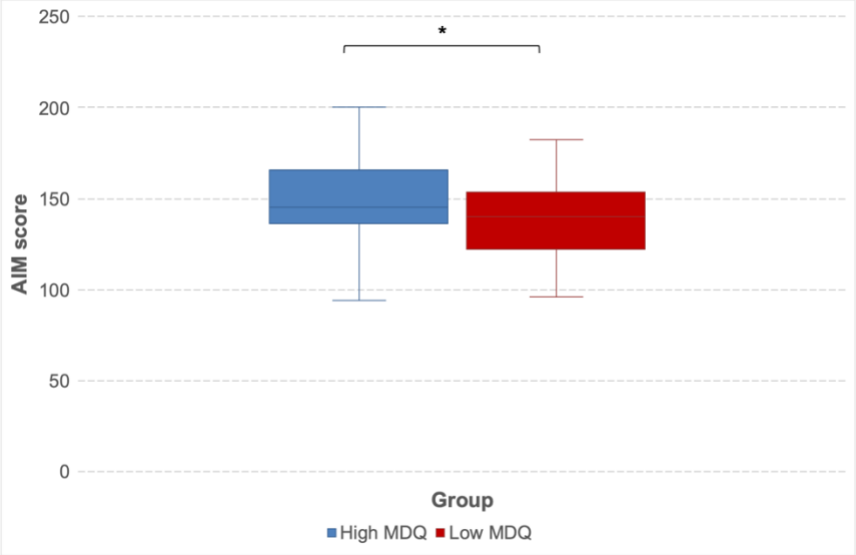


Figure 2: Affect Intensity measure results. Box plot showing median AIM response and spread of data. * $p < .05$

2.3.3.2 Affective Lability

Adding to this, high MDQ participants also had significantly higher self-reported levels of changeability in mood as measured by the ALS-SF (fig. 3) ($t(72) = 9.01$, $p < .001$), and this was seen across the domains of lability between anxiety and depression ($t(72) = 7.47$, $p < .001$), depression and elation ($t(72) = 8.47$, $p < .001$), and anger ($t(72) = 5.56$, $p < .001$) (fig. 4).

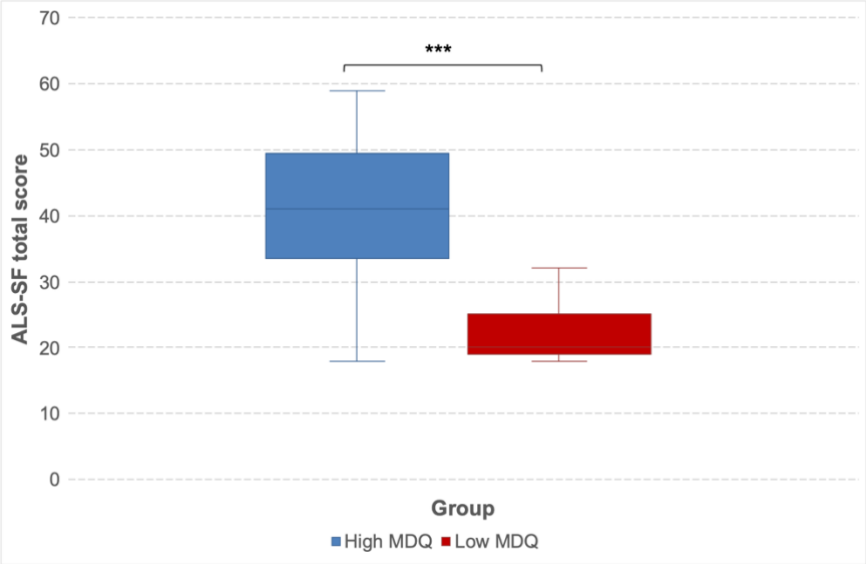


Figure 4: Total Affective Lability Scale measure results. Box plot showing median ALS-SF response and spread of data. *** p < .001

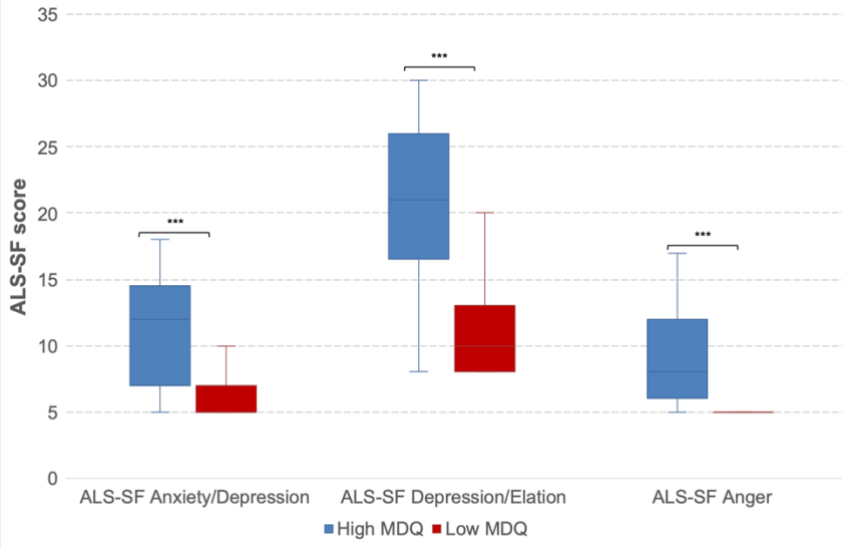


Figure 3: Affective Lability Scale results broken down by domain. Box plot showing medians and spread of data across anxiety/depression, depression/elation, and anger domains. *** p < .001

2.3.3.3 McLean Screening Instrument for Borderline Personality Disorder

Participants in the high MDQ group had significantly greater scores on the McLean Screening Instrument for BPD ($t(72) = 8.57$, $p < .001$) (fig. 5). However, only four participants in the high MDQ group screened in on this measure (scoring ≥7).

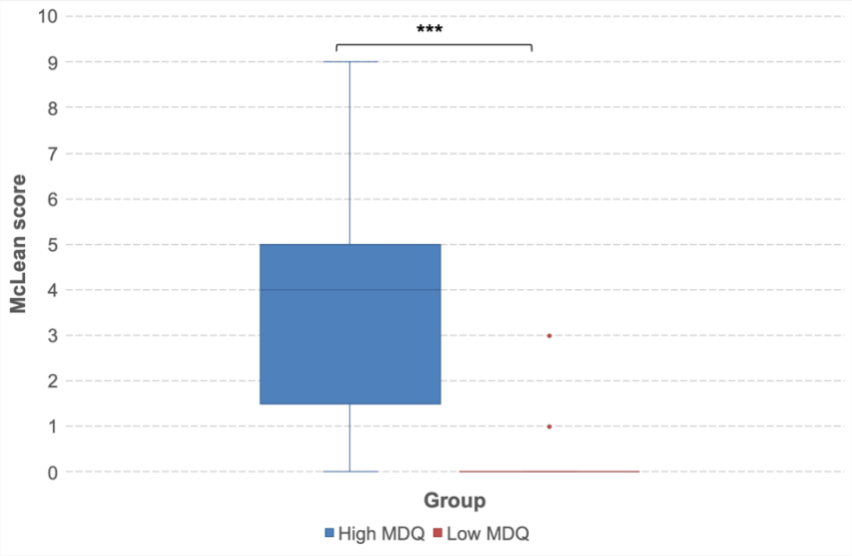


Figure 5: McLean Screening Instrument for BPD. Box plot showing median and spread of responses to the screening tool for BPD. *** p < .001

2.3.3.4 Sleep

Similarly, high MDQ participants reported significantly poorer sleep condition than low MDQ participants on the SCI-R ($t(72 = 3.93$, $p < .001$) (fig. 6), although only two participants in this group screened in for a sleep disorder (adjusted score ≤2).

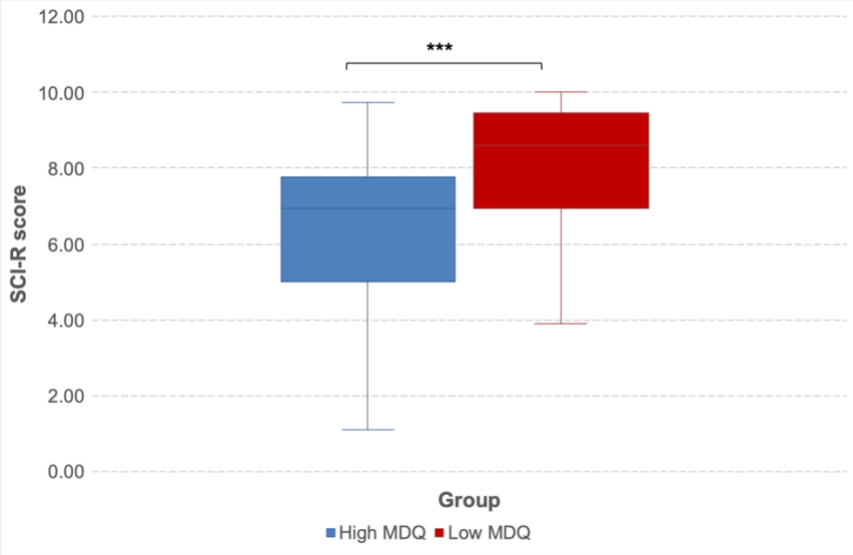


Figure 6: Sleep Condition Indicator. Box plot showing median and spread of responses for this measure of sleep.

*** $p < .001$

2.3.3.5 Impulsiveness

High MDQ participants had higher levels of self-reported impulsivity as measured by the BIS-II ($t(72) = 4.34$, $p < .001$) (fig. 7), and this was seen across the domains of attention ($t(72) = 4.52$, $p < .001$), motor ($t(72) = 2.81$, $p < .006$), and non-planning ($t(72) = 2.53$, $p < .014$) (fig. 8).

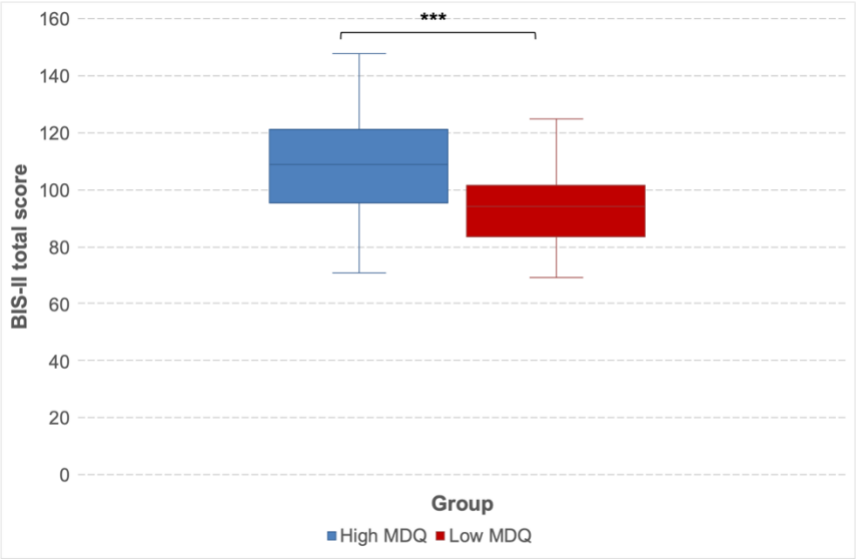


Figure 7: Total Barratt Impulsiveness Scale results. Box plot showing median and spread of responses on this measure.

*** p < .001

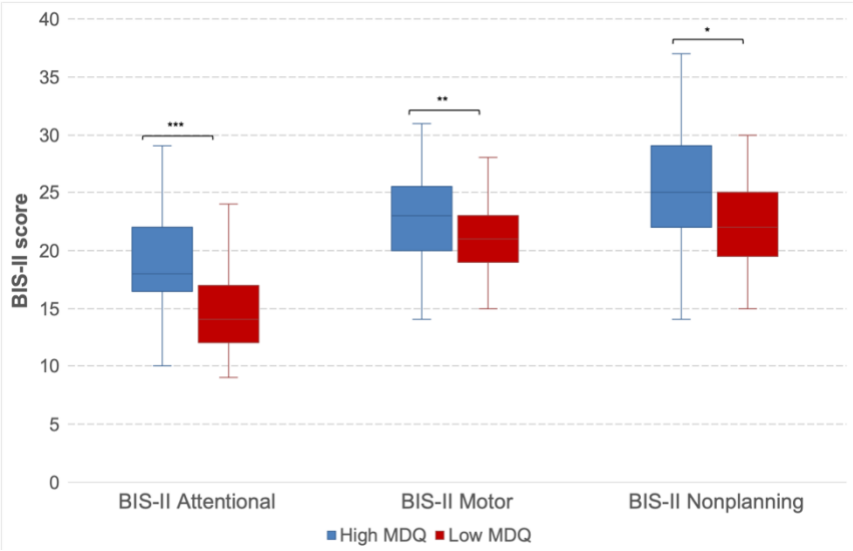


Figure 8: Barratt Impulsiveness Scale results broken down by domains. Box plot showing medians and spread of data across the attentional, motor, and non-planning domains.

* *p* < .05, ** *p* < .01, *** *p* < .001

2.4 Discussion

2.4.1 The COMET Study

The COMET study aimed to investigate mood instability in a sample of volunteers distinguished by their responses on the MDQ, a common screening tool for BD. Participants who were in the high MDQ group reported experiencing more intense moods, and were more changeable between moods than those in the low MDQ group. These self-reported experiences, particularly in mood changeability, are important to recognise given the wider aim of identifying and exploring mood instability, or short and rapid fluctuations in mood, in this sample. It is hypothesised that this subjective trait marker of mood instability can be detected on a more objective daily measure of mood over a 10-week time scale, and that this longitudinal analysis will aid us in investigating concurrent changes in behavioural, cognitive, and neural states.

Secondary to trait mood markers, it was also observed that high MDQ participants self-reported poorer sleep and greater levels of impulsiveness. Whilst this begins to suggest a profile of disrupted and maladaptive behaviour that is similar to that seen during the course of mood disorders, it is expected that longitudinal monitoring of these symptoms will also shed light on the particular mechanisms by which mood instability presents and sustains across time. Thus, further examination of these behavioural markers, along with mood symptoms and neural connectivity, is able to inform us of the distinct mechanisms of mood instability that may result in depressive and manic symptoms, as well as the associated instabilities that may predict and define functional

outcome. Such consideration can both transform our understanding of mood instability and help us to better target therapeutic interventions in mood disorders.

2.4.2 COMET Sample Limitations

Despite the strengths of the study design in enabling the investigation of the longitudinal and multi-modal correlates of mood instability, a number of limitations are noted and should be considered in the critical appraisal of current findings. Firstly, whilst the clinical use of the MDQ aims to aid in determining individuals at risk for BD, it is known that the onset of the disorder most commonly occurs in late adolescence and early adulthood (Baldessarini et al., 2012). Given the wider age range of participants in the current high MDQ group, this presents difficulties in determining the nature of risk, both in determining those who are at risk to mood disorders and experiencing subclinical levels of mood symptoms, and those who may be experiencing distinct changes in mood outside of a propensity to develop mood disorders. This is especially pertinent when considering age, in a similar manner to gender and cultural influences on mood and mood reporting. For instance, age and age-related beliefs and attitudes, particularly those of stoicism and cautiousness, are known to mediate the reporting of mood disturbance (Yong, 2006), suggesting that this caveat of the sample – both in determining their risk of developing mood disorders and in understanding the severity of self-reported mood change – may bear important implications for the longitudinal monitoring of mood instability. Although this potential effect of age is not further investigated or accounted for in subsequent analyses, future research could consider this interaction by focussing on age in the future analysis of COMET data, particularly by investigating the potential influence of mood-related

environmental or contextual differences as provided by the concurrent recording of life events (OxLeq data), as well as conducting future follow-up studies targeted at exploring the age-dependent and longitudinal risk of mood instability and mood disorders.

In a similar manner, the presence of those with and without a clinical DSM-IV axis I diagnosis in the high MDQ group, as well as the exclusion of those with a family history of BD, can present altering streams of investigation. Therefore, it may be that the nature of mood instability differs to varying degrees in individuals distinguished by such characteristics, for example in those who meet criteria for BD, MDD, and those who do not; changes with age, particularly those surpassing the critical period of adolescence and early adulthood; and also, those that come with the genetic predisposition to develop BD through family history. Whilst the current study is unable to account for the nuances in mood instability that may present as a consequence of these characteristic differences, future follow-on studies could aim to disentangle the similarities and differences in the affective, behavioural, and neural trajectories that may develop.

The current study utilised the clinically validated cut-offs of the MDQ to differentiate participants based on their risk propensity to develop BD. While the MDQ is known as a sensitive and specific tool for the screening of BD (Hirschfeld et al., 2000), there are a number of points to consider in its use for the investigation of mood instability. Firstly, the current methodology assumes that there is a relationship between a positive MDQ screen, or confirmation of risk for BD, and the presence of mood instability. Whilst it is known that mood instability is a core characteristic of BD, employing a more

continuous approach to the consideration of MDQ scores, rather than as a categorical variable, may have allowed for a more nuanced consideration of the relationship between BD symptomatology or phenotype, rather than risk, and mood instability. This is especially pertinent given that the majority of those who screened in on the MDQ (the high MDQ group) did not meet DSM criteria. Secondly, in order to more sensitively understand the transdiagnostic nature of mood instability, using responses to a self-report mood changeability scale, such as the Affect Lability Scale (ALS) (Oliver & Simons, 2004), as a method to distinguish the sample instead of the MDQ, may have aided in better capturing the phenotypic nature of mood instability, outside of the confounds of a risk propensity to develop BD. Whilst this was not possible given the wider aims of the grant which supported this study, results from future studies employing such varied methodologies could help shed further light on the trajectories of mood instability that may follow in subclinical and clinical populations, including those with BD and MDD.

2.4.3 Current Research Questions

Given the breadth of data collected as part of this exploratory study during my doctoral studies, it is important for me to select and tailor my research questions and analyses to a subset of the data at hand, whilst also recognising its part in the wider story. To this end, I am particularly interested in understanding the nature of mood instability. What is mood instability? How does it present over time and how can we measure it? Who experiences mood instability? Given that we know of it as a core feature of BD, can we use a measure for BD to distinguish those who experience mood instability, and does this predict the onset of disorder?

Delving into this further in order to better elucidate its phenotypic nature, is mood instability reflected in behavioural markers, such as circadian rhythms, or neural instabilities? What can this tell us about the temporal scale of such changes given the dynamic process of mood instability?

In order to answer these questions, I present analyses of mood, behavioural, and neural data from the COMET study in subsequent chapters. I start by investigating the longitudinal mood data collected to detect mood instability, and then go on to explore differences in circadian rest-activity patterns as a potential behavioural correlate. This is followed by an examination of neuroimaging data in order to study the related neural mechanisms at play during rest and what they may tell us about the neural underpinnings and dynamics of mood instability. In particular, neural data will be analysed in a number of ways in order to both identify and determine the functional networks that subserve mood instability, and to explore the dynamic properties of this activity across time. It is hoped that this combined analysis of functional and dynamic properties in the clinical, behavioural, and neural representation of mood instability will aid us in building a better understood profile that can ultimately inform clinical practice and therapeutic intervention.

Chapter 3 | Identifying mood instability using daily remote monitoring and the Mood Disorder Questionnaire (MDQ): a modern phenotyping tool for mood disorders

3.1 Introduction

Mood instability – or rapid oscillations of intense affect, with difficulty in regulating these oscillations or their behavioural consequences (Marwaha, Parsons, & Broome, 2013) – is a prominent feature of a range of psychiatric disorders, particularly BD. Mood instability has been highlighted as a risk factor for the development of BD and is thought to characterise its longitudinal course (Henry et al., 2001). Whilst the clinical significance of this instability is now recognised – owing to its inclusion in the DSM criteria (American Psychiatric Association (APA), 2013) for BD and various mood and related disorders, and its association with comorbid difficulties such as alcohol misuse, neurotic symptoms, and suicidal ideation (Marwaha, Parsons, Flanagan, et al., 2013) – little is understood of the behavioural and cognitive implications and underlying neural mechanisms of mood instability. Its position as a transdiagnostic tool, nevertheless, can aid us in better understanding the intricacies of related mood disorders, as well as highlight the importance of a dynamic, or temporal, basis across which such disorders develop and progress.

Whilst mood experiences, such as intensity and valence, are particularly noteworthy symptoms in a range of disorders, the experience of mood instability has only recently been considered under this classification. Nevertheless, its significance across a

range of disorders has been reported, from BD and MDD, to post-traumatic stress disorder (PTSD) and borderline personality disorder (BPD) (Marwaha, Parsons, Flanagan, et al., 2013). In addition to being symptoms of such disorders, numerous studies have also begun to highlight how mood instability may aid in differentiating between such disorders, such that patients with BPD, for example, have been shown to have greater instability in relation to positive and negative affect and distress (Ebner-Priemer et al., 2007) than those with major depression (Trull et al., 2008), who in turn display a pattern of changeability in positive and negative affect that is associated with the day-night cycle compared to healthy controls (Peeters, Berkhof, Delespaul, Rottenberg, & Nicolson, 2006).

Building on this, the significance of mood instability as a risk factor across these disorders has also been reported. Further emphasising the diagnostic overlap of BD with MDD and BPD, studies have shown that some of the earliest signs of illness present as mood swings and episodic changes in mood (Chanen et al., 2008; Correll et al., 2007). Such difficulties, particularly in regulating mood, are often also seen in children who go on to develop mood and anxiety disorders (Stringaris, Cohen, Pine, & Leibenluft, 2009), further supporting its predictive nature. Taken together, increasing evidence has pointed to the clinical significance of mood instability as a characterising, differentiating, and predictive feature of a range of mood disorders. However, little is understood of its wider significance, both in terms of the mechanisms by which it develops in the wider population (as a risk factor) and the relationship it has with other physiological homeostatic mechanisms (as a symptom). A better understanding of these processes can aid us in developing more rigorous conclusions grounded in scientific backing in order to begin to consider mood instability as a potential target for

treatment. Arguably the disorder in which mood instability is most prominent, an exploration of mood instability in BD is beginning to do just this, by transforming and further developing our understanding of this otherwise heterogenous disorder.

Ongoing mood instability, as opposed to distinct episodes of depression and mania is now established as the hallmark of BD (Henry et al., 2008; MacQueen et al., 2003). This is particularly important given the shortcomings of current treatment options, such as that of lithium, which remains the first-line pharmacological treatment of the disorder but with limited efficacy. Whilst it aims to target distinct episodes in order to prevent relapse (Goodwin, 2003), a growing body of evidence suggest that the majority of patients remain both symptomatic between episodes and at a high risk for relapse (MacQueen et al., 2003). Given the limitations of lithium treatment and other pharmacological and psychological treatment options and their over-reliance on targeting distinct mood episodes, the case for further exploring the phenomenon of mood instability is strengthened. This is particularly important given the relatively infrequent experience of distinct mood episodes – especially that of mania or hypomania – and the observation that euthymic periods are far more consistently characterised by significant sub-threshold mood swings over day-to-day or week-to-week periods (see

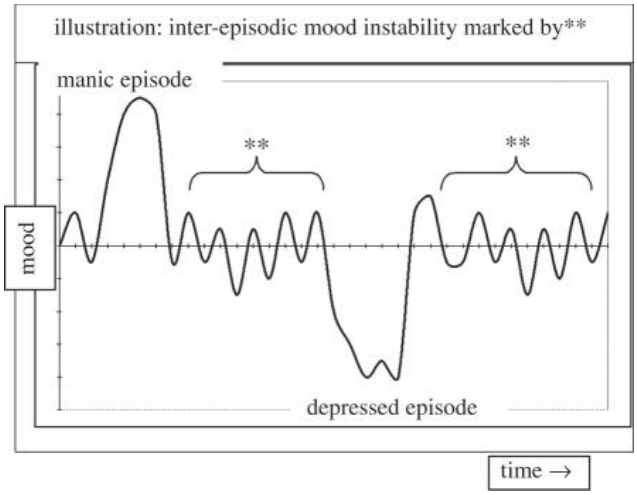


Figure 9: A diagram of the course of BD. Period of mood instability are shown in between distinct episodes of depression and mania. Reproduced from Bonsall et al. (2012).

fig. 9). Thus, it is this more frequent experience of mood instability, which lends itself to functional impairment, that has been suggested as a novel target for treatment (Bonsall et al., 2012; Johnson, 2005; Scott & Colom, 2008).

In order to further illuminate the patterns of mood instability seen in BD patients, Bonsall et al. (2012) followed "stable" and "unstable" patients using high-frequency prospective automated monitoring, via the True Colours system (www.truecolours.nhs.uk) (True Colours Team Department of Psychiatry University of Oxford) over a period of up to four years. Interestingly, they found a complex pattern of dynamic mood changeability in unstable patients, suggesting that the time series of instability was highly non-linear. They suggested that identification of this non-linear approach, where a patient's predicted mood can differ above or below their mean mood score on a week-to-week scale, could aid in better understanding the course of their illness. This pattern of distinct dynamic and non-linear instability seemed to not only show distinct deviation from stability, but also suggested a relationship with regular periodic cyclic patterns (such as in the case of circadian rhythms), and irregular aperiodic or chaotic patterns. It is these chaotic patterns that are thought to be more representative of mood instability in BD, particularly given that self-reported mood assessments have been shown to follow this aperiodic pattern (Gottschalk, Bauer, & Whybrow, 1995), and that complex physiological processes are also thought to be associated with such dynamics. Therefore, if mood instability is the phenotypic representation of such chaotic and aperiodic dynamics, the underlying neural mechanisms, as well as associated behavioural dynamics, of this pattern remain to be uncovered.

A consideration of mood instability outside of particular diagnoses or disorders provides a stringent method of analysing these complex dynamics. As well as being a feature of BD and other related disorders, mood instability has a prevalence of 13.9% in the general population (Marwaha, Parsons, Flanagan, et al., 2013). It is more commonly reported in women in early adulthood and also shares many of the sociodemographic features of psychiatric disorders such as BD, MDD, and anxiety disorders, for example higher levels of unemployment and lower marital rates. In Marwaha et al.'s (2013) study of mood instability in the general population, they found strong associations between instability and symptoms of non-psychotic psychopathologies, as well as increased suicidal thinking and healthcare service use. Thus, considering that mood instability is fairly common in the general population and presents with significant social and vocational difficulties not dissimilar to those with a diagnosis, suggests that we may be able to better explore its associated dynamics in subclinical, medication-naïve populations.

The Mood Disorder Questionnaire (MDQ) (Hirschfeld et al., 2000) has been identified as a sensitive and specific screening tool for BD in both outpatient populations (Hirschfeld et al., 2000) and in the general population (Hirschfeld et al., 2003). Considering the fact that mood instability is a core feature of BD and has a population prevalence rate of 13.9% (Marwaha, Parsons, Flanagan, et al., 2013) leads us to question whether the MDQ is also sensitive in detecting this instability across time. This is an especially pertinent question in light of recent evidence which has expressed a need for more stringent exploration and analysis of the dynamic nature of mood instability (Broome et al., 2015), in order to identify concurrent behavioural, cognitive,

and neural instabilities which may aid in developing targets for treatment, as well as inform us of the nature of related psychopathologies.

The emergence of new technologies and the ubiquity of internet access has been suggested as a sensitive avenue for prospective monitoring of daily mood and concurrent behavioural and cognitive states. Such methods are known to provide more objective and accurate reflections of mood changeability, and thus avoid recall biases that often present when retrospectively recalling mood states at the clinic. In BD patients, the True Colours (True Colours Team Department of Psychiatry University of Oxford) system was developed to do this, based on National Institute for Health and Clinical Excellence (NICE) guidelines (NICE, London) that emphasise the importance of monitoring symptoms in order to facilitate early intervention and to prevent or minimise the impact of episodes in BD (Simon, Budge, Price, Goodwin, & Geddes, 2017). Such methods can also be applied to the experimental exploration of mood instability in otherwise healthy populations, not only for the ease by which it can provide high-frequency data across time, but also for the inexpensive and far-reaching opportunities it presents. Thus, in addition to prospective and remote mood monitoring, technologies in the form of remote sensors, for instance health- or smart-watches and smartphones, can also be utilised in order to capture the concurrent behavioural and physiological factors that may be at play (Glenn & Monteith, 2014).

The COMET study aims to combine the above goals in order to explore the potential interaction and neural underpinnings of mood instability and behavioural and cognitive function. To do this, volunteers were selected to participate based on their responses on the MDQ so that those who screen in were in the “high MDQ” group. Both groups

were observed remotely on a number of measures across a 10-week study period, ranging from prospective mood and activity monitoring to cognitive assessments and neuroimaging procedures.

The current chapter focuses on identifying and exploring mood instability and its clinical presentation in the COMET sample, with the aim of assessing whether longitudinally collected mood ratings can identify mood instability in groups distinguished by MDQ scores. It is predicted that those who screened in on the MDQ, and thus were part of the high MDQ group, will go on to show significant levels of mood instability as measured by this high-frequency remote monitoring methodology. This mood instability is also predicted to be reflected in increased levels of depressive and manic symptomatology, highlighting an association between instability and psychopathology.

3.2 Methods

The current chapter focuses on analyses and results from mood data collected as part of the COMET study. The particular methodology used for the collection of this data can be found in *chapter 2, section 2.2.1* for the MDQ, *2.4.2* for the daily mood assessments (I-PANAS-SF), and *2.5.4* for the weekly mood assessments (True Colours). A more thorough description of the participants recruited in the study can be found in *chapter 2, section 2*; as well as sample characteristics in *section 3*. The remainder of this section will focus, thus, on presenting the analysis methods for this data.

3.2.1 Participants

All seventy-four participants who completed the COMET study are included in current analyses. Thirty-seven of these participants were in the high MDQ group and 37 in the low MDQ group.

3.2.2 Daily Mood Monitoring (I-PANAS-SF)

The International Positive and Negative Affect Schedule Short-Form (I-PANAS-SF) is a 10-item self-report measure of mood[9]. The ten items (equally split between positive affect states and negative affect states) are derived from the original 20 PANAS items (Watson, Clark, & Tellegen, 1988) but were further condensed into a short form to be implemented effectively on an international scale by reducing ambiguities associated

[9] Please see *appendix 2.4* for an iPad copy of the I-PANAS-SF scale used.

with certain adjectives and thus, increasing clarity. Participants were asked to rate the way they felt in the past 24 hours (or since they last completed the scale if longer than 24 hours) on a scale ranging from 0 to 4, with a higher score indicating greater severity.

All I-PANAS-SF data collected using iPads (*Apple Inc*) were sent remotely, via Wi-Fi, to the COMET study database, housed on a secure university-held server. Researchers were then able to extract and download these data for analyses. All data were required to be converted into readable *.csv* files. Each participant could have up to 51 I-PANAS-SF entries, corresponding to each of 50 testing days during the 10-week study period (plus one extra to account for any testing issues, for example a drop in Wi-Fi connectivity).

Each raw data file contained all the data provided by one participant. I-PANAS-SF data was split into ratings for its composite ten items (“upset”, “hostile”, “alert”, “ashamed”, “inspired”, “nervous”, “determined”, “attentive”, “active”, “afraid”). Each item was scored on a 5-point likert scale ranging from 0 to 4. A date and time stamp for the beginning of each entry was included. Researchers were then able to calculate a daily positive affect score based on the sum score of all the positive adjectives (“alert”, “attentive”, “active”, “determined”, and “inspired”); and a negative affect score based on the sum score of all the negative adjectives (“afraid”, “ashamed”, “hostile”, “nervous”, and “upset”). A sum mood score was also determined by subtracting the negative affect score from the positive affect score.

To check whether the sum mood score is an appropriate summary mood measure for the current sample (as it inherently assumes that positive affect and negative affect

are opposite ends of the same spectrum), correlational analyses will be conducted on the positive and negative affect data. If these data are not anticorrelated – indicating that positive and negative affect scores represent separate mood dimensions – the sum mood score will be discounted from further analyses throughout this thesis as it is not a valid summary mood measure.

A number of methods were then employed in order to better understand the temporal nature of this data, in terms of both mood states reported over the 10-week period and mood changeability, or instability, observed over this period.

3.2.2.1 Weekly I-PANAS-SF data

In order to begin to determine the effect of time on mood data reported, as well as to visualise this potential interaction, data were first collapsed into weekly aggregate scores. To do this, I was able to use the daily time stamps to calculate an “absolute day” score corresponding to the day in the 10-week study period each entry belonged to, out of 70 days (as opposed to the “test day” variable which corresponded to the day in the 50-day testing window).

Weekly positive and negative affect, as well as sum mood if appropriate, were then calculated by taking the mean of scores in each 7-day window. A weekly variability score for each of these mood domains was also calculated by taking the standard deviation across each 7-day window. In order to account for the large data size, a MATLAB (The MathWorks Inc., 2010) script was prepared to carry out these calculations.

3.2.2.1.1 Analysis of weekly I-PANAS-SF data

A repeated measures ANOVA was conducted to analyse the effect of group (high MDQ or low MDQ; the between-subjects factor), time (week; the within-subjects factor), and group by time interaction for positive affect, negative affect, and sum mood if appropriate. Separate ANOVAs were also conducted for weekly average and weekly variability measures within these mood domains. Analyses were carried out using the SPSS software (IBM Corp, 2017).

3.2.2.2 Variability as measured by the tRMSSD (I-PANAS-SF data)

The Root Mean Square of Successive Differences (RMSSD) (von Neumann, Kent, Bellinson, & Hart, 1941) has been suggested as a measure of variability that takes into account the variance of trial to trial differences, as opposed to overall trial variation as measured by the standard deviation. In this sense, it takes into account gradual shifts in the mean and is particularly sensitive to temporal, or time-based, recordings. Whilst traditionally a measure used in calculating heart rate variability due to its sensitivity to high frequency heart fluctuations (Berntson, Lozano, & Chen, 2005), it can be particularly appropriate in the study of stability and variability in mood due to its time domain nature and sensitivity in detecting trial by trial fluctuations.

The equation for RMSSD is given here:

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

where *N* equals the number of recordings or intervals (in this case, a maximum of 51), and *x* is the value of one recording (or mood score). This definition, however, assumes that recordings are equally spaced in time (e.g., one recording every day at the exact same time). This is not the case with the data collected here wherein samples have been recorded at different times of day and the time difference between consecutive samples therefore varies. Using the formula above with such variable time differences may result in artefactually high or low values of RMSSD. To address this, I use the *timed* RMSSD (*t*RMSSD) (Taquet et al., in prep, 2020) defined as follows:

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

where t_i corresponds to the time at which sample x_i was recorded. For this data, the *t*RMSSD is thus obtained by first calculating each successive difference in mood (positive affect, negative affect, and sum mood if used) over each successive time difference between recordings. This value is then squared and the result is averaged before the square root of the total is calculated (Shaffer & Ginsberg, 2017).

Using this method, a set of individual *t*RMSSD measures are obtained for each participant, corresponding to variability in positive affect, negative affect, and sum

mood if appropriate. Again, in order to account for the large amount of data collected, an R script and toolbox (R Core Team, 2013) was used to carry out these calculations.

3.2.2.2.1 Analysis of *t*RMSSD I-PANAS-SF data

Independent samples *t*-tests were carried out on the resulting data, in order to investigate group differences in variability in positive affect, negative affect, and if included, sum mood, as measured by the *t*RMSSD. Analyses were conducted using the SPSS software (IBM Corp, 2017).

3.2.3 Weekly Mood Monitoring (True Colours)

All True Colours data were collected through the True Colours website and stored on a secure university-held server[10]. Raw data were downloaded by the researcher and converted from *.JSON* to readable *.csv* files. Aggregate scores were calculated for each of the three scales.

3.2.3.1 The Altman Self-Rating Mania Scale (ASRM)

The ASRM is a short, 5-item multiple choice, self-report questionnaire that assesses the severity of manic and hypomanic symptoms in the past week (Altman et al., 1997). The scale corresponds to several central DSM-IV criteria for mania (Altman, Hedeker, Peterson, & Davis, 2001), namely positive mood, self-confidence, sleep patterns, speech, and activity levels. Each of the five responses for the five questions are scored from 0 to 4, and an overall sum score is calculated (a higher score indicating greater

[10] Please see *appendix 2.7* for copies of the True Colours questionnaires used.

severity of symptoms). As it is often used as a screening instrument, a score of six or higher indicates a high probability of a manic or hypomanic condition and may indicate a need for treatment and/or further clinical attention. Thus, a score of five or lower is less likely to be associated with significant symptoms of mania. This is based on a rating of 85.5% for sensitivity and 87.3% for specificity (Altman et al., 1997).

3.2.3.2 The Quick Inventory of Depressive Symptomatology (QIDS)

The QIDS is a 16-item self-report measure of depressive symptoms (Rush, Giles, & Schlesser, 1996). Participants are asked about the severity of a number of symptoms in the past seven days, or one week, with each item corresponding to the nine symptom domains of major depressive disorder as outlined in the DSM-IV. Items measure depressed mood, loss of interest or pleasure, concentration/decision-making, self-outlook, suicidal ideation, energy/fatigability, sleep, weight/appetite change, and psychomotor changes (Rush et al., 2003). Each item is scored from 0 to 3, and a maximum sum score of 27 can be obtained. A higher score indicates greater severity of depressive symptoms, such that a score of 6 to 10 represents mild depression, 11 to 15 moderate depression, 16 to 20 severe depression, and 21 to 27 represents very severe depression (0-5 denotes no symptoms).

3.2.3.3 The Generalised Anxiety Disorder Scale (GAD-7)

The GAD-7 is a short, 7-item self-report scale commonly used as a screening tool and severity assessment for anxiety disorder (Spitzer et al., 2006). Participants are asked about their experiences of a number of symptoms in the past week. Each item in the

scale corresponds to symptom items for Generalised Anxiety Disorder (GAD) in the DSM-IV and are scored from 0 to 3. A total score is calculated by summing responses across the seven items, with a maximum score of 21. A higher score indicates greater severity, such that a total score of 0 to 5 represents mild anxiety, 6 to 10 moderate anxiety, 11 to 15 moderately severe anxiety, and 15 to 21 represents severe anxiety. The GAD-7 has a sensitivity rating of 89% and specificity of 82% (Spitzer et al., 2006).

3.2.3.4 Analysis of True Colours data

As well as weekly sum scores for each of the three scales, overall average and variability scores were also obtained by calculating the mean and standard deviation for each participant across the 10-week study period.

Repeated measures ANOVAs were then conducted using the SPSS software (IBM Corp, 2017) to determine the effect of group (high MDQ or low MDQ; the between-subjects factor), time (week; the within-subjects factor), and group by time interaction for the ASRM, QIDS, and GAD-7 scales. Post-hoc *t*-tests were subsequently conducted to test group differences in variability scores.

3.2.4 Correlational Analyses

Correlational analyses were conducted to test the relationship between overall daily mood, as measured by positive affect, negative affect, and sum mood if included, and overall weekly clinical measures of mood as measured by the ASRM, QIDS, and GAD-7. These analyses were run on both average and variability – as measured by the standard deviation and *t*RMSSD – measures of daily mood, and average and

variability measures of weekly True Colours responses, in order for the relationship between symptomatology and mood experiences and instability to be explored.

Analyses were carried out using the SPSS software (IBM Corp, 2017).

3.2.5 Analysis of mood as a function of diagnosis in the high MDQ group

Using the data gathered from SCID assessments[11], the high MDQ group were further split into those who met criteria for at least one DSM-IV axis I disorder and those who did not. Independent samples *t*-tests were then carried out using SPSS (IBM Corp, 2017) to test for group differences in average and variability (as measured by both standard deviation and *t*RMSSD) in positive affect, negative affect, and if included, sum mood; and in the ASRM, QIDS, and GAD-7 scales for mania, depression, and anxiety.

[11] Please see *chapter 2, section 2.5.1* and *3.2* for SCID details and results.

3.3 Results

Sample characteristics and demographic data can be found in *chapter 2, section 3.1*.

3.3.1 Descriptive Statistics

3.3.1.1 Observations

	High MDQ		Low MDQ	
	Mean (SD)	*Median (spread)*	*Mean (SD)*	*Median (spread)*
I-PANAS-SF (days)	47.65 (3.69)	49.00 (36.00-51.00)	49.05 (1.96)	50.00 (43.00-51.00)
True Colours (weeks)	9.22 (1.47)	10.00 (2.00-10.00)	9.22 (1.16)	10.00 (4.00-10.00)

Table 6: Number of observations (days/weeks). Averages and spread included.

Descriptive statistics for the average number of days (for I-PANAS-SF data) and weeks (for the True Colours data) provided by participants in the high MDQ and low MDQ groups are presented in table 6.

Shapiro-Wilk tests indicated that the number of daily and weekly observations did not follow a normal distribution for the high MDQ group (I-PANAS-SF: $W(37) = .79$, $p < .001$; True Colours: $W(37) = .55$, $p < .001$) and the low MDQ group (I-PANAS-SF: $W(37) = .82$, $p < .001$; True Colours: $W(37) = .71$, $p < .001$). Thus, nonparametric tests were conducted to test for group differences.

Mann-Whitney tests indicated that there were no significant differences in the number of I-PANAS-SF observations between the high MDQ and low MDQ groups ($U = 550.00$, $p = .137$, $r = .17$) and in the number of True Colours observations between

the two groups (U = 674.00, p = .898, r = .02). The distribution of these observations can also be seen in figure 10.

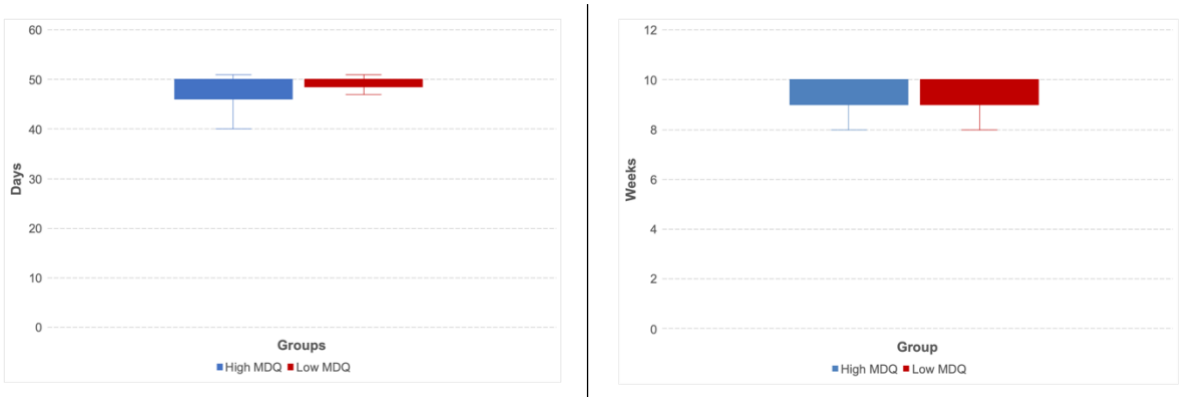


Figure 10: Distribution of I-PANAS-SF data in days (left) and distribution of True Colours data in weeks (right).

3.3.1.2 I-PANAS-SF sum mood measure

I-PANAS-SF sum mood score is calculated as I-PANAS-SF positive affect minus I-PANAS-SF negative affect. Therefore, it assumes that positive and negative items are opposite ends of the same spectrum, and that the sum score is an overall summary measure. However, correlational analyses on positive affect and negative affect scores for all participants (regardless of group, outliers removed so n = 70) showed that the scales were not anticorrelated, $r(68)$ = .08, p = .500, suggesting that positive and negative affect scores represent separate mood dimensions. Individual correlational analyses in each group confirmed this (high MDQ: $r(33)$ = .25, p = .156; low MDQ: $r(33)$ = -.17, p = .330).

Therefore, the sum mood score is not a valid summary mood measure for the daily I-PANAS-SF data. Subsequent analyses throughout the thesis will only focus on the positive and negative affect scores.

3.3.1.3 I-PANAS-SF data

		High MDQ	Low MDQ
		Mean (SD)	*Mean (SD)*
Positive Affect I-PANAS-SF	*Average*	6.74 (2.74)	6.21 (3.97)
	Variability (SD)	3.16 (.82)	2.40 (1.11)
	tRMSSD	4.0e-5 (1.5e-5)	3.4e-5 (2.0e-5)
Negative Affect I-PANAS-SF	*Average*	2.75 (2.21)	1.14 (1.54)
	Variability (SD)	2.26 (1.12)	1.27 (0.96)
	tRMSSD	2.8e-5 (1.5e-5)	1.6e-5 (1.4e-5)

Table 7: Daily mood ratings as measured by the I-PANAS-SF. Averages and standard deviations (SD) are shown for average mood and variability as measured by SD and *t*RMSSD.

Table 7 shows the descriptive statistics for each of the three variables (average, standard deviation, and *t*RMSSD) within the two mood domains (positive affect and negative affect) across the 10-week study period. Shapiro-Wilk tests carried out on these data showed that the majority of distributions were normal[12].

3.3.1.4 True Colours data

	High MDQ	Low MDQ
	Mean (SD)	*Mean (SD)*
ASRM	2.30 (1.84)	.40 (0.71)
QIDS	5.33 (2.97)	1.76 (1.43)
GAD-7	3.80 (3.12)	.98 (1.20)

Table 8: Weekly mood ratings as measured by the True Colours questionnaires. Averages and standard deviation (SD) are shown.

[12] Please see *appendix 3.1* for the full set of Shapiro-Wilk test results for this data.

Average scores across the (maximum) 10 weeks of ASRM, QIDS, and GAD-7 scales for high MDQ and low MDQ participants are shown in table 8. Shapiro-Wilk tests carried out on this data also confirmed normality[13].

Using the cut-off scores or severity markers identified by researchers, a number of high MDQ participants met criteria for moderate to severe symptoms across the mania, depression, and anxiety scales. Two high MDQ participants scored an average of 6 or higher across the 10-week period on the ASRM, indicating a high probability of a manic or hypomanic condition; two met criteria for moderate depression as measured by the QIDS (and a further 16 met criteria for mild depression); and two met criteria for moderately severe anxiety on the GAD-7 (a further 7 met criteria for moderate anxiety). It is worth noting that one of the two who met criteria for moderate depression and moderately severe anxiety was the same high MDQ participant. All other participants, including all low MDQ participants, did not meet criteria (or fell into the lowest category – mild) across the three measures.

[13] Please see *appendix 3.2* for a full set of Shapiro-Wilk test results for this data.

3.3.2 Daily Mood Monitoring (I-PANAS-SF)

3.3.2.1 Weekly I-PANAS-SF data

3.3.2.1.1 Positive affect

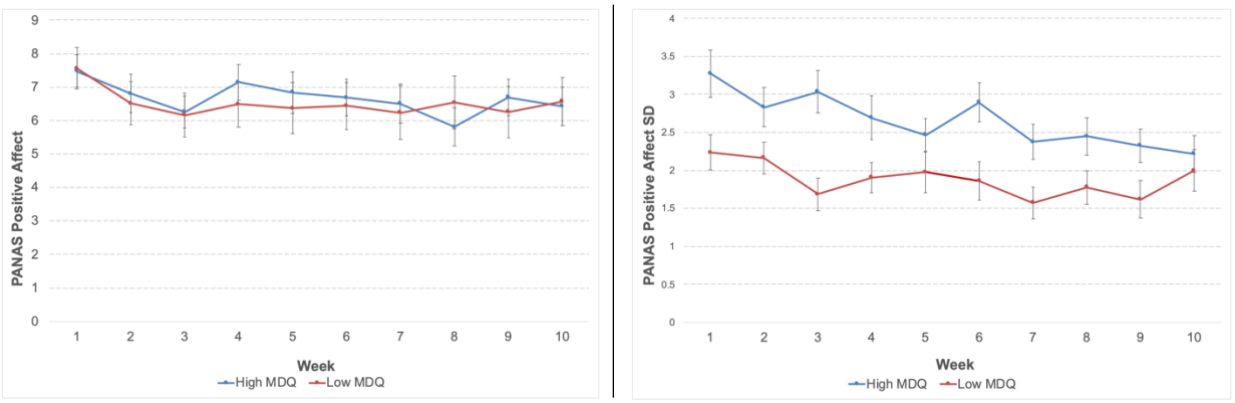


Figure 11: Average positive affect across weeks (left). Variability (SD) in positive affect across weeks (right). Error bars represent ± 1 *SEM*.

Results revealed a significant effect of group, such that the high MDQ group had greater variability in their positive affect scores compared to the low MDQ group, $F(1, 60) = 11.96$, $p < .001$ (fig. 11, right). There was no significant effect of group for average positive affect scores, $F(1, 67) = 0.04$, $p = .850$ (fig. 11, left).

Results also showed a significant main effect of time (fig. 11), such that participants reported lower positive affect ratings across the 10-week period, $F(4.56, 305.45) = 2.98$, $p = .015$[14], and also became less variable in their positive affect ratings across this period, $F(9, 540) = 3.04$, $p < .001$.

[14] Sphericity violated: Mauchly's $W = .06$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .51$.

There was no significant group by time interaction for both the average and variability in positive affect scores (average: $F(4.56, 305.45) = 0.81$, $p = .537$; variability: $F(9, 540) = 1.24$, $p = .267$).

3.3.2.1.2 Negative affect

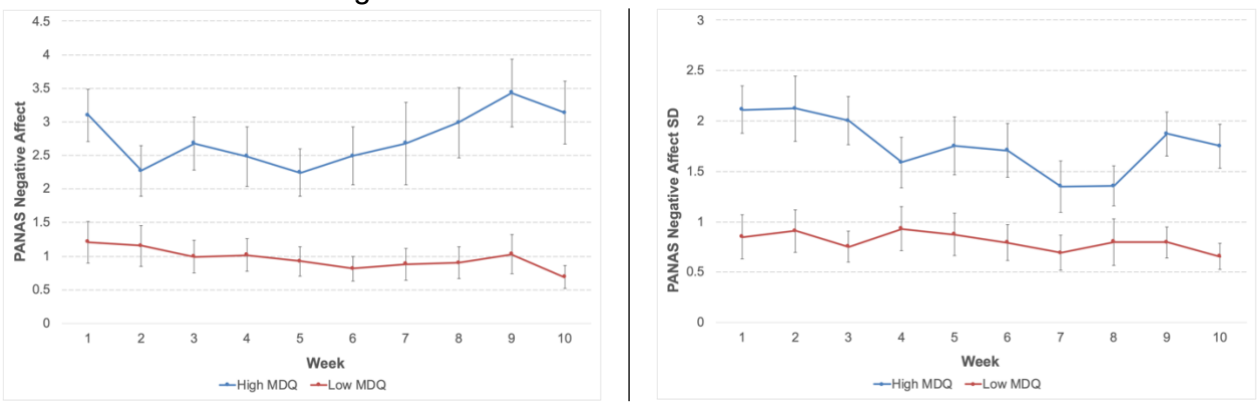


Figure 12: Average negative affect across weeks (left). Variability (SD) in negative affect across weeks (right). Error bars represent ± 1 *SEM*.

A significant effect of group was found such that the high MDQ group reported greater average negative affect scores (fig. 12, left), $F(1, 67) = 17.21$, $p < .001$, as well as greater variability in negative affect scores (fig. 12, right), $F(1, 60) = 17.01$, $p < .001$.

There was no significant main effect of time for either the average or variability in negative affect scores (average: $F(5.48, 366.79) = 1.62$, $p = .148$[15]; variability: $F(6.60, 396.02) = 1.88$, $p = .076$[16]). The group by time interaction was also not significant for both average and variability scores (average: $F(5.48, 366.79) = 1.74$, $p = .117$; variability: $F(6.60, 396.02) = 1.30$, $p = .252$).

[15] Sphericity violated: Mauchly's $W = .06$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .61$.
[16] Sphericity violated: Mauchly's $W = .19$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .73$.

3.3.2.2 *tRMSSD as a measure of variability*

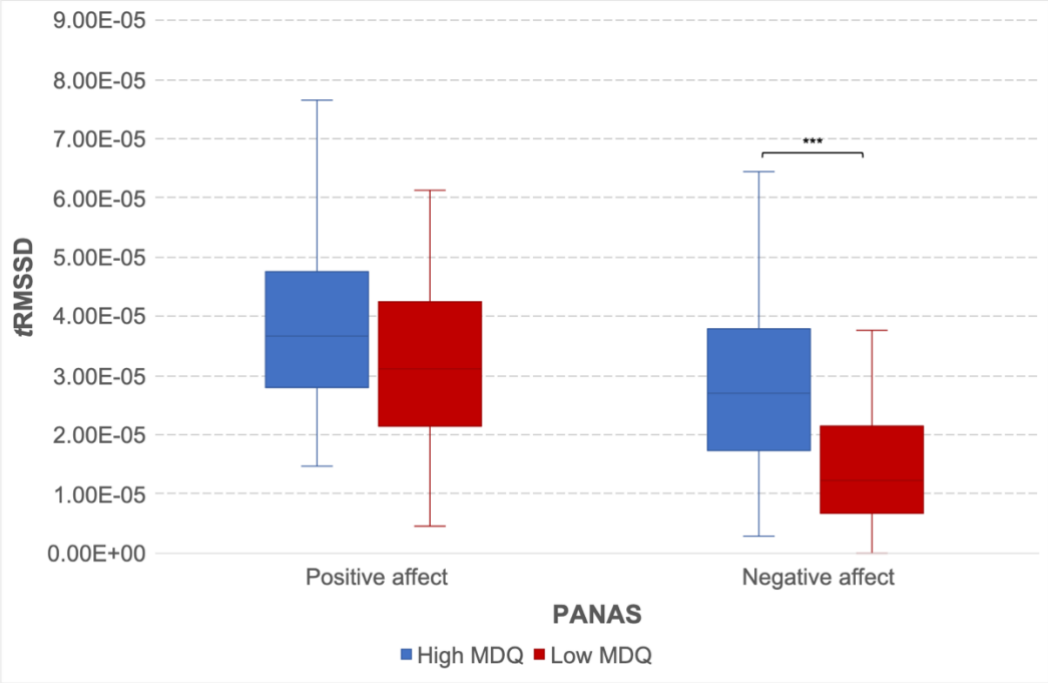


Figure 13: *t*RMSSD scores across the domains of positive affect and negative affect for high MDQ and low MDQ groups. *** p < .001.

As can be seen from fig. 13, high MDQ participants were significantly more variable in negative affect, $t(72) = 3.52$, $p < .001$, as measured by the *t*RMSSD, than low MDQ participants. Statistical tests on positive affect variability as measured by the *t*RMSSD did not reveal significant group differences, $t(72) = 1.50$, $p = .138$.

3.3.3 Weekly Mood Monitoring (True Colours)

3.3.3.1 Mania

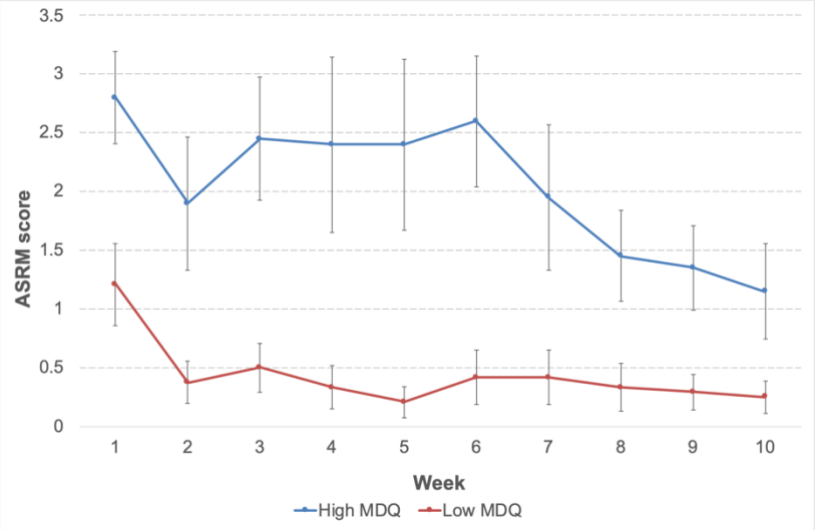


Figure 14: Symptoms of mania as measured by the ASRM. Average scores across the 10-week study period. Error bars represent ± 1 *SEM*.

There was a significant effect of group, such that individuals in the high MDQ group reported increased scores on the ASRM compared to the low MDQ group (fig. 14), $F(1, 42) = 17.11$, $p < .001$. Post-hoc tests on SD data also showed that there was more variability in the high MDQ group (1.81 ± 1.08) compared to the low MDQ group (0.48 ± 0.55), $t(72) = 6.67$, $p < .001$.

Results also revealed a significant main effect of time (fig. 14), $F(4.94, 207.66) = 3.60$, $p = .004$[17], such that participants reported less manic symptoms over the 10-week period. There was no significant group by time interaction, $F(4.94, 207.66) = 1.39$, $p = .231$.

[17]Sphericity violated: Mauchly's $W = .02$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .55$.

3.3.3.2 Depression

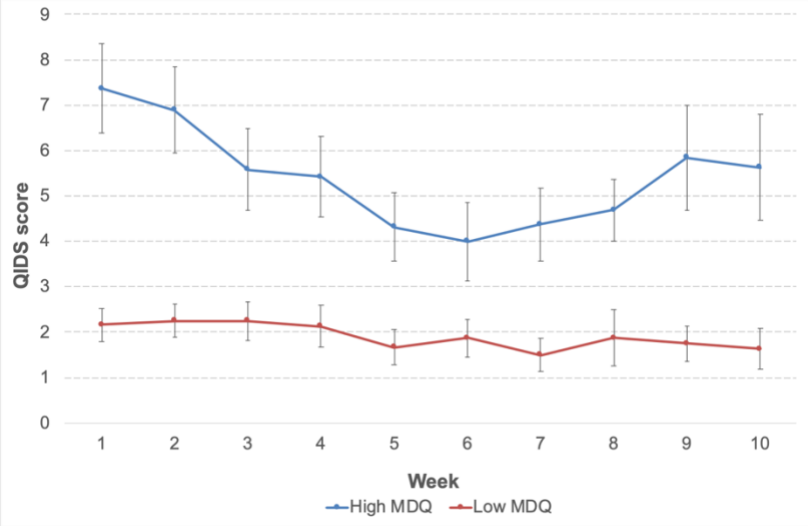


Figure 15: Symptoms of depression as measured by the QIDS. Average scores across the 10-week study period. Error bars represent ± 1 *SEM*.

Results showed a significant effect of group, such that the high MDQ group reported increased scores on the QIDS scale compared to low MDQ group (fig. 15), $F(1, 41) = 21.24$, $p < .001$. Post-hoc tests on SD data also revealed significantly greater variability in the high MDQ group (2.54 ± 1.47) compared to the low MDQ group (1.11 ± 0.80), $t(72) = 5.22$, $p < .001$.

There was a significant main effect of time, $F(5.69, 233.43) = 4.56$, $p < .001$[18], such that participants reported fewer depressive symptoms across the 10-week period. There was also a significant group by time interaction, $F(5.69, 233.43) = 2.52$, $p = .025$.

[18] Sphericity violated: Mauchly's $W = .09$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .63$.

3.3.3.3 Anxiety

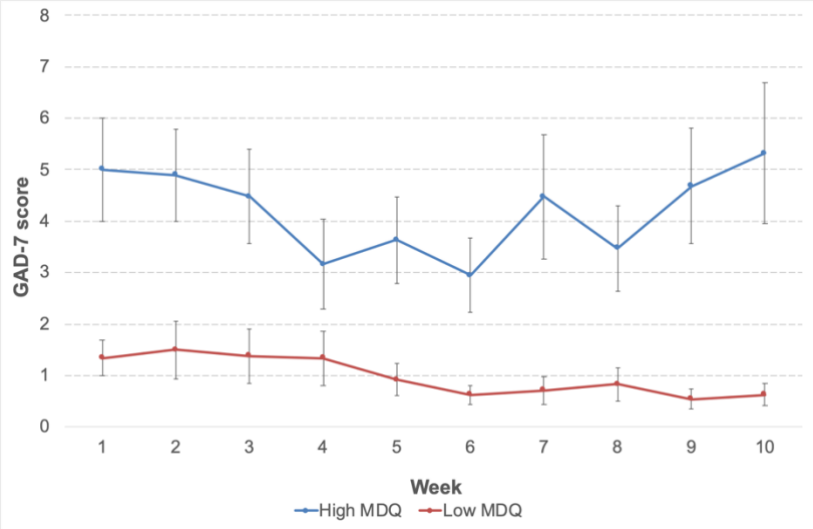


Figure 16: Symptoms of anxiety as measured by the GAD-7. Average scores across the 10-week study period. Error bars represent ± 1 *SEM*.

There was a significant effect of group, $F(1, 41) = 16.25$, $p < .001$, such that the high MDQ group reported increased levels of anxiety compared to the low MDQ group (fig. 16). Post-hoc tests on SD data also showed significantly greater variation in the high MDQ group (2.27 ± 1.50) compared to the low MDQ group (0.97 ± 0.90), $t(72) = 4.53$, $p < .001$.

Results also revealed a significant main effect of time, $F(4.01, 164.25) = 2.55$, $p = .041$[19], such that participants reported more anxiety symptoms across the 10-week period. There was no significant group by time interaction, $F(4.01, 164.25) = 2.18$, $p = .073$.

[19] Sphericity violated: Mauchly's $W = .02$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .45$.

3.3.4 Relationship between daily (I-PANAS-SF) and weekly (True Colours) mood monitoring

		High MDQ (*n*=37)						Low MDQ (*n*=37)					
		ASRM		**QIDS**		**GAD-7**		**ASMR**		**QIDS**		**GAD-7**	
		Average	*SD*	*Average*	*SD*	*Average*	*SD*	*Average*	*SD*	*Average*	*SD*	*Average*	*SD*
Positive Affect	*Average*	.09	.05	-.12	-.21	.01	-.18	.20	.16	**-.33***	-.32	-.09	-.24
	SD	.18	.15	.31	.20	.21	.16	.07	.13	-.03	.12	.27	.24
	tRMSSD	.06	.07	.27	-.02	.23	.09	.07	.15	.11	.07	.29	.28
Negative Affect	*Average*	**.45****	.23	**.46****	.21	**.47****	**.40***	.03	.04	.30	.16	**.43****	**.36***
	SD	**.36***	.30	**.55****	**.48****	**.49****	**.64****	.06	.14	**.45****	**.44****	**.68****	**.68****
	tRMSSD	**.36***	.29	**.40***	.31	**.43****	**.53****	.05	.17	**.35***	**.36***	**.66****	**.54****

Table 9: Pearson Product-Moment Correlations of the True Colours scales with daily mood. Both absolute (average as measured by the mean) and variability (as measured by SD and tRMSSD (daily mood only)) are shown. * $p < .05$, ** $p < .01$

Although table 9 show a number of interesting correlational patterns, only the following associations survived a Bonferroni adjusted *p*-value of .001. Variability in negative affect was significantly positively associated with average QIDS, and variability in GAD-7 in the high MDQ group, such that increased variability in negative affect was associated with an increase in absolute depressive symptoms (QIDS) and an increase in variability in anxiety symptoms (GAD-7).

In the low MDQ group, variability in negative affect was significantly positively associated with average GAD-7 and variability in GAD-7, such that increased variability in negative affect was associated with an increase in both absolute and variability in anxiety symptoms (GAD-7) in this group.

However, it should be noted that despite surviving a Bonferroni correction, none of these correlations are significantly different from the other group, as assessed by Fishers Z test.

3.3.6 Mood as a function of diagnosis in the high MDQ group

		With diagnosis (n=9)	No diagnosis (n=28)
		Mean (SD)	*Mean (SD)*
Positive Affect	*Average*	6.73 (3.46)	6.74 (2.55)
	SD	3.19 (0.87)	3.14 (0.82)
	tRMSSD	4.0e-5 (1.7e-5)	4.0e-5 (1.5e-5)
Negative Affect	*Average*	**4.10 (2.11)***	**2.31 (2.09)***
	SD	2.71 (0.94)	2.11 (1.15)
	tRMSSD	3.2e-5 (1.1e-5)	2.7e-5 (1.6e-5)
ASRM		6.71 (2.93)	6.63 (2.38)
QIDS		3.11 (0.68)	3.01 (0.62)
GAD-7		4.30 (1.62)	4.19 (1.01)

Table 10: Average and standard deviation for mood and True Colours scores by diagnosis (high MDQ group only). * $p < .05$

As can be seen in table 10, high MDQ participants with a diagnosis (*n*=9) had significantly greater average negative affect scores, $t(35) = -2.24$, $p = .032$, than those without a diagnosis (fig. 17).

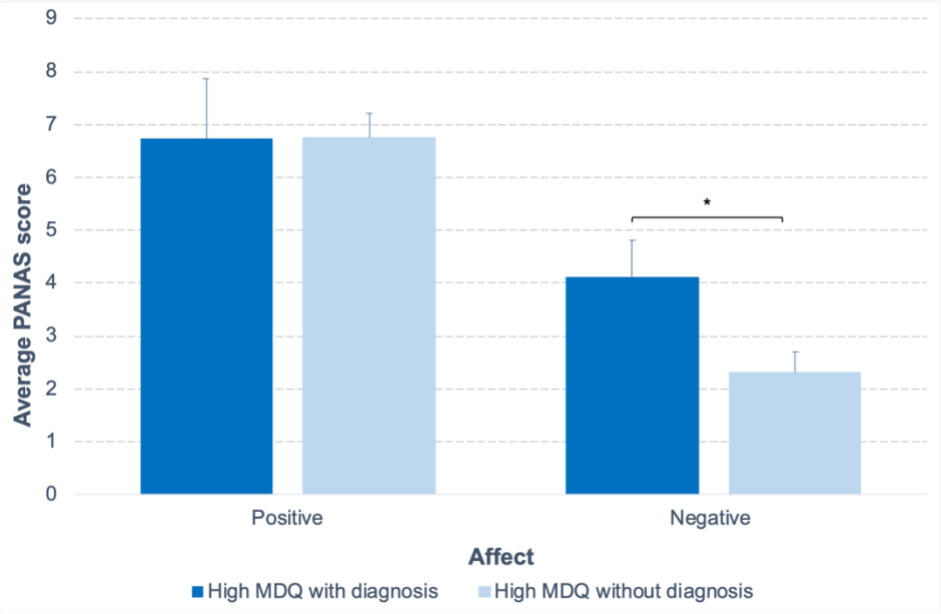


Figure 17: Average mood scores as a function of diagnosis in the high MDQ group. * $p < .05$. Error bars represent $\pm$ 1 *SEM*.

3.4 Discussion

High MDQ individuals showed greater variability in their daily mood ratings across the 10-week study period compared to matched low MDQ participants. Within this, they were more variable in their ratings of both positive and negative affect, reflecting symptoms of elevated and depressed mood. This was further supported by clear distinctions in the variability of their scores on the clinical rating scales for mania, depression, and anxiety. Together, these results support the hypothesis of increased levels of mood instability in individuals in the general population who show dimensions of BD as measured by a positive screen on the MDQ.

Participants in the high MDQ group also showed differences in average scores, suggesting absolute differences in the levels of negative affect experienced, and in symptoms of mania, depression, and anxiety. Together with previous evidence suggesting the presence of mood instability in a range of mood disorders (Broome et al., 2015), this result indicates that identification of instability may not strictly be specific to BD in itself, but may also characterise mood instability as a feature of related or overlapping disorders. Combining this with the finding that mood symptoms across all modes of assessment showed a significant effect of time, nevertheless, emphasises the dynamic nature of mood instability. It is this concept of dynamic activity across time that is explored in relation to behavioural symptoms and neural mechanisms in subsequent chapters, and is suggested as a key component of mood disorders such as BD and MDD.

Delving into the finding of mood instability further, it is noted that although variation across the mood domains is observed, particular differences in absolute negative mood are also reported. Outside of variability or instability in mood, participants in the high MDQ group reported significantly greater levels of negative affect across the 10-week study period. This is particularly interesting given the fact that the MDQ targets symptoms of mania and hypomania, and raises questions of the nature of mood instability, or mood disorder, that may be observed here.

For instance, we know that depressive symptoms and episodes are far more frequent in BD than mania or hypomania (Bonsall et al., 2012), and that patients often go undiagnosed or misdiagnosed with major depressive disorder (MDD) for around three years before a correct diagnosis of BD is made (Hirschfeld, 2007). Thus, if we are observing significant negative mood in individuals at risk of developing BD as the MDQ dictates, does this suggest that the high MDQ sample are currently in a depressed episode or that low mood is characteristic of the euthymic state in BD? Alternatively, if we consider the growing body of evidence that suggests mood instability as a feature across mood disorders (Broome et al., 2015), we are led to question whether this increased level of negative affect may instead be symptomatic of a related disorder, such as MDD. Whilst we are currently unable to fully test the direction of this relationship, if any, present findings do shed light on the particular details of this effect.

When we consider the diagnoses that were made, or the axis I criteria that were met in the high MDQ group, we see the presence of both BD and MDD symptomatology (see *chapter 2*). Not only is this interesting given the validity of the MDQ as a screening tool for BD, but also in that high MDQ participants distinguished by diagnosis

(regardless of classification) showed distinct and significant differences in negative affect, such that those with a diagnosis reported significantly greater levels of negative mood across the 10-week study period compared to those without a diagnosis. Additionally, this was further supported by the finding that an increase in absolute and variability in negative affect was significantly associated with an increase in symptoms of depression and anxiety across groups, and also in symptoms of mania in the high MDQ group. Taken together, these observations suggest an association between low mood and clinical symptomatology, and is strengthened by diagnosis regardless of classification.

Therefore, although we see a relationship between mood instability and negative mood, we are unable, as of yet, to determine whether this is a characteristic of BD depression or a feature of MDD – or alternatively, disordered affect in its own right. Nevertheless, it does begin to highlight the complexities of understanding mood instability once diagnostic criteria are taken into account, and further supports the idea of mood instability as both a feature of, and transdiagnostic marker across disorders (Panchal, Kaltenboeck, & Harmer, 2019).

In support of Marwaha et al. (2013)'s findings, we are also able to detect a relationship between mood instability and clinical symptomatology as measured by both the weekly True Colours (True Colours Team Department of Psychiatry University of Oxford) clinical assessments and the outcomes from SCID assessments (American Psychiatric Association (APA), 2013). This further supports the link between mood instability and non-psychotic psychopathologies (Marwaha, Parsons, Flanagan, et al., 2013).

Importantly however, this also lends to the idea that the MDQ may be a sensitive tool in detecting mood instability in the general population. Whilst the sensitivity and specificity of the MDQ as a screening tool for BD has been established (Hirschfeld et al., 2000), its ability to detect significant mood instability across time presents important implications to our current understanding of mood disorders. According to Hirschfeld (2002), the MDQ has a sensitivity rating of 28% and specificity rating of 97% for BD in the general population. From our diagnostic assessments, only 4 (10%) out of 9 (24%) participants in the high MDQ group who met criteria for an axis I disorder were diagnosed with BD (BD II and BD NOS). Whilst this is in keeping with the MDQ's ability to correctly identify those without a disorder (75% did not meet diagnostic criteria), the overlapping sensitivity of the MDQ in detecting disordered mood in the current sample again points to both the heterogeneous nature of BD, and its significant clinical overlap with MDD. However, functional impairment was not assessed in the current sample and is otherwise required for a full clinical screen of BD, suggesting that a component of functional severity may predict the onset of BD, in addition to mood instability. Whilst this is not examined in the current study, further studies involving BD patients with mood instability may be able to distinguish the nature of mood instability in BD from that in otherwise healthy populations.

Nevertheless, the MDQ was found to be a sensitive tool in detecting mood instability across time. From multiple methods of analyses, both investigating the effect of time across weeks and assessing day-by-day variation (using *t*RMSSD), the significant effect of dynamic mood changeability across time was highlighted. Additionally, all participants, regardless of group, seemed to become less variable in positive affect

across time, despite the high MDQ group being more variable overall. One reason for this tapering of affect over time could be that the mere act of logging and recording one's mood over time led to an increase in self-awareness, which in turn may have led to an increase in symptom management and self-treatment. This relationship between self-awareness and symptom relief as a consequence of high-frequency mood monitoring has often been reported in BD patient groups (Faurholt-Jepsen et al., 2013; Sachs, 1996; Saunders et al., 2017), and echoes some of the core principles of mood regulation that are taught in psychological therapies such as cognitive behavioural therapy (CBT) (Basco & Rush, 2005).

Further research on the current dataset can begin to build a profile of the dynamic nature of mood instability observed here. Whilst we are only able to speculate on the potential reasons for the effect of time on mood instability and symptoms, a closer examination of concurrent behavioural patterns may help to shed light on the correlates of mood instability and its progression or maintenance over time. By again considering the suggestion that mood instability is a reflection of chaotic aperiodic cyclic patterns (Bonsall et al., 2012), it follows that other such instabilities in behavioural, cognitive, and ultimately neural mechanisms, should also present. Thus, analysis of these associated instabilities across the same time scale, in the same sample who present with mood instability, will aid us in better understanding both the mechanisms by which these instabilities develop and are maintained, as well as the factors that may determine progression to psychopathology, be it BD, MDD, or another related disorder.

Building on the foundation of mood instability presented in this chapter, subsequent chapters aim to do just this – by first exploring the potential behavioural correlates of mood instability across time, and then by examining the functional connectivity patterns which may subserve this instability. Special consideration is given to understanding the temporal nature of this phenomenon in order to best capture its dynamic characteristics.

Chapter 4 | Circadian rest-activity patterns in mood instability: an actigraph study

4.1 Introduction

Disturbed sleep and activity patterns are a core feature of many psychiatric disorders and can help to both distinguish between disorders and predict the onset and severity of illness. However, more and more evidence points to the idea that these disturbances are part of wider differences and problems in the phase and structure of the circadian rhythm, or the 24-hour rest-activity pattern (Foster et al., 2013; Scammell, Arrigoni, & Lipton, 2017). It is known that the circadian rhythm is a homeostatic mechanism that controls cyclical variation in physiology and behaviour and is fundamental for health and well-being (Lyall et al., 2018). These rhythms are also ubiquitous in nature, sharing features with other cyclical biological rhythms that underly body temperature, hormone levels, and even mood and cognition (Bunney & Bunney, 2000; McClung, 2007; Reppert & Weaver, 2001). Thus, these wider circadian rhythms, underlying rest-activity patterns, are known to be significantly implicated in psychiatric illness, particularly in mood disorders where major clinical symptoms include disruptions in sleep and wakefulness, difficulties with social rhythms, and changes in appetite (Boivin, 2000; Bunney & Bunney, 2000; McClung, 2007).

When considering the role of these rhythms in mood disorders, seasonal affective disorder (SAD) is often presented as providing the most resounding evidence for disruption in circadian rhythms. Patients with SAD present with depressive symptoms that occur only in the winter months when there are shorter days and later dawns (Magnusson & Boivin, 2003), suggesting an interaction between circadian rhythms

and depressive symptomatology. Similarly, lowered mood in MDD is associated with changes in the sleep-wake pattern such that the tendency to experience disrupted sleep (Souetre et al., 1988), changes to the rhythmic nature of body temperature (Souetre et al., 1988) and hormone and neurotransmitter levels (McClung, 2007; Monteleone & Maj, 2008), and rhythmic variations in severity of mood symptoms (Gordijn, Beersma, Bouhuys, Reinink, & Van den Hoofdakker, 1994) present. Together, these symptoms of circadian rhythm disruption and accompanying psychomotor retardation are core features of melancholia (Parker et al., 1995) and are often illustrated in studies using objective measurements of activity, or actigraphy, through greater levels of activity during sleep, lowered levels of activity during the day, and thus, a resulting lowered amplitude of circadian rhythm (Burton et al., 2013).

The experience of oscillations in mood in BD, particularly between episodes of depression and mania, furthers this. As with MDD, sleep problems are common in depressive episodes and take the form of insomnia or hypersomnia in 23-78% of patients (Harvey, 2007), whereas manic episodes are often associated with a reduced need for sleep in 69-99% of patients (Rock, Goodwin, Harmer, & Wulff, 2014). Further, across the course of the disorder, BD patients are known to present with delayed onset of the sleep-wake phase and to also have lower levels and delayed timing of melatonin secretion, the hormone primarily involved in underlying human circadian rhythm, compared to MDD patients (Nurnberger et al., 2000; Robillard et al., 2014, 2013). In terms of clinical implications, the therapeutic efficacy of stabilising these rhythms has been reported (Goodwin, 2009; Yatham et al., 2006), and highlights a mechanism by which disruption in circadian rhythm may interact with disruption in mood regulation.

A molecular clock, responsible for regulating circadian rhythms, is located in the suprachiasmatic nucleus (SCN) in the hypothalamus and involves a number of genes known to determine and control its function. It has been suggested that abnormal behaviour in this clock is more prevalent in patients with mood disorders such as BD and MDD (McClung, 2007), and that genetic sleep disorders involving circadian rhythm disruption are highly comorbid with depression and anxiety (Hamet & Tremblay, 2006; Shirayama et al., 2003). Furthermore, antidepressant and mood stabilising medication are reported to alleviate such circadian rhythm disruption, and non-pharmacological therapies such as bright light therapy and components of cognitive behavioural therapy (CBT) are known to target and reset this disturbance. Whilst also confirming the importance of circadian rhythm activity in mood disorders, such findings of both a neurobiological basis for disturbance and the effect of mood regulating treatment indicate a broader neurobiological and shared basis for mood disorders and circadian rhythms.

This theory of associated instability between circadian rhythms and mood has been tested behaviourally and experimentally where the onset of hypomania and mania has been reported in those with induced sleep deprivation (Wu & Bunney, 1990). Furthermore in Pinho et al.'s (2016) study of biological rhythms, depressive symptoms and functional impairment, they found that BD patients had a significant relationship between the severity of their depressive symptoms and the degree of circadian, or rest-activity cycle, disruption such that disruption in this cycle was associated with poor psychosocial functioning. The persistence of this disruption in euthymic periods additionally supports the idea of a relationship between this disruption and mood regulation. In particular, circadian instabilities during euthymia have been reported,

such that BD patients show reduced daytime activity (Harvey, Schmidt, Scarnà, Semler, & Goodwin, 2005) and greater fragmentation of daily rest-activity patterns (Jones, Hare, & Evershed, 2005). Not only have several studies found that sleep-wake disturbances persist in euthymic periods in the majority of BD patients such that they also report difficulties in initiating and maintaining sleep and experience early morning awakening (Boland & Alloy, 2013), disturbances in these rhythmic patterns during euthymia have been associated with a greater severity of depressive and manic episodes over a 12-month period (Gruber et al., 2011) and were found to be more associated with a history of psychosis and suicidal attempts (Sylvia et al., 2012).

Whilst consistent patterns of circadian rhythm disruptions are shown throughout the course of BD, these studies are often confounded by the effects of medication, scar effects of repeated mood episodes, severity of illness, and the presence of comorbidities. Studying these patterns in at-risk groups, thus, enables us to navigate around this in order to understand both the nature of such disruptions during the course of the disorder and the risk factors they may present for its development. Rock et al. (2014) aimed to do just this in their study of at-risk bipolar phenotype participants identified using the Mood Disorder Questionnaire (MDQ). Using data collected from actigraphs worn over two weeks, they found that at-risk participants had significantly lower circadian relative amplitude, a differentiation marker of daytime and night-time activity, driven by increased movement or activity during rest periods compared to controls. Interestingly, the researchers reported that these disruptions persisted even when those who went on to meet diagnostic criteria for BD were excluded from analyses. Bullock and Murray (2014) furthered this in their actigraph study of at-risk for BD participants by finding that the high vulnerability group not only had lower levels

of circadian relative amplitude, as in Rock et al.'s (2014) study, but that this effect was also modulated by mood such that those with a history of depression had the lowest circadian amplitude, and that variance in this marker was more strongly associated with proneness to mania rather than depression. Together, these results suggest the importance of circadian rhythm disruptions, particularly those pertaining to rhythm amplitude, in the prodrome of BD and further indicates that disruptions in underlying neurobiological mechanisms to regulate and maintain such behaviour may be core to mood disorders.

Considering that mood instability, outside of distinct episodes of depression and mania, is now thought of as a central and vital feature of BD and other mood disorders, leads us to examine the role of circadian rhythm disruption in mood instability, given what is already known from the BD and MDD literature. If circadian rhythms form part of a crucial neurobiological homeostatic mechanism responsible for regulating rest-activity patterns and mood, amongst other things, it follows that disruption in homeostasis could result in overall instabilities in such downstream components such as sleep, activity, and mood. It also follows that such disruption is dynamic and susceptible to temporal change, highlighting the internal clock-based rhythmic nature of circadian patterns and the oscillating nature of mood instability. Both components are also sensitive to environmental influence, be it changes or manipulations in day/night periods (particularly noticed in the seasonal experience of circadian rhythm disruption and depression in SAD) or cognitive emotional processing involving reward, for instance. In order to continue our understanding of mood instability, particularly given its potential to help transform and develop new therapeutic targets, it is vital that we better understand its wider role in disrupting neurobiological homeostatic

mechanisms such as circadian rhythms. Whilst previous literature has begun to show the importance of this in BD and at-risk groups, concurrent monitoring of mood instability and rest-activity patterns over a longitudinal time period is lacking and would provide more conclusive support for the hypothesis of a shared homeostatic mechanism underlying mood, behavioural, and neural instabilities.

The current study and analyses aim to do just this, by investigating the presence of circadian or rest-activity disruptions in high MDQ participants over a longitudinal time-course. In particular, an examination of the relationship between such patterns and the objective experience of mood instability is sought, in order to provide more nuanced evidence for the particular homeostatic mechanisms at play behind mood and behavioural regulation. Therefore, the present aim is to extend previous findings by assessing whether longitudinal rest-activity disruption, or instability, is also a feature of mood instability. If so, a secondary objective is to determine the relationship and components of this disruption with mood instability in a sub-clinical and medication-naïve group. Thus, it is predicted that those who screen in on the MDQ and are shown to have mood instability (see *chapter 3*), have greater variability in their rest-activity cycle across time, as well as specific disruptions with daytime and sleep activity. This disruption is also predicted to be more closely associated with variability across longitudinally collected mood measures, highlighting a shared relationship between mood instability and circadian rhythm disruptions.

Findings of these analyses will not only further the current literature of circadian rhythm disruptions in mood disorders and at-risk groups by incorporating dynamic clinical and temporal elements, but will also begin to shed light on the putative underlying

mechanisms of mood instability and associated behavioural instabilities. Such investigation will set the foundation for more specialised analyses of dynamic functionality in underlying neural homeostatic mechanisms (*chapters 5* and *6*) in order to continue building a translational neuroscientific profile of mood instability that can transform our current understanding of mood disorders.

Whilst previous research to date has highlighted the presence of circadian rhythm disruptions across both the prodrome and course of mood disorders such as BD and MDD, the particular components of this disruption and methods used to measure this behaviour have remained inconsistent. Perhaps highlighting the complex nature of circadian rhythm and sleep, analysis of this process can often involve self-report questionnaire measures of chronotype, biological measures of melatonin secretion, genetic studies, and studies involving the use of wearable actigraph devices. In order to provide the best measure of longitudinal behaviour and patterns, and to also follow the trend of employing new technology-based remote-monitoring devices, the current study aims to use the latter actigraph approach to study circadian rhythms. Whilst data provided by such devices provide proxy markers of circadian sleep and activity, the frequency and time course over which data is collected, as well its perceived tolerability, scalability, and use in patient populations is important and noted.

4.2 Methods

The current chapter focuses on analyses and results from actigraphy data collected as part of the COMET study, measuring rest-activity patterns. A summary of the particular methodology used for the collection of this data can be found in *chapter 2, section 2.5.4*. A wider description of the methodology used in the collection of mood data can also be found in *chapter 2*; as well as thorough description of overall participants recruited in the study in *chapter 2, section 2*, and overall sample characteristics in *section 3*. The remainder of this chapter will focus, thus, on presenting the particulars of the data collected and the analysis methods used for this data.

4.2.1 Participants

Out of the seventy-four participants who completed the COMET study, only those who had provided at least 50 days of actigraphy data, corresponding to the maximum of 50 days of mood data collected, are included in current analyses. Sixty-two participants are thus included in these analyses, 31 of which are in the high MDQ group and 31 in the low MDQ group.

4.2.2 Device and equipment

All participants were equipped with wrist-worn GENEActiv Original actigraphs (ActivInsights Ltd, UK), which they wore consecutively for 28 days at a time. To account for the 10-week study period, participants wore three watches throughout the duration of the study. In order to facilitate battery life for each 28-day period, actigraph sampling frequency was set to 25Hz.

The actigraphs used contain a tri-axial accelerometer integrated in microelectromechanical systems and measure raw acceleration in gravitational units with a range of +/- 8g (1g = 9.8 m/s^2). The main output measure representing participants' moment-to-moment activity is the gravity subtracted signal vector magnitude of acceleration (Esliger et al., 2011), given by the equation:

$$\text{Acceleration magnitude} = \left(\sum \sqrt{x^2 + y^2 + z^2} - g\right)$$

Where *x*, *y*, and *z* are the three raw signals and 1g is subtracted to account for acceleration due to gravity. Negative values were rounded to zero, as per the Euclidean Norm Minus One (ENMO) (Hildebrand, van Hees, Hansen, & Ekelund, 2014; van Hees et al., 2014).

4.2.3 Data pre-processing

Data were pre-processed using the *GGIR* package (van Hees et al., 2013) for R version 3.4.2 (R Core Team, Vienna). Only data included between the first and last midnight of actigraph recording were analysed for each participant. The *GGIR* non-wear algorithm ensured that any suspected actigraph removals were identified and missing intervals imputed with the average of similar time points from other full days of recording. Any days with more than three hours of missing data were excluded from further analyses (Bromundt et al., 2011; McGowan, Goodwin, Bilderbeck, & Saunders, 2019).

4.2.3.1 Rest-activity variables

Non-parametric circadian rhythm analysis (NPCRA) variables (Van Someren et al., 1999) reflecting the structure of rest-activity patterns were calculated using the *GGIR* algorithm. Parameters included a marker for the average phase onset and activity levels for the 5-hour period of lowest activity in a given 24-hour period (L_5), the 10-hour period of greatest activity in a given 24-hour period (M_{10}), a marker for within-day consolidation of rest-activity states (IV or intradaily variability), and a marker for the consistency of rest-activity patterns between days (IS or interdaily stability). A marker of amplitude strength, measuring the difference in activity between the most active 10-hour period (M_{10}) and least active 5-hour period (L_5), was also calculated and referred to as Relative Amplitude (RA). The equation for RA is give below.

$$\mathrm{RA} = \frac{M_{10} - L_5}{M_{10} + L_5}$$

Please see table 11 for a full description of the variables, including identification of their proxy marker.

Variable name	Description	Proxy marker
L_5 onset	Onset of the lowest five hours of activity in a 24-hour period.	Sleep/rest onset.
L_5 activity	Activity levels over the lowest five hours of activity in a 24-hour period, after L_5 onset.	Sleep/rest activity.
M_{10} onset	Onset of the most active ten hours in a 24-hour period.	Day/active onset.
M_{10} activity	Activity levels over the greatest ten hours of activity in a 24-hour period, after M_{10} onset.	Day/diurnal activity.
Relative Amplitude (RA)	Differentiation score of activity during the ten most active hours in a 24-hour period (M_{10} activity) compared to activity during the five least active hours in a 24-hour period (L_5 activity). Scored between 0-1, with a lower RA representing lower differentiation.	Differentiation between day and night, or activity during active and rest states. A lower score represents less difference in activity between day and night.
Intradaily Variability (IV)	Difference in activity within a day. Greater values represent greater rhythm fragmentation.	A variability marker. Greater fragmentation indicates more transitions between rest and active states.
Interdaily Stability (IS)	Difference in activity across days. Greater values represent greater stability of rhythm.	A stability marker. Greater stability indicates more consistency of rest-activity patterns between days.

Table 11: Description of rest-activity pattern variables, including proxy marker association.

4.2.4 Procedure

4.2.4.1 Actigraph set-up

Participants were set up with their first actigraph at their screening visit. Actigraphs were configured using the GENEActiv software (ActivInsights Ltd, UK). For configuration, each participant's height and weight were entered, and BMI calculated. Participants were required, where possible, to wear the device on their non-dominant wrist, and record of this was also entered into the configuration software.

Actigraphs were given to participants to wear immediately after being configured by the researcher, as recording also started immediately. Participants were asked to wear the devices for 24 hours a day for the duration of each 28-day period. They were also made aware that the devices were completely waterproof and had light and activity sensors.

Where possible, the majority of participants made separate research visits after 28 days to return actigraphs that had ceased recording and to collect new ones. The same process as above was followed for these visits.

Where participants were unable to make such visits, new actigraphs were configured by the researcher and mailed to the participant, with instructions on when and how to begin recording (via button press on the device). In these instances, participants returned all three full actigraphs to the researcher at their final study visit.

4.2.4.2 Data extraction

Data were extracted from the actigraphs at return, using the GENEActiv software. All data were extracted in *.bin* files and stored on secure university-held servers. These files were then converted to *.csv* files, also through the same software, in order to be pre-processed through the *GGIR* package.

4.2.5 Analyses

Two data files were outputted by the *GGIR* pre-processing package. The first held overall summary data for each actigraph (across a maximum of 28 days), and the second included day-by-day summary measures for each actigraph.

Within the overall summary output, data for L_5 onset, L_5 activity, M_{10} onset, M_{10} activity, IS and IV were included. IS and IV variables were not available in daily summary measures. RA was calculated for both data sets, using the equation described above.

Prior to the main statistical analyses being run, demographics were explored and descriptive statistics presented, particularly those pertaining to actigraph recording and with potential relevance to rest-activity patterns such as season at study entry and the presence of seasonal clock/time change (BST to GMT, and vice-versa).

4.2.5.1 Overall analyses

Independent samples t-tests were carried out on overall summary data, in order to investigate group differences in L_5 onset, L_5 activity, M_{10} onset, M_{10} activity, RA, IS and IV, as proxy markers of sleep and day and variability markers of sleep-rest activity patterns. Analyses were conducted using the SPSS software (IBM Corp, 2017).

4.2.5.2 Weekly rest-activity data

In order to investigate the effect of time on rest-activity patterns as well as to visualise this potential interaction across groups, data from daily summary measures were first collapsed into weekly aggregate scores. Daily time stamps recorded by the actigraphs were used, and weekly scores across the five rest-activity variables were then calculated by taking the mean of scores in each 7-day window. A weekly variability score for each of these variables was also calculated by taking the standard deviation (SD) across each 7-day window.

A repeated measures ANOVA was conducted using SPSS (IBM Corp, 2017) to analyse the effect of group (high MDQ or low MDQ; the between-subjects factor), time (week; the within-subjects factor), and group by time interaction for L_5 onset, L_5 activity, M_{10} onset, M_{10} activity, and RA. Separate ANOVAs were also conducted for weekly average and weekly variability measures within these five variables.

4.2.5.3 Relationship between rest-activity patterns and mood

4.2.5.3.1 Overall summary markers

In order to begin to understand the relationship between rest-activity patters and mood, correlational analyses were employed on summary data for rest-activity variables (L_5 onset, L_5 activity, M_{10} onset, M_{10} activity, RA, IS and IV) and mood[20] (positive affect and negative affect). These analyses were conducted on both average and variability – as measured by the SD and *t*RMSSD – measures of mood in order for the relationship between rest-activity patterns and mood experiences and instability to be explored.

4.2.5.3.2 Rest-activity patterns and mood across time

Linear mixed-effects models (LMMs) were used to analyse the effect of group on the relationship between rest-activity patterns and mood across weeks. These analyses were conducted using the *lme4* package (version 1.-17) (Bates, Mächler, Bolker, & Walker, 2015) in the R statistical programming language (R Core Team, 2019) using R Studio (R Studio Team, 2016). LMMs were chosen as they allow for simultaneous estimation of between-subjects and between-recording variance, and therefore yield advantages over traditional analyses of variance (Baayen, Davidson, & Bates, 2008; Helbing, Draschkow, & Võ, 2020; Kliegl, Wei, Dambacher, Yan, & Zhou, 2011).

[20] Please see *chapter 3, section 2*, for an explanation of mood scoring and analyses.

Two analysis models were run in order to explore this relationship over time and in relation to concurrent mood, and to test for group differences. Therefore, LMMs were defined such that group and time (LMM 1) or group and mood (LMM 2) were entered as fixed effects and participant ID as the random effect, resulting in:

LMM 1:

$$\text{rest} - \text{activity variable} \sim (time \times group) + mood + (1 \mid participant\ ID)$$

where the interaction between group and time, controlling for mood, was tested.

LMM 2:

$$\text{rest} - \text{activity variable} \sim (mood \times group) + time + (1 \mid participant\ ID)$$

where the interaction between group and mood, controlling for time, was tested.

All five-weekly rest-activity variables (L_5 onset, L_5 activity, M_{10} onset, M_{10} activity, and RA) were entered as dependent variables, and the relationship with mood tested across both domains (positive affect and negative affect). Time and mood were *z*-scored in order to meet the assumptions of LMM analysis.

Within these weekly measures of rest-activity patterns and mood, both absolute (average as measured by the mean) and variability (as measured by SD) markers were explored in a combination of four model designs:

	Rest-activity variable	Mood
Model 1	Average	Average
Model 2	Average	SD
Model 3	SD	Average
Model 4	SD	SD

Table 12: LMM designs in order to account for the relationship between absolute and variability markers of rest-activity patterns and mood.

For each LMM, estimated regression coefficients together with the *t*-statistic are presented for each of the main effects (time, group, and mood) and interaction effect (time by group or mood by group). *P*-values were calculated using Satterthwaite's degrees of freedom method via the *lmerTest* package (version 3.1-0) (Kuznetsova, Brockhoff, & Christensen, 2017).

4.2.5.3.3 Group comparisons of correlation coefficients

In order to further test this relationship over time, group comparisons using independent samples *t*-tests were carried out on correlation coefficients. Correlational analyses were first conducted for each individual participant's rest-activity pattern and mood data. These correlation coefficients were then z-transformed, and group differences were explored, using the same design configuration as that used in LMM analyses (table 12). These analyses were run using both the R and R Studio (R Core Team, 2013) packages and SPSS (IBM Corp, 2017).

4.3 Results

Overall sample characteristics and demographic data can be found in *chapter 2*, *section 3.1*.

4.3.1 Descriptive statistics

4.3.1.1 Actigraphy demographic data

	High MDQ (*n*=31)	Low MDQ (*n*=31)
Gender *[m:f]*	11:20	12:19
Handedness *[right:left]*	27:4	26:5
GENEActiv hand *[right:left]*	5:26	5:26
Age *[mean (SD)]*	24.58 (6.84)	25.19 (7.06)
Height (cm) *[mean (SD)]*	170.11 (8.74)	170.87 (9.51)
Weight (kg) *[mean (SD)]*	67.99 (15.17)	66.00 (12.61)
BMI *[mean (SD)]*	23.36 (4.22)	22.44 (2.61)

Table 13: Demographic data for high MDQ and low MDQ groups.

Descriptive statistics specific to the sixty-two participants whose actigraphy data were analysed are presented in table 13. No statistically significant association between group and gender ($X(1) = 0.07$, $p = .793$), handedness ($X(1) = 0.13$ $p = .718$), or hand GENEActiv device was worn on ($X(1) = 0.00$, $p = 1.00$) was found. Further, no significant difference in age ($t(60) = 0.35$, $p = .730$), height ($t(60) = -0.33$, $p = .745$), weight ($t(60) = 0.56$, $p = .576$), and BMI ($t(60) = 1.04$, $p = .304$) between the groups was reported.

4.3.1.2 Seasons at study entry

	High MDQ	Low MDQ
Spring	8	14
Summer	5	2
Autumn	11	7
Winter	7	8

Table 14: Seasons at study entry. Number of high MDQ and low MDQ participants shown.

Table 14 and fig. 18 present the number of participants who entered the study during each of the four seasons. No statistically significant association between group and season at study entry, $X(3) = 3.88$, $p = .275$, was found.

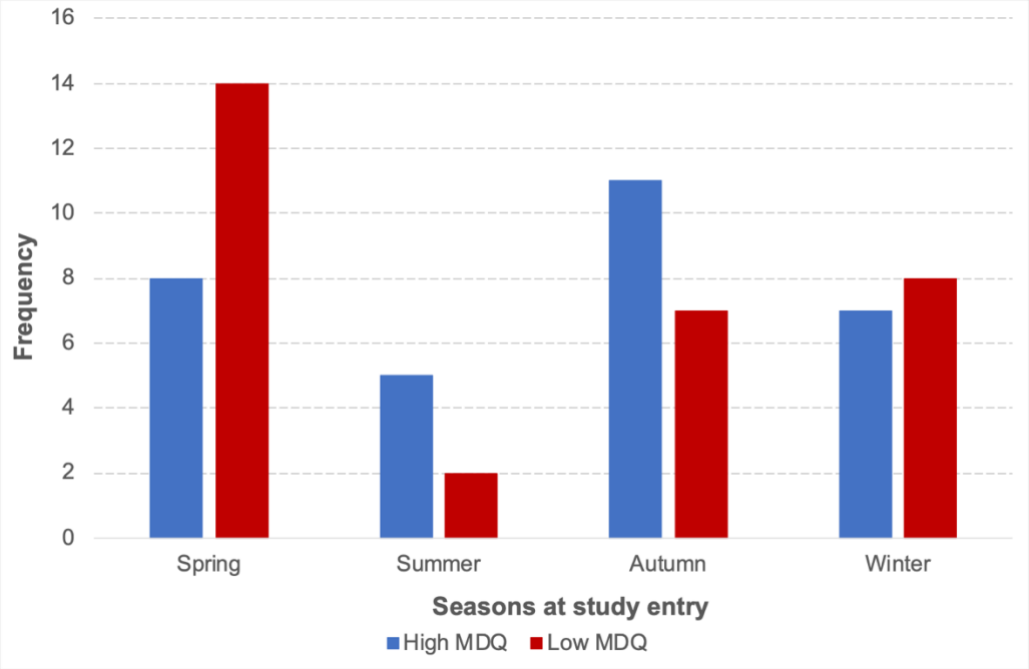


Figure 18: Seasons at study entry. Proportion of high MDQ and low MDQ participants shown.

4.3.1.3 Clock/time change

	High MDQ	Low MDQ
Clock change *(BST → GMT and GMT → BST)*	13	14
No clock change	18	17

Table 15: Participants who experienced a time change during participation in the COMET study.

Table 15 and fig. 19 show the number of participants who took part in the study during a seasonal time change, either from British Summer Time (BST) to Greenwich Mean Time (GMT) or vice-versa. There was no statistically significant association between group and seasonal clock change, $X(1) = 0.07$, $p = .798$.

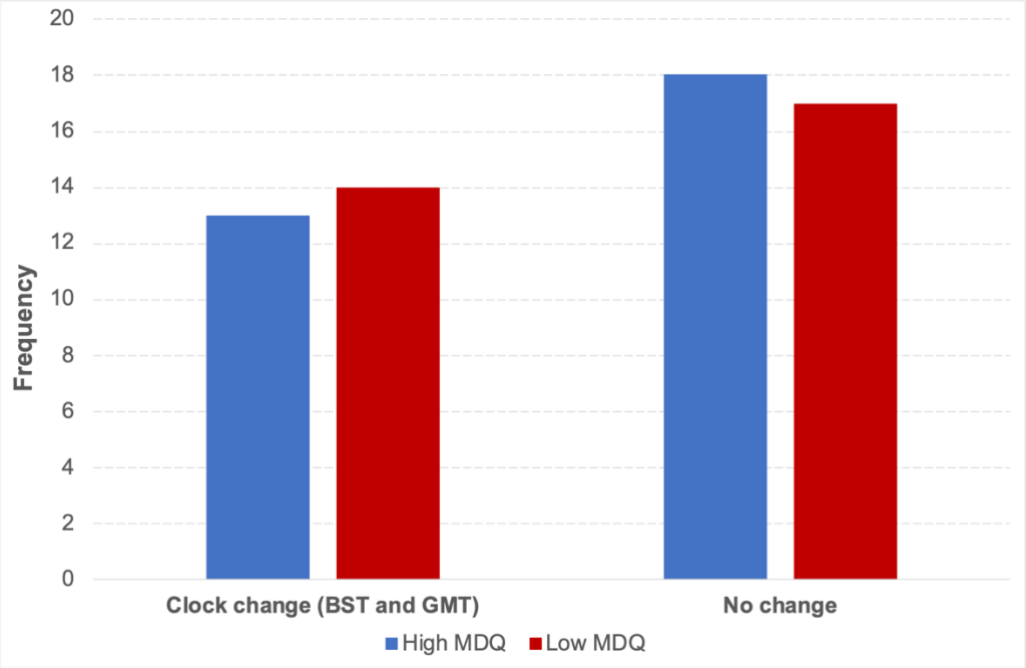


Figure 19: Proportion of participants who experienced a seasonal time change.

4.3.1.4 Observations

	High MDQ		Low MDQ	
	Mean (SD)	*Median (spread)*	*Mean (SD)*	*Median (spread)*
Days	65.94 (6.25)	66.00 (54.00-79.00)	65.39 (8.57)	67.00 (51.00-81.00)
Weeks	9.39 (.99)	9.00 (8.00-11.00)	9.39 (1.26)	10.00 (7.00-12.00)

Table 16: Number of observations (days/weeks). Averages and spread included.

Descriptive statistics for the average number of days and weeks of actigraphy data recorded in the high MDQ and low MDQ groups are shown in table 16.

A Shapiro-Wilk test indicated that the number of days of actigraphy data recorded did follow a normal distribution for the high MDQ group ($W(31) = 0.98$, $p = .736$) and low MDQ group ($W(31) = 0.95$, $p = .170$). Thus, parametric tests were conducted to test for group differences in the number of daily recordings. A Shapiro-Wilk test indicated however, that the number of weeks of actigraphy data did not follow a normal distribution for both the high MDQ ($W(31) = 0.88$, $p = .002$) and low MDQ ($W(31) = 0.90$, $p = .007$) groups, and so non-parametric tests were conducted to test for group differences in this data.

An independent samples *t*-test indicated that there was no significant difference in the number of days of actigraphy data recorded between the groups, $t(60) = 0.29$, $p = .774$ (fig. 20, left). A Mann-Whitney test also indicated that there was no significant difference in the number of weeks of actigraphy data recorded between the groups, $U = 467.00$, $p = .842$, $r = -.00$ (fig. 20, right).

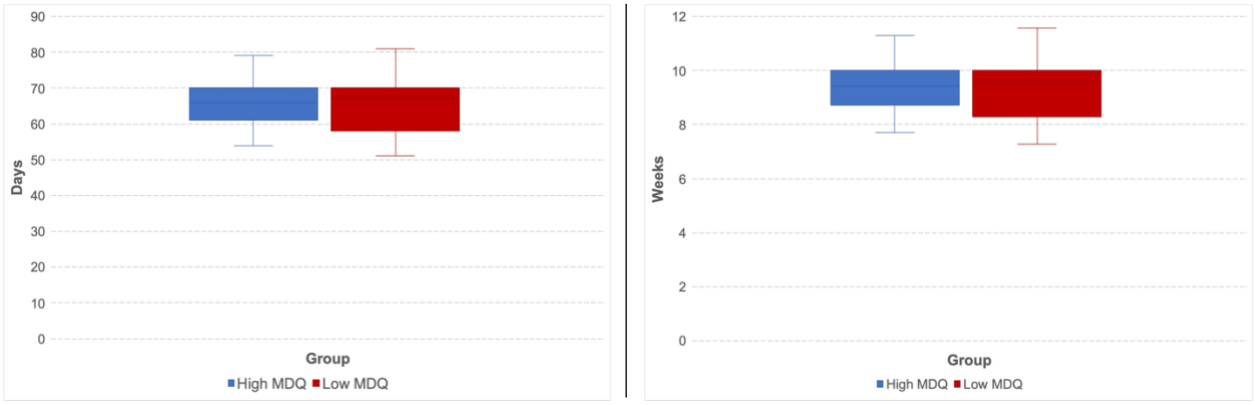


Figure 20: Distribution of actigraphy data in days (left). Distribution of actigraphy data in weeks (right).

4.3.2 Overall rest-activity data

		High MDQ	Low MDQ
		Mean (SD)	Mean (SD)
L_5	Onset (hh:mm)	02:13 (1.46)	02:26 (2.40)
	Activity	6.19 (1.78)	6.16 (2.29)
M_{10}	Onset (hh:mm)	13:20 (2.19)	12:53 (2.61)
	Activity**	**49.78 (12.71)**	**62.26 (19.74)**
RA*		**.77 (.07)**	**.81 (.06)**
IS		0.31 (0.09)	0.36 (0.12)
IV		1.03 (0.18)	1.07 (0.22)

Table 17: Overall rest-activity markers as measured by actigraphs. Averages and standard deviations (SD) are shown. Mean L5 onset and M10 onset are shown as 24-hour times. * $p < .05$, ** $p < .01$

Table 17 presents overall average and variability data for each of the seven rest-activity variables (L_5 onset, L_5 activity, M_{10} onset, M_{10} activity, RA, IS, and IV) across

groups. Shapiro-Wilk tests carried out on these data showed that the majority of distributions were normal[21].

High MDQ participants had lower M_{10} activity and RA, both of which were significantly different (M_{10} activity: $t(60) = -2.96$, $p = .004$; RA: $t(60) = -2.33$, $p = .023$) (fig. 21).

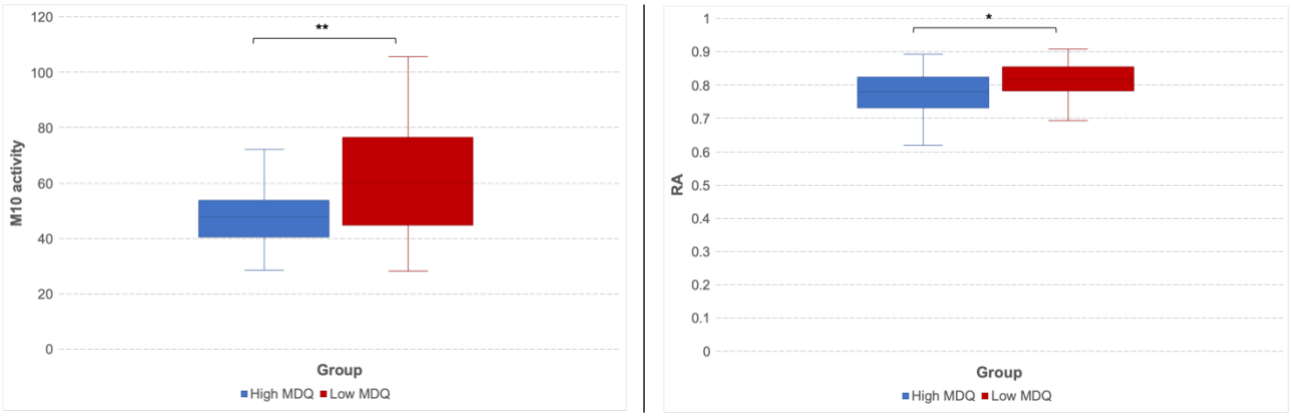


Figure 21: Overall M10 activity between groups (left). Overall RA between groups (right). * $p < .05$, ** $p < .01$

No statistically significant group differences in L_5 onset ($t(60) = -0.44$, $p = .659$), L_5 activity ($t(60) = 0.04$, $p = .966$), M_{10} onset ($t(60) = 0.72$, $p = .473$), IS ($t(60) = -1.59$, $p = .118$), and IV ($t(60) = -0.88$, $p = .383$) were found (figs. 22 to 24).

[21] Please see *appendix 4.1* for the full set of Shapiro-Wilk test results for this data.

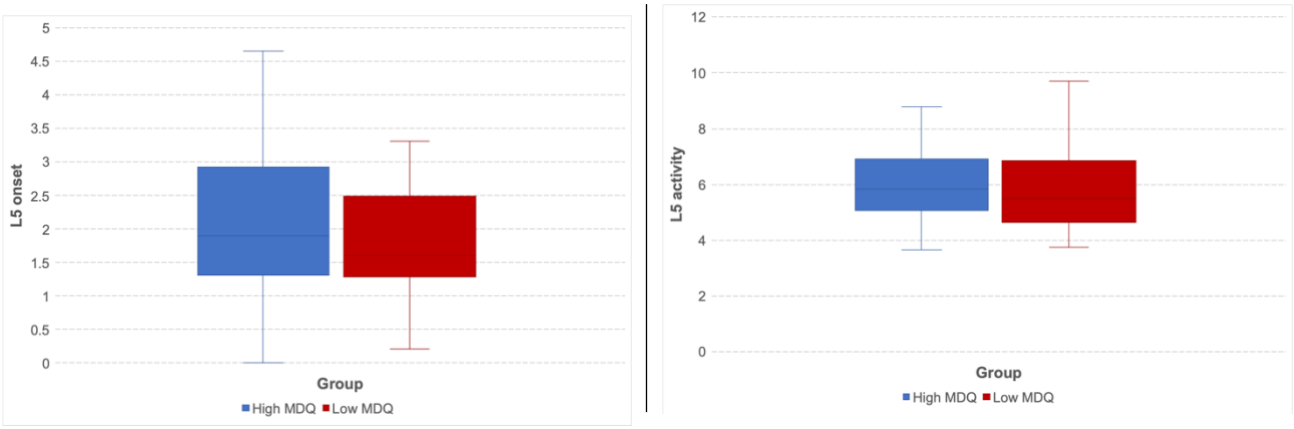


Figure 22: Overall L5 onset between groups (left). Overall L5 activity between groups (right).

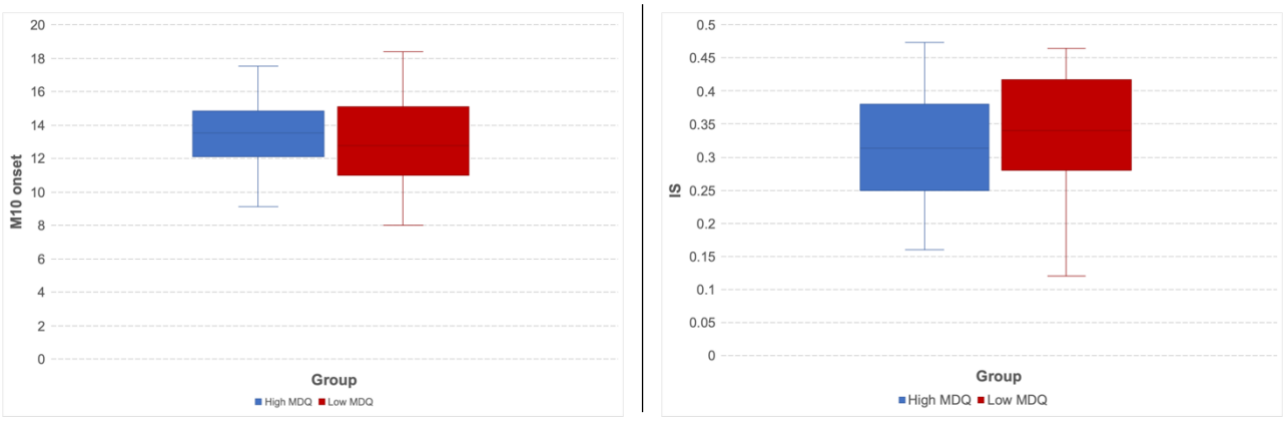


Figure 23: Overall M10 onset between groups (left). Overall IS between groups (right).

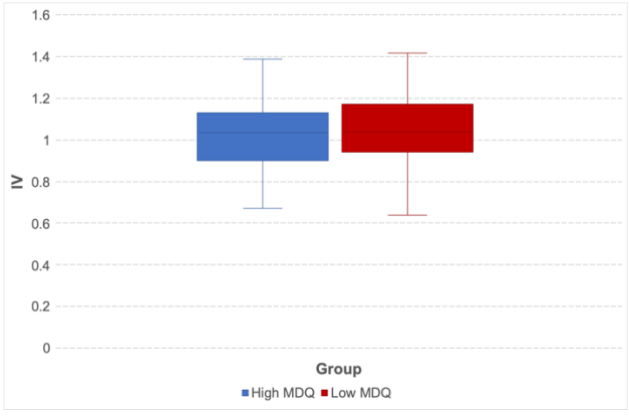


Figure 24: Overall IV between groups.

4.3.3 Weekly rest-activity data

4.3.3.1 L_5 onset

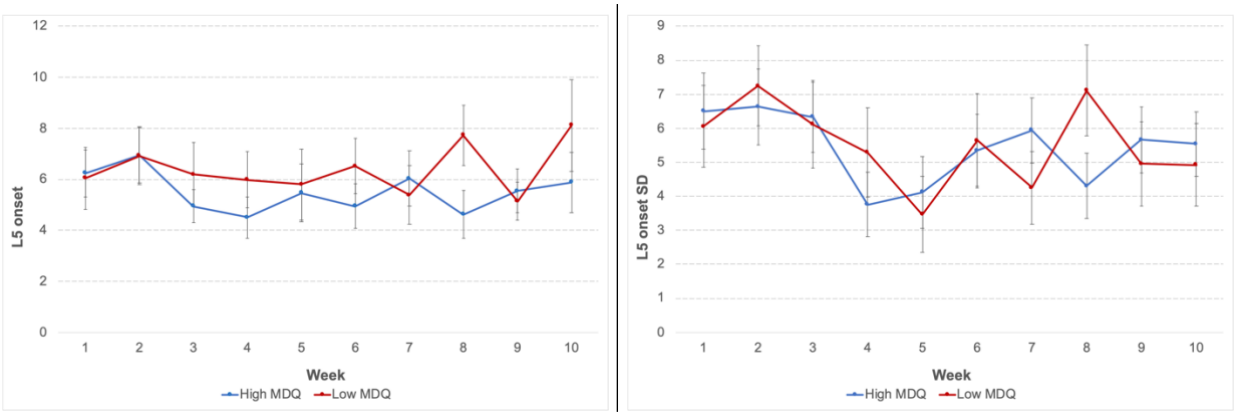


Figure 25: Average L5 onset across weeks (left). Variability in L5 onset across weeks (right). Error bars represent ± 1 *SEM*.

Results revealed no significant main effect of group on average ($F(1, 37) = 0.75$, $p = .391$) or variability ($F(1, 31) = 0.01$, $p = .937$) in L_5 onset across the 10-week period. Whilst no main effect of time was also found for average L_5 onset ($F(6.40, 236.95) = 0.97$, $p = .448$)[22] (fig. 25, left), a significant main effect of time was found for variability in L_5 onset ($F(6.57, 203.79) = 2.37$, $p = .026$)[23] (fig. 25, right).

There was no significant group by time interaction for both average ($F(6.40, 236.95) = 1.01$, $p = .424$) and variability ($F(6.57, 203.79) = 1.20$, $p = .304$) in L_5 onset.

[22] Sphericity violated: Mauchly's $W = .13$, $p < .01$. Greenhouse-Geisser correction used, $\varepsilon = .71$.
[23] Sphericity violated: Mauchly's $W = .08$, $p = .006$. Greenhouse-Geisser correction used, $\varepsilon = .73$.

4.3.3.2 L_5 activity

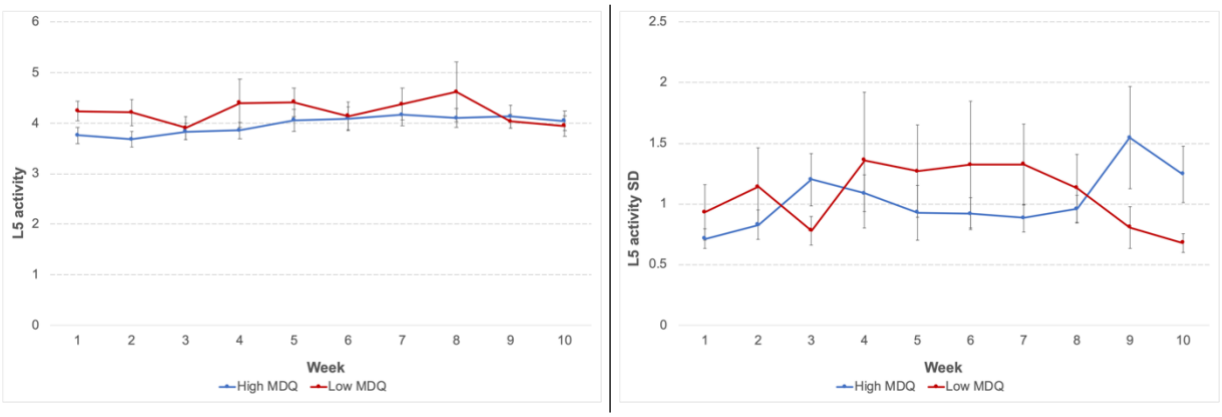


Figure 26: Average L5 activity across weeks (left). Variability in L5 activity across weeks (right). Error bars represent ± 1 *SEM*.

No statistically significant main effect of group or time was found in average (group: $F(1, 37) = 1.08$, $p = .304$; time: $F(3.43, 126.91) = 1.17$, $p = .325$[24]) (fig. 26, left) or variability (group: $F(1, 31) = 0.06$, $p = .813$; time: $F(5.35, 165.87) = 0.47$, $p = .809$[25]) (fig. 26, right) in L_5 activity across the 10-week period.

There was also no significant group by time interaction for average ($F(3.43, 126.91) = 0.85$, $p = .483$) and variability ($F(5.35, 165.87) = 1.67$, $p = .141$) in L_5 activity.

[24] Sphericity violated: Mauchly's $W = .01$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .38$.
[25] Sphericity violated: Mauchly's $W = .03$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .60$.

4.3.3.3 M_{10} onset

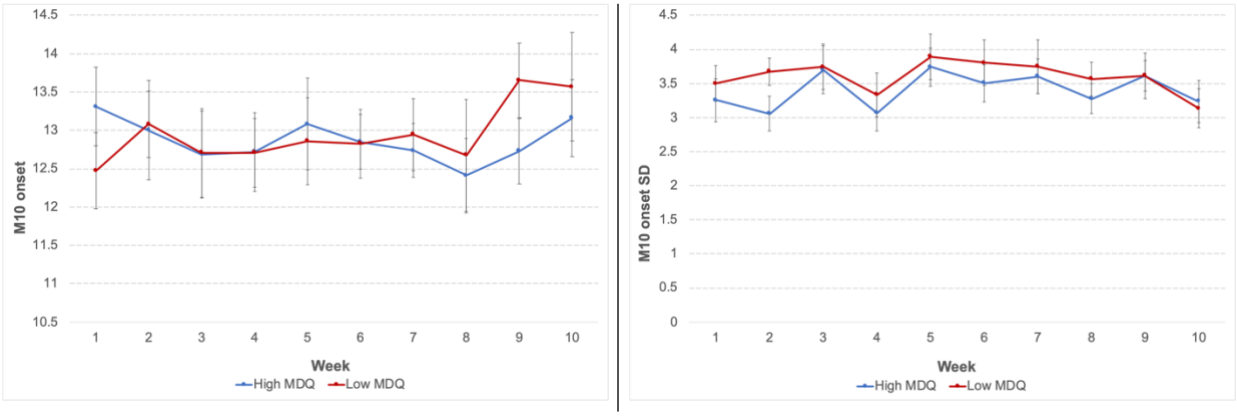


Figure 27: Average M10 onset across weeks. (left). Variability in M10 onset across weeks (right). Error bars represent ± 1 *SEM*.

No statistically significant main effect of group or time was found in average (group: $F(1, 37) = 0.03$, $p = .864$; time: $F(6.01, 222.27) = 0.67$, $p = .677$[26]) (fig. 27, left) or variability (group: $F(1, 31) = 0.73$, $p = .399$; time: $F(9, 279) = 1.43$, $p = .174$) (fig. 27, right) in M_{10} onset across the 10-week period.

There was also no significant group by time interaction for average ($F(6.01, 222.27) = 0.57$, $p = .758$) and variability ($F(9, 279) = 0.29$, $p = .977$) in M_{10} onset.

[26] Sphericity violated: Mauchly's $W = .15$, $p < .05$. Greenhouse-Geisser correction used, $\varepsilon = .67$.

4.3.3.4 M_{10} activity

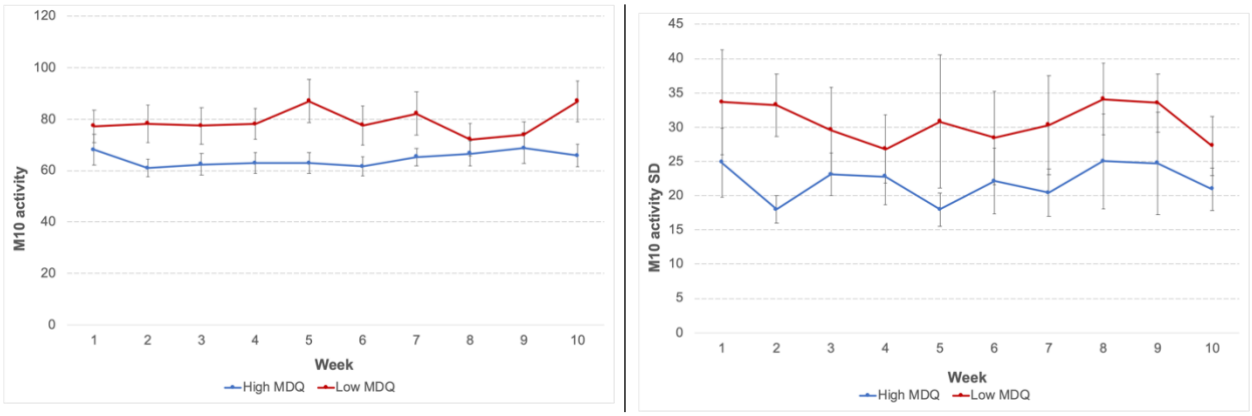


Figure 28: Average M10 activity across weeks (left). Variability in M10 activity across weeks (right). Error bars represent ± 1 *SEM*.

A significant main effect of group was found such that high MDQ participants had lower average M_{10} activity levels than low MDQ participants ($F(1, 37) = 4.70$, $p = .037$). No significant main effect of group was found for variability in M_{10} activity ($F(1, 31) = 1.97$, $p = .170$). No significant main effect of time was found in both average (F (4.89, 180.75) = 1.05, $p = .387$[27]) (fig. 28, left) and variability ($F(4.68, 144.96) = 0.86$, $p = .505$[28]) (fig. 28, right) in M_{10} activity.

There was also no significant group by time interaction for average ($F(4.89, 180.75) = 1.62$, $p = .160$) and variability (F (4.68, 144.96) = 0.53, $p = .741$) in M_{10} activity.

[27] Sphericity violated: Mauchly's $W = .03$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .54$.
[28] Sphericity violated: Mauchly's $W = .03$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .52$.

4.3.3.5 RA

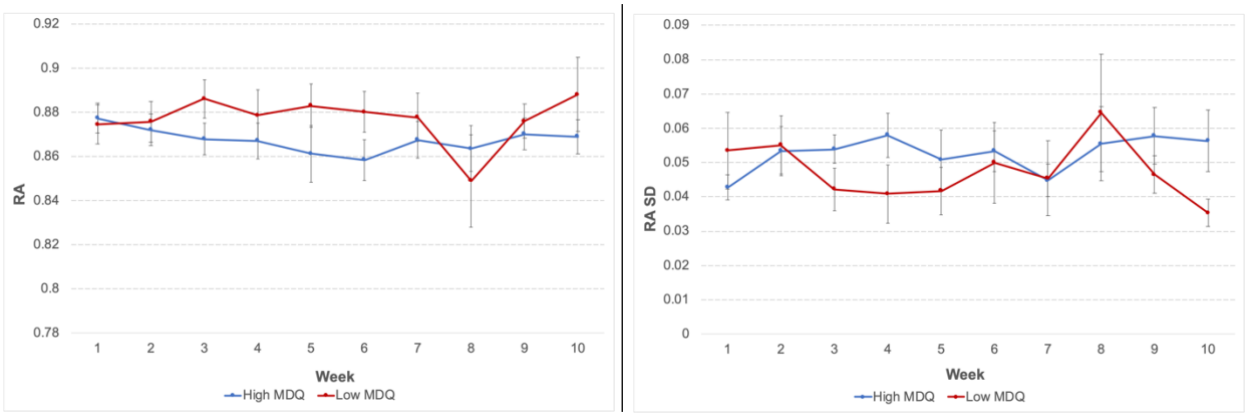


Figure 29: Average RA across weeks (left). Variability in RA across weeks (right). Error bars represent ± 1 *SEM*.

No statistically significant main effect of group or time was found in average (group: $F(1, 37) = 1.07$, $p = .308$; time: $F(4.46, 164.93) = 1.08$, $p = .371$[29]) (fig. 29, left) or variability (group: $F(1, 31) = 0.81$, $p = .377$); time: $F(5.33, 165.29) = 0.70$, $p = .630$[30]) (fig. 29, right) in RA across the 10-week period.

There was also no significant group by time interaction for average ($F(4.46, 164.93) = 0.98$, $p = .425$) or variability ($F(5.33, 165.29) = 0.96$, $p = .447$) in RA.

[29] Sphericity violated: Mauchly's $W = .02$, $p < .001$. Greenhouse-Geisser correction used, $\varepsilon = .50$.
[30] Sphericity violated: Mauchly's $W = .07$, $p = .005$. Greenhouse-Geisser correction used, $\varepsilon = .59$.

4.3.4 Actograms

Representative example actograms displaying 24-hour activity patterns in three high MDQ and three low MDQ participants are shown in figure 30.

Actograms from individuals in the low MDQ group (D-F) show clear distinctions in activity levels during rest (L_5) and activity (M_{10}) periods, or night and day. More striking are the activity patterns of high MDQ participants (A-C) that show significant reductions in both daytime activity (M_{10}) and thus, relative amplitude (RA). A high MDQ participant with particularly low RA and daytime activity (M_{10} activity) can be seen in C, with the median representation shown in A.

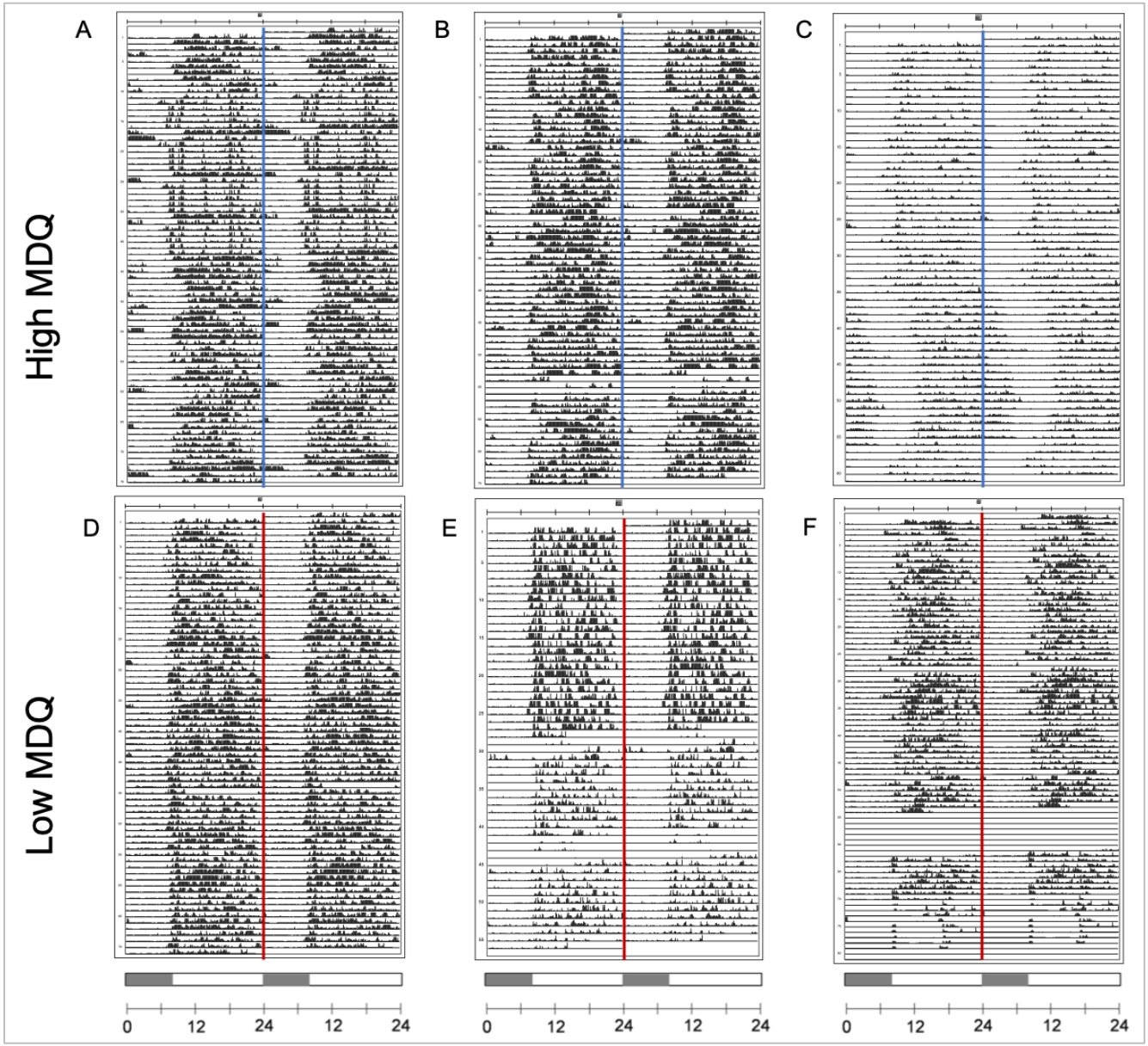


Figure 30: Representative actograms of rest-activity patterns. Visual inspection of double-plotted 24-h actograms generated from participants' rest-activity patterns reflect the characteristic differences detected between study groups. Shaded portion of scale bar represents interval between 00:00 and 08:00 h as a reference guide. Actograms were generated using ActogramJ (http://actogramj.neurofly.de/).

4.3.5 Relationship between rest-activity patterns and mood

4.3.5.1 Correlations between overall rest-activity markers and mood

		L_5 Onset		L_5 Activity		M_{10} Onset		M_{10} Activity		RA		IS		IV	
		High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
Positive Affect	*Average*	-.21	.30	.07	-.08	-.07	-.16	.14	-.25	-.00	-.22	-.04	.08	.13	.04
	SD	-.01	-.09	-.16	-.14	-.11	-.11	.28	-.10	.29	-.09	-.14	.02	.16	.06
	tRMSSD	-.04	-.26	-.17	-.06	-.31	-.09	**.39***	.17	.35	.11	-.18	-.12	**.41***	.18
Negative Affect	*Average*	.08	-.23	-.20	-.05	-.16	-.26	.28	.15	.30	.11	-.07	.07	.16	.29
	SD	.10	-.24	-.19	-.07	.05	-.17	.18	.05	.22	-.03	-.02	-.01	.10	.16
	tRMSSD	.12	-.13	-.25	-.07	-.05	-.11	.20	.18	.27	.13	.05	-.07	.12	.20

Table 18: Pearson Product-Moment correlation coefficients of the overall rest-activity variables with mood (average and variability as measured by SD and tRMSSD) between groups.

* $p < .05$, ** $p < .01$

As can be seen from table 18, M_{10} activity and IV were significantly associated with variability (as measured by *t*RMSSD) in positive affect in the high MDQ group. However, Fishers Z test revealed that these were not significantly different from the low MDQ group (M_{10} activity: $z = 0.89$, $p = .374$; IV: $z = 0.94$, $p = .437$).

It should also be noted that none of these correlations survived a Bonferroni adjusted *p*-value of .001.

4.3.5.2 Rest-activity patterns and mood across time (LMMs): Group differences in the relationship between rest-activity patterns and time, controlling for mood (LMM 1)

4.3.5.2.1 L_5 onset

		L_5 onset		
			Estimate	*t*
		Average		
Mood	Average	Time	-0.97	-1.91
		Group	0.92	1.35
		Positive affect	0.49	1.90
		Time x group	**0.70**	**2.14***
		Time	-0.90	-1.76
		Group	0.68	0.95
		Negative affect	-0.27	-1.09
		Time x group	0.64	1.95
	SD	Time	-0.98	-1.90
		Group	0.86	1.22
		Positive affect	-0.08	-0.39
		Time x group	**0.68**	**2.08***
		Time	-1.01	-1.96
		Group	0.76	1.07
		Negative affect	-0.21	-0.98
		Time x group	**0.70**	**2.12***
		SD		
	Average	**Time**	**-1.09**	**-2.30***
		Group	0.29	0.39
		Positive affect	0.31	1.19
		Time x group	0.54	1.78
		Time	**-1.01**	**-2.13***
		Group	0.02	0.02
		Negative affect	-0.32	-1.39
		Time x group	0.49	1.60
	SD	**Time**	**-1.12**	**-2.35***
		Group	0.22	0.29
		Positive affect	-0.12	-0.65
		Time x group	0.54	1.78
		Time	**-1.17**	**-2.47***
		Group	0.04	0.05
		Negative affect	-0.36	-1.84
		Time x group	0.57	1.87

Table 19: Results of the linear mixed-effects model (LMM) for L5 onset with group by time interactions, including estimated regression coefficients together with the t-statistic. * p < .05

Table 19 reveals a significant group by time interaction for L_5 onset, controlling for average and variability in mood across the domains of positive affect and negative affect. Thus, high MDQ participants differ from low MDQ participants in their L_5 onset over time, over and above differences in absolute mood and mood instability.

Results also show a significant main effect of time on variability in L_5 onset, controlling for average and variability in mood and group, such that time accounts for changes in variability in L_5 onset over and above differences in group and mood (both absolute mood and mood instability).

No statistically significant main effect of group, controlling for both average and variability in mood, on average and variability in L_5 onset was found. Also, no significant effect of mood (average and variability) on average and variability in L_5 onset was found.

4.3.5.2.2 M_{10} activity

		M_{10} activity		
			Estimate	*t*
		Average		
Mood	Average	Time	-0.89	-0.43
		Group	**17.36**	**2.88****
		Positive affect	1.74	1.32
		Time x group	1.40	1.05
		Time	-0.66	-0.31
		Group	**16.56**	**2.72****
		Negative affect	-0.95	-0.87
		Time x group	1.21	0.90
	SD	Time	-0.09	-0.04
		Group	**18.04**	**3.02****
		Positive affect	1.97	2.29*
		Time x group	0.99	0.74
		Time	-0.93	-0.45
		Group	**17.11**	**2.83****
		Negative affect	-0.29	-0.32
		Time x group	1.36	1.01
		SD		
	Average	Time	-0.58	-0.34
		Group	6.44	1.56
		Positive affect	1.27	1.21
		Time x group	0.37	0.33
		Time	-0.24	-0.14
		Group	5.26	1.24
		Negative affect	-1.48	-1.66
		Time x group	0.14	0.12
	SD	Time	-0.62	-0.36
		Group	6.32	1.52
		Positive affect	-0.17	-0.24
		Time x group	0.34	0.30
		Time	-0.63	-0.36
		Group	6.20	1.49
		Negative affect	-0.30	-0.40
		Time x group	0.34	0.31

Table 20: Results of the linear mixed-effects model (LMM) for M10 activity with group by time interactions, including estimated regression coefficients together with the t-statistic.

* $p < .05$, ** $p < .01$

As can be seen from table 20, there was a significant main effect of group on average M_{10} activity, controlling for both average and variability in mood across the domains of positive affect and negative affect, and time. Therefore, high MDQ participants differ

from low MDQ participants in their levels of M_{10} activity over and above differences in mood (both absolute mood and mood instability) and time.

No significant main effect of time, controlling for average and variability in mood, and group by time interaction, again controlling for average and variability in mood, on average M_{10} activity was found. Furthermore, there was no significant effect of mood, across average and variability in positive affect and negative affect, on average M_{10} activity.

No statistically significant effect of group, time, or group by time interaction, controlling for average and variability in mood, on variability in M_{10} activity were found. The effect of average and variability in mood on variability in M_{10} activity was also not significant.

4.3.5.2.3 Other rest-activity variables

No statistically significant effects of group, time, or group by time interaction, controlling for average and variability in mood, on both average and variability in L_5 activity, M_{10} onset, and RA were found. Similarly, no effect of mood on these rest-activity variables were found. Please see *appendix 4.2* for a full break down of the statistics for these variables.

4.3.5.3 Rest-activity patterns and mood across time (LMMs): Group differences in the relationship between rest-activity patterns and mood, controlling for time (LMM 2)

4.3.5.3.1 L_5 onset

		L_5 onset		
			Estimate	*t*
		Average		
Mood	Average	Time	0.06	0.37
		Group	0.90	1.31
		Positive affect	0.55	0.67
		Positive affect x group	-0.05	-0.10
		Time	0.05	0.32
		Group	0.68	0.93
		Negative affect	-0.60	-0.78
		Negative affect x group	0.24	0.41
	SD	Time	0.02	0.1
		Group	0.88	1.25
		Positive affect	-0.76	-1.26
		Positive affect x group	0.53	1.28
		Time	0.02	0.12
		Group	0.77	1.09
		Negative affect	-0.39	-0.61
		Negative affect x group	0.16	0.36
		SD		
	Average	Time	-0.29	-1.89
		Group	0.27	0.36
		Positive affect	0.21	0.27
		Positive affect x group	0.05	0.09
		Time	-0.30	-1.95
		Group	-0.10	-0.12
		Negative affect	0.01	0.01
		Negative x group	-0.30	-0.52
	SD	**Time**	**-0.33**	**-2.14***
		Group	0.24	0.32
		Positive affect	-0.80	-1.41
		Positive affect x group	0.52	1.33
		Time	**-0.34**	**-2.24***
		Group	0.10	0.13
		Negative affect	-1.09	-1.84
		Negative affect x group	0.57	1.36

Table 21: Results of the linear mixed-effects model (LMM) for L5 onset with group by mood interactions, including estimated regression coefficients together with the t-statistic. * $p < .05$

Table 21 reveals a significant main effect of time on variability in L_5 onset, controlling for variability in mood and group, such that time accounts for changes in variability in L_5 onset over and above differences in group and mood instability.

No statistically significant main effect of group, mood, or group by mood interaction, controlling for time, on average and variability in L_5 onset was found. Also, no significant effect of time on average L_5 onset was found.

4.3.5.3.2 L_5 activity

		L_5 activity		
			Estimate	*t*
		Average		
Mood	Average	**Time**	**0.11**	**2.55***
		Group	0.30	1.43
		Positive affect	-0.04	-0.16
		Positive affect x group	0.01	0.08
		Time	**0.11**	**2.54***
		Group	0.31	1.41
		Negative affect	0.06	0.29
		Negative affect x group	-0.03	-0.21
	SD	**Time**	**0.10**	**2.29***
		Group	0.30	1.43
		Positive affect	**-0.40**	**-2.47***
		Positive affect x group	**0.27**	**2.41***
		Time	**0.10**	**2.33***
		Group	0.28	1.30
		Negative affect	**-0.41**	**-2.45***
		Negative affect x group	**0.25**	**2.12***
		SD		
	Average	Time	2.31e-02	0.46
		Group	1.71e-02	0.12
		Positive affect	4.76e-03	0.02
		Positive affect x group	9.61e-03	0.08
		Time	0.02	0.35
		Group	0.05	0.34
		Negative affect	0.21	1.01
		Negative affect x group	-0.11	-0.66
	SD	Time	0.02	0.44
		Group	0.02	0.14
		Positive affect	-0.02	-0.14
		Positive affect x group	0.02	0.21
		Time	0.02	0.48
		Group	0.06	0.39
		Negative affect	-0.06	-0.36
		Negative affect x group	0.09	0.68

Table 22: Results of the linear mixed-effects model (LMM) for L5 activity with group by mood interactions, including estimated regression coefficients together with the t-statistic.
* $p < .05$

Table 22 reveals a significant main effect of time on average L_5 activity, controlling for average mood and group, such that time accounts for changes in average L_5 activity over and above differences in group and absolute mood.

Results also show a significant mood variability by group interaction for average L_5 activity, as well as main effects of time and variability in mood. Thus, whilst both mood instability and time account for average L_5 activity levels, high MDQ participants differ from low MDQ participants in their relationship between mood instability and average L_5 activity.

No statistically significant effects of group, mood, or group by mood interaction, controlling for time, on variability in L_5 activity were found. The effect of time on variability in L_5 activity was also not significant.

4.3.5.3.3 M_{10} activity

		M_{10} activity		
			Estimate	*t*
		Average		
Mood	Average	Time	1.16	1.73
		Group	**17.28**	**2.87****
		Positive affect	3.17	0.80
		Positive affect x group	-1.05	-0.40
		Time	1.11	1.66
		Group	**16.23**	**2.65***
		Negative affect	-0.00	-0.00
		Negative affect x group	-0.87	-0.32
	SD	Time	1.26	1.88
		Group	**18.25**	**3.05****
		Positive affect	-3.46	-1.37
		Positive affect x group	**4.04**	**2.30***
		Time	1.07	1.58
		Group	**17.12**	**2.83****
		Negative affect	-0.73	-0.27
		Negative affect x group	0.39	0.20
		SD		
	Average	Time	-0.08	-0.15
		Group	6.45	1.56
		Positive affect	6.25	1.96
		Positive affect x group	-3.47	-1.66
		Time	-0.00	-0.00
		Group	5.71	1.34
		Negative affect	-4.09	-1.46
		Negative affect x group	2.16	0.98
	SD	Time	-0.14	-0.25
		Group	6.36	1.53
		Positive affect	-1.14	-0.55
		Positive affect x group	0.73	0.51
		Time	-0.15	-0.28
		Group	6.36	1.52
		Negative affect	-2.53	-1.15
		Negative affect x group	1.69	1.08

Table 23: Results of the linear mixed-effects model (LMM) for M10 activity with group by mood interactions, including estimated regression coefficients together with the t-statistic.

* $p < .05$, ** $p < .01$

As can be seen from table 23, there was a significant main effect of group on average and variability in M_{10} activity, controlling for both time and mood. Therefore, high MDQ participants differ from low MDQ participants in their levels of M_{10} activity over and above differences in time and mood.

Results also show a significant variability in positive affect by group interaction, such that high MDQ participants differ from low MDQ participants in their relationship between positive mood instability and average M_{10} activity.

No statistically significant effects of group, mood, or group by mood interaction, controlling for time, on variability in M_{10} activity were found. The effect of time on variability in M_{10} activity was also not significant.

4.3.5.3.4 RA

		RA		
			Estimate	*t*
		Average		
Mood	Average	Time	-0.00	-1.39
		Group	0.01	1.22
		Positive affect	0.01	0.50
		Positive affect x group	-0.00	-0.27
		Time	-0.00	-1.52
		Group	0.01	1.07
		Negative affect	0.01	0.95
		Negative affect x group	-0.01	-0.93
	SD	Time	-0.00	-1.07
		Group	0.01	1.28
		Positive affect	**0.01**	**2.32***
		Positive affect x group	**-0.01**	**-2.02***
		Time	-0.00	-1.15
		Group	0.01	1.31
		Negative affect	**0.02**	**2.85****
		Negative affect x group	**-0.01**	**-2.46***
		SD		
	Average	Time	2.58e-04	0.19
		Group	-5.16e-03	-1.25
		Positive affect	-7.15e-03	-1.21
		Positive affect x group	4.25e-03	1.17
		Time	4.13e-04	0.31
		Group	-2.26e-03	-0.50
		Negative affect	**-1.16e-02**	**-2.02***
		Negative affect x group	**1.01e-02**	**2.22***
	SD	Time	1.99e-04	0.15
		Group	-4.96e-03	-1.17
		Positive affect	-2.34e-03	-0.49
		Positive affect x group	1.75e-03	0.55
		Time	6.35e-05	0.05
		Group	-4.20e-03	-0.95
		Negative affect	**-1.12e-02**	**-2.27***
		Negative affect x group	**8.31e-03**	**2.38***

Table 24: Results of the linear mixed-effects model (LMM) for RA with group by mood interactions, including estimated regression coefficients together with the t-statistic. * p < .05, ** p < .01

As can be seen from table 24, there was both a significant main effect of variability in mood, controlling for time, and variability in mood by group interaction for average RA. Therefore, whilst instability in positive and negative affect accounts for average RA

over and above time, high MDQ participants differ from low MDQ participants in their relationship between mood instability and average RA.

Results also show a significant main effect of both average and variability in negative affect, controlling for time, on variability in RA. Additionally, there was a significant negative affect (both average and variability) by group interaction for variability in RA. Thus, whilst both absolute negative affect and instability in negative affect accounts for variability in RA, over and above time, high MDQ participants differ from low MDQ participants in their relationship between negative mood (both absolute and instability) and variability in RA.

4.3.5.3.5 Other rest-activity variables

No statistically significant effects of group, mood, or group by mood interaction, controlling for time, on both average and variability in M_{10} onset were found. Similarly, no effect of time on M_{10} onset was found. Please see *appendix 4.2* for a full break down of the statistics for this variable.

4.3.5.4 Group comparisons of correlation coefficients

	L_5 Onset *(Average)*		**L_5 Activity** *(Average)*		**M_{10} Onset** *(Average)*		**M_{10} Activity** *(Average)*		**RA** *(Average)*	
	High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
Positive Affect *(Average)*	.08	.08	-.00	-.07	-.05	-.05	.01	.08	-.02	.10
Negative Affect *(Average)*	-.08	-.06	-.03	-.08	.07	-.08	.04	-.10	.06	-.04

Table 25: Average Pearson Product-Moment correlation coefficients between average rest-activity variables and average mood across time.

As illustrated in table 25, there was no significant group difference in weekly correlation coefficients between average rest-activity variables (L_5 onset, L_5 activity, M_{10} onset, M_{10} activity, and RA) and average mood (positive affect and negative affect).

	L_5 Onset *(Average)*		**L_5 Activity** *(Average)*		**M_{10} Onset** *(Average)*		**M_{10} Activity** *(Average)*		**RA** *(Average)*	
	High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
Positive Affect *(SD)*	-.03	.07	-.13	-.01	**-.05***	**.16***	-.00	.12	.09	.07
Negative Affect *(SD)*	-.10	.01	-.18	-.03	-.02	-.09	.06	-.12	**.19****	**-.09****

Table 26: Average Pearson Product-Moment correlation coefficients between average rest-activity variables and variability (as measured by SD) in mood across time.

* $p < .05$, ** $p < .01$

Table 26 shows significant group differences in weekly correlation coefficients between average M_{10} onset and variation in positive affect ($t(59) = -2.33$, $p = .023$), and average RA and variation in negative affect ($t(58) = 2.82$, $p = .007$).

	L_5 Onset *(SD)*		**L_5 Activity** *(SD)*		**M_{10} Onset** *(SD)*		**M_{10} Activity** *(SD)*		**RA** *(SD)*	
	High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
Positive Affect *(Average)*	.02	-.00	.04	-.03	.03	-.03	.03	-.11	.06	-.08
Negative Affect *(Average)*	.01	-.11	.03	-.10	**.09***	**-.11***	-.10	-.10	-.02	.07

Table 27: Average Pearson Product-Moment correlation coefficients between variability in rest-activity variables (as measured by SD) and average mood across time. * p < .05

Table 27 shows a significant group difference in weekly correlation coefficients between variation in M_{10} onset and average negative affect, $t(58) = 2.14$, $p = .037$.

	L_5 Onset *(SD)*		**L_5 Activity** *(SD)*		**M_{10} Onset** *(SD)*		**M_{10} Activity** *(SD)*		**RA** *(SD)*	
	High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
Positive Affect *(SD)*	-.02	.06	-.02	-.12	-.04	.01	.01	-.00	-.03	.02
Negative Affect *(SD)*	-.06	-.06	-.03	-.01	.03	-.00	.02	-.05	**-.11***	**.10***

Table 28: Average Pearson Product-Moment correlation coefficients between variability in rest-activity variables and variability in mood across time, as measured by SD. * p < .05

As can be seen from table 28, there was a significant group difference in weekly correlation coefficients between variability in RA and variability in negative affect, $t(58) = -2.18$, $p = .033$.

It should be noted that significant results did not survive a Bonferroni adjusted alpha level of .003 across comparisons (tables 25-28).

4.4 Discussion

Individuals in the high MDQ group who also went on to show significant mood instability had a notably lower amplitude of circadian rhythm, signalling an association between mood instability and lower differentiation between day and night activity. Delving into this further, this lowering of amplitude seemed to be driven by the fact that high MDQ participants are less active during the day, compared to those in the low MDQ group. When considering concurrent ratings of mood, a number of interesting observations were made, suggesting that while the oscillating nature of mood instability has a role to play in predicting and regulating circadian rhythms, the degree to which its individual rest and activity components are affected may be further influenced by the severity of mood instability.

This close relationship between circadian patterns, mood instability, and MDQ grouping was noted in markers of daytime activity and relative amplitude where absolute group differences had already been noted, such that the high MDQ group differed from the low MDQ group in their association with daytime activity and mood instability in the positive affect domain, while the combined influence of mood instability in both the positive and negative affect domains seemed to interact with relative amplitude to a differing degree in the high MDQ group compared to the low MDQ group. These more complex relationships were also discovered in markers of sleep which, whilst not significantly different between groups, showed that time significantly accounted for sleep onset and activity differences between the groups, with activity differences also being driven by the interaction between high MDQ grouping and mood instability. Taken together, these results support the hypothesis of

greater disruption in circadian rest-activity patterns in the high MDQ group, but also demonstrate the complexities and nuances of this relationship with mood instability.

The finding of dampened circadian relative amplitude confirms what is seen in other studies involving both patients with BD and MDD (e.g. Burton et al., 2013; Rock et al., 2014). Whilst confirming the role of circadian rhythm disruption in mood disorders, this effect also begins to suggest a wider disturbance in the mechanism responsible for regulating the cycle of daytime and night-time activity. However, it seems that the particular process by which this occurs varies greatly. Currently I find that lowered daytime activity with no disruption in sleep, is the driving force behind this amplitude effect, whilst the majority of previous literature has reported significant disruptions in sleep. Although it is true that these two mechanisms work together – that higher levels of activity during sleep or rest periods often lead to lower levels of activity during the day – the fact that we did not see this pattern can indicate a number of things.

Firstly, the majority of previous research into this effect has included relatively short periods of monitoring (usually around 2 weeks, e.g. Rock et al., 2014). As the current COMET study monitored participants over 10 weeks in order to more accurately capture the dynamic nature of mood instability across time, suggests that any sleep disruptions previously noted could be relatively acute and thus, that lowered movement during the day may be more typical of the mood disorder phenotype. Secondly, varied results may also inform us of the nature of sleep monitoring using wearable actigraph devices. Whilst we know that these devices are sensitive to body movement measured on the *x*, *y*, and *z* planes, it is often noted that monitoring sleep via such proxy markers is problematic for its derivative nature (McGowan et al., 2019).

Although this is somewhat overcome by more nuanced measures such as the measurement of melatonin secretion, polysomnography, and sleep diaries, the fact that the current study did not find such effects on sleep in a relatively large and longitudinal sample also suggests that the experience of sleep disruption may present in acute and more severe forms of illness. Nevertheless, the finding of lowered daytime activity in the high MDQ group, without associated disruptions in sleep, present interesting implications for our understanding of mood disorders.

Along with low mood, prolonged fatigue, a lack of energy, and changes in movement and psychomotor retardation are long established components of depression (Buyukdura, McClintock, & Croarkin, 2011). This change in movement, often presenting as a result of a cluster of associated symptoms, is particularly important to acknowledge given current findings. Considering previous analysis of mood in our current sample (see *chapter 3*), we know that as well as showing mood instability, the current high MDQ group are also significantly higher in absolute negative mood. Taken together, this finding of significantly lower levels of movement and activity during the day, a symptom we know is often associated with depressed episodes, further suggests an overall depressed mood in this group. Thus, regardless of the experience of mood instability, combined analysis here suggests that the high MDQ group were displaying two distinct and objective symptoms of depression over the 10-week study period, both (a) absolute low mood, and (b) lower levels of movement or activity during the day.

Despite this further evidence for overall depressed mood, it is again difficult to tease apart whether this is a wider feature of the prodrome or course of BD, and thus a BD

depressive episode, or an indication of MDD. We know from clinical observations that mood instability is a feature of a range of disorders, including both BD and MDD (Broome et al., 2015), and the high MDQ group include a number of participants who also meet diagnostic criteria for MDD as well as BD (see *chapter 2*). Nonetheless, given that diagnostic criteria for many psychiatric disorders, including BD and MDD, are not necessarily biologically distinct, and that mood instability is core to both, it is not surprising that current findings of lowered circadian relative amplitude and daytime activity persist outside of clear clinical or functional impairment. Instead, current findings of such circadian rhythm disruptions during the experience of mood instability further strengthen the notion of this instability, and its associated behavioural profile, as a transdiagnostic marker across mood disorders.

When exploring the temporal relationship between mood and rest-activity markers, we were able to uncover a more nuanced relationship that highlighted the complexities in regulating mood and circadian patterns. Relative amplitude – the differentiation marker that takes into consideration measurements of both daytime and night-time, or rest-activity period, activity – is key here. The finding that mood instability, particularly in negative affect, predicted both absolute relative amplitude and variability, or stability, in relative amplitude, over and above time, and that it also showed differences in dynamic association with group, suggests that a common mechanism underlying regulation between rest and activity periods, and mood, may be at play. For instance, an overarching homeostatic mechanism may be responsible for both regulating mood and the balance of daily circadian rest-activity patterns, thus suggesting that a disruption in this mechanism may cause dysregulation in these downstream symptoms.

When delving into the individual components of this circadian amplitude marker, results further the presence of a differing relationship between the high MDQ and low MDQ groups in relation to daytime and night-time activity markers and mood instability, albeit to a differing degree to those seen in the relative amplitude domain. Namely, the high MDQ group differed from the low MDQ group in their association between night-time activity and mood instability in both the positive and negative affect domains, while daytime activity showed a differing association with instability in only positive affect between the groups. However, the fact that this differing association between mood instability and group became clearer in reference to a circadian amplitude marker highlights the importance of considering disruptions in both rest and activity periods in tandem. When considering these temporal findings as part of the wider group results, we thus see that high MDQ participants have lowered levels of relative amplitude which shows particular association with mood instability, and is in turn driven by lower levels of daytime activity in the high MDQ group and a closer relationship between sleep and mood instability also in this group.

This pattern of results lends further to those reported in patients with mood disorders. It may be that disruptions in daytime activity are some of the initial symptoms of mood dysregulation, resulting perhaps as a consequence of mood instability primarily in the positive affect domain, but it is the more objective experience of sleep rhythm disruption that is indicative of worsening mood instability encompassing both positive and negative affect, and mood disorder (Lyall et al., 2018; Ng et al., 2015). Whilst additional research is needed in order to further replicate and explore this putative link in those with mood instability both with and without mood disorders, distinct differences

in these rhythms between groups discernible by their experiences of mood instability, as well as close association between these circadian patterns and mood instability across a longitudinal temporal scale, highlights the complex nature of mood instability and related dynamic processes.

Therefore, a clear understanding of the profile of mood instability, combining an investigation of the neural basis in addition to the clinical and behavioural ones established thus far, will enable us to draw more concrete connections with the clinical and behavioural presentation of mood instability in BD and MDD, and may aid us in better distinguishing between the distinct experiences of depression and mania that characterise their course. Subsequent chapters aim to do just this – by first establishing the distinct functional connectivity patterns that present during mood instability, and by then going on to explore how dynamic changes in these networks associated with changeability in mood may present evidence of an underlying disruption in neural homeostatic mechanisms to regulate mood and associated behaviours, such as those of circadian rest-activity patterns.

The current findings also present interesting implications for the utility of monitoring circadian rest-activity patterns in mood disorders. As noted, and despite the fact that the sample were not formally diagnosed and reported no functional impairment, distinct rest-activity patterns were reported and highlighted significant disruptions in circadian rhythms. The sensitivity of this finding shares features with other studies in both at-risk groups (Rock et al., 2014), and patient groups such as McGowan et al. (2019). In particular, this latter study used longitudinal monitoring to show distinct differences in the rest-activity patterns of patients with mood instability and a diagnosis

of BD or borderline personality disorder (BPD). Using GENEActiv actigraphs, the researchers were able to show that BPD patients had notably phase delayed circadian rest-activity patterns compared to BD patients, who in turn showed a significantly different profile of activity involving lower levels of rhythm fragmentation compared to healthy controls. Taken together, these results were able to demonstrate the value of such longitudinal monitoring in patient groups who experience substantial clinical overlap and misdiagnosis, and in combination with current findings employing the same measurement techniques, highlights the distinct profile of circadian rest-activity patterns that present with differing experiences of mood instability.

Building on this, the monitoring of circadian rest-activity patterns may present useful clinical implications for clinicians and patients, and indeed those who are at-risk for mood disorders. If we are able to use experimental findings, such as the current ones, to identify distinct circadian profiles across sub-clinical and diagnostic categories, outcomes can inform us of targets for behavioural intervention that may alleviate symptoms and regulate mood. Studies into the benefits of exercise as an adjunct treatment for mood disorders (e.g. Hearing et al., 2016) are in line with this, particularly in the mechanism by which it has been shown to both reduce depression and increase positive affect (Bartholomew, Morrison, & Ciccolo, 2005). Therefore, future studies could also incorporate behavioural interventions into the longitudinal monitoring of mood, circadian rhythms and underlying neural instabilities in order to better determine the particular mechanisms by which behavioural changes may contribute to mood regulation.

Mood instability is associated with distinct differences in circadian rest-activity rhythms and sensitive patterns of changeability in these clinical and behavioural domains across time. Despite the fact that findings provide further support for low or depressed mood in our sample characterised by mood instability by showing notably lower levels of daytime activity as the motivation for differences in circadian relative amplitude, the value of such findings particularly given their close relationship to dynamic mood instability, is important. Overall, the two branches of results – those that identify significant differences in patterns across high MDQ and low MDQ groups, and those that implicate the concurrent monitoring of mood instability to the dynamic nature of these patterns across time – provide evidence for shared imbalances in underlying homeostatic mechanisms. It is hoped that further research to identify the neural basis of this homeostatic mechanism may help to better understand the unique and distinct ways imbalance in such regulatory systems may lead to mood disorders.

Chapter 5 | Exploring resting-state functional connectivity patterns in mood instability

5.1 Introduction

Whilst advances have been made in understanding the clinical, behavioural, and cognitive profile of mood disorders, many questions around its pathophysiology, or neurobiological basis, still remain. The use of functional magnetic resonance imaging (fMRI) methods, however, can help to elucidate the underlying neurobiology (Vargas et al., 2013), paving the way for more nuanced analyses of mood disorders that are rooted in neuroscience. Owing to the large amount of clinical and behavioural overlap between mood disorders such as BD and MDD, this understanding of the neurobiological mechanisms may help to distinguish between disorders, predict onset and severity, and inform us of novel targets for therapeutic intervention. In addition, and due to a current lack of such investigation in mood instability, a consideration of the pathophysiology of BD and MDD can also aid us in determining the overarching and shared neural homeostatic mechanisms that may be disrupted.

Many studies utilising functional MRI methods in mood disorders have focused on task-dependent functional connectivity in order to assess the neurobiological processes that are active in response to cognitive and affective demands. Whilst results from these studies have shed some light on the neural circuits involved in mood disorders, findings have often lacked consistency due to differing scanning techniques, variations in study protocols, and sample characteristics that may be influenced by scar effects of repeated mood episodes, medication use, and the experience of comorbidities. Additionally, neural circuits identified via this method are

also restricted to brain regions activated as a result of neuropsychological demands, and thus, often lack generalisability about the overall functioning of the brain in mood disorders.

Instead, resting functional MRI is increasingly employed to measure the basal activity of the brain unrelated to cognitive performance, and has been shown to represent functional connectivity networks of the brain that may be distinct and intrinsic to certain disorders (Van Den Heuvel & Pol, 2011). Functionally relevant and distinct resting state networks (RSNs) in the brain are identified from patterns of spatial and temporal coherence in spontaneous functions in BOLD MRI signal (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995). Analyses of such data can be conducted in a number of different ways, with researchers often exploring the temporally and spatially distinct whole brain components that underlie RSNs activated in psychiatric samples using an independent components analysis (ICA), as well as seed-based analysis that uses a-priori defined regions of interest (ROIs) to investigate specific associations with all other voxels in the entire brain.

These static methods are particularly advantageous in the study of complex and heterogenous disorders such as BD and MDD, and also allows simultaneous exploratory and hypothesis-driven analyses to be carried out in order to more comprehensively investigate the intricacies of functional connectivity. While this method can also be subject to the limitations inherent in task-based functional connectivity discussed above (e.g., variations in study protocols and clinical sample characteristics), its strong reliability is important to note. In studies of test-retest reliability, resting-state fMRI has consistently been shown to be reliable across a

number of commonly reported RSNs (default, control, and attention), a number of analysis metrics (including ICA) (Noble, Scheinost, & Constable, 2019; Zuo & Xing, 2014), and in comparison to task-functional MRI measures with the goal of biomarker discovery (Cao et al., 2014; Elliott et al., 2020).

In order to explore these functional connectivity networks at rest, participants are required to remain awake yet to rest with their eyes closed, or to alternatively gaze at a fixation cross if presented, during the fMRI scan (Williamson & Allman, 2012). Despite the fact that such sequences are commonly added to study scanning protocols, results from such data, particularly when considering mood disorders, are still in their infancy. Therefore, a consideration of neural circuits and functional connectivity identified during task-based fMRI, combined with those at rest, can aid us in understanding the particular neurobiological mechanisms that may be at play during differing mood symptoms over the course of disorders such as BD and MDD, and may also guide us in predicting the shared neural characteristics that define mood instability.

In task-based fMRI scans measuring cognitive affective processing, abnormalities are usually found in limbic structures including the amygdala and hypothalamus, and in regions of the prefrontal cortex (PFC) including the orbital and medial prefrontal cortex (OMPFC), as well as various connections between the two (Price & Drevets, 2012) across both MDD and BD, accounting for most major mood-related symptoms. Delving into this further, MDD patients are reported to have increased activation in the amygdala, orbitofrontal cortex (OFC), and PFC when showing attentional biases towards negative facial expressions (Wagner et al., 2004), areas known to be involved

in emotional processing and executive functions. The severity of depressive symptoms in these patients is also known to be associated with increased activation in limbic areas such as the hippocampus, insula, and anterior cingulate cortex (ACC) during the processing of negative facial expressions (Anand et al., 2005; Elliott et al., 2011; Lee et al., 2008), and it is this effect that has also been reported in BD.

In their systematic review and meta-analysis of the neural correlates of emotional processing in BD and MDD, Delvecchio et al. (2012) argued that increased limbic engagement, particularly involving the parahippocampal gyrus and amygdala, formed part of the core phenotype of cognitive affective processing in mood disorders, but that clear distinctions in regions existed. For instance, BD, but not MDD, was associated with reduced activation in the ventrolateral PFC, an area known to be involved in inhibitory control. As difficulties with inhibition, particularly within manic episodes, is a core feature of the disorder, this suggests that processing in this region and its associated circuits is specific to the experience of BD (Cerullo et al., 2009; Chen et al., 2006). In a similar fashion, increased activation in the thalamus, particularly the pulvinar, was found to be associated with BD rather than MDD while processing negative facial expressions. As this particular “higher order” region is known to have various cortical connections (Pessoa & Adolphs, 2010), it has been proposed that overamplification towards emotionally salient information helps to explain the difficulties in fluctuating mood in BD, while the suppression of activation in the same region during the processing of positive facial expressions in MDD points to the dampening of reactivity towards positive information associated with depression (Rottenberg et al., 2005). A combination of connections between these cortical, striatal, and thalamic regions are also known to be intrinsically related to reward

processing, a core yet differential cognitive symptom in mood disorders, and particularly implicates regions such as the caudate nucleus (Abler et al., 2008; Giuseppe Delvecchio et al., 2012) and basal ganglia (Abler et al., 2008; Hwang et al., 2006; Strakowski et al., 2005; Strakowski et al., 2002).

Thus, there is increased evidence implicating particular neural circuits, often in differential ways so as to differentiate between specific mood disorders in the domain of cognitive affective processing using task-dependent fMRI techniques. However, the observation that these cognitive affective difficulties are often core to the experience of mood disorders – for example the overlap between negative biases and rumination in depression, or between reward processing abnormalities and impulsivity in mania – suggests that the associated neural circuits could also be differentially connected outside of task demands, or at rest.

This consistency in patterns, suggesting an overarching pathophysiological marker, has been reported in resting-state fMRI studies in MDD. Wang and colleagues (2012) commented on the robust nature of findings involving cortico-limbic structures in MDD, such that abnormal connectivity in regions such as the thalamus and amygdala were thought to represent the persistent and core feature of negative biases and maladaptive emotional perception in depressed patients. Further, the consistent finding of abnormal connectivity in the default mode network (DMN) in these patients, including within the regions of the PFC and cingulate cortex, also begins to highlight a differential marker of functional connectivity associated with mood disorders. When contrasting these findings with those seen in patients with BD, researchers have again reported overall markers of functional connectivity disruption in BD, and have

highlighted differential patterns in such connectivity that may distinguish between BD and MDD. For instance, Marchand et al. (2013) found increased connectivity between the posterior cingulate cortex (PCC) and regions involving the insula in BD patients compared to MDD, and this association was modulated by severity of depressive symptoms and current suicidal ideation. In a similar fashion, Anand et al. (2009) reported overall abnormalities in cortico-limbic functional connectivity in BD patients that was in line with that seen in MDD, but that the severity of this association seemed to distinguish BD from MDD. These studies suggest that such functional neuroimaging techniques are able to characterise the similarities and differences between neural connectivity and pathophysiology in mood disorders and could thus, lead to the development of diagnostic procedures that may aid us in differentiating between their clinical presentations. However, a more thorough understanding of functional connectivity in mood disorders, particularly within the experience of BD characterised by changeability in affect, can shed light on the particular neural mechanisms that underlie mood instability.

In their systematic review of resting state functional MRI studies in BD, Vargas and colleagues (2013) found a similar pattern of connectivity to that found in task-dependent data. For instance, BD patients were consistently reported to show differential patterns of functional connectivity in the PFC with the ACC and limbic areas including the amygdala, insula, and thalamus (Anand et al., 2009; Chepenik et al., 2010) compared to healthy controls. However, variations in the nature of connectivity was also reported, such that some studies found increased connectivity between these regions (Anticevic et al., 2013), whilst others instead found it to be decreased (Anand et al., 2009). Further, differences in the patterns of connectivity were often

noted within patients, such that patients in a depressive episode differed from those in a manic episode, who in turn differed from those currently euthymic; and it was this pattern of differential connectivity depending on mood state that has been suggested as the reason for such heterogenous results.

Investigation of these functional connectivity patterns during euthymia can thus aid us in teasing apart the core underlying patterns of brain connectivity in BD (Blumberg et al., 2003) and also in elucidating the distinct pathophysiological differences between BD and MDD (Vargas et al., 2013). When focusing on these euthymic patients, Syan and collegues (2018) found a consistent pattern of functional connectivity in the DMN, fronto-parietal network (FPN) and salience network (SN) which was comparable to that found in healthy controls, but that patients who had a history of significant mood episodes involving psychosis often reported hyperconnectivity in the DMN. Again, when assessing connectivity with specific limbic and striatal regions, they found consistent atypical functional connectivity patterns with the amygdala, PFC, and cingulate cortex. Together, whilst these results suggest a pattern of general stability in broad resting state networks during euthymia, the consistent presence of differences in connectivity between regions such as the amygdala, insula, and PFC, areas known to be involved with cognitive and emotional processing, may reflect patterns of overall BD pathophysiology.

We are able to use the findings from studies in MDD and BD, particularly euthymic BD, when considering the patterns of functional connectivity that may be intrinsic to mood instability. Whilst the direction of results has often yielded inconsistent patterns of connectivity, it is increasingly clear that limbic structures involving the amygdala and

its projection to regions such as the insula, are important. For example, amygdala dysfunction is known to be implicated in the development of BD, in both adolescent studies and in those with genetic risk (Garrett & Chang, 2008). Whilst this region is involved with the processing of emotionally salient information across BD and MDD, the widespread and consistent evidence for its role in the prodrome, aetiology, and maintenance of BD, involving both its structure and function, and its interaction with prefrontal modulatory regions and emotional response regions such as the insula (Garrett & Chang, 2008), suggest that it may be a core neurobiological feature of an underlying disruption in mood regulation. The role of the insula, known to be associated with both mood regulation and self-awareness (Craig, 2009; Damasio & Carvalho, 2013; Gogolla, 2017) such that it acts to promote emotion regulation and flexible behaviour, further lends itself to this by representing a mechanism of emotional homeostasis with projections to related cyclic behaviours, such as that seen in mood instability (see *chapter 4*). Taken together, mood instability is expected to be reflected in functional connectivity abnormalities that are core to BD and MDD, particularly concerning regions associated with cognitive affective processing and emotion regulation such as the amygdala and insula.

Functional connectivity analyses of resting fMRI data in the COMET study aims to explore these patterns in mood instability. Owing to the novel nature of such analyses in a sub-clinical and medication-naïve sample, an exploratory approach will be taken where I am interested in investigating whether dysregulation in regions associated with emotional stability persist outside of explicit cognitive demands and diagnoses, and as a feature or correlate of mood instability. To do this, we are first required to build a profile of the whole brain connectivity patterns that may underlie the distinct

mechanisms of mood instability and its specific associations with emotional regulation regions such as the amygdala and insula (current chapter), before going on to explore the particular dynamic mechanisms by which nuances in connectivity may be related to the temporally dynamic experience of mood instability (*chapter 6*). In order to address the first part of this aim, the current study intends to implement two complementary neuroimaging analyses to study the RSNs that may underlie mood instability, namely: (a) whole brain analysis using ICA; and (b) seed-based analysis, with the amygdala and insula as specific ROIs. It is hoped that this exploratory work will shed further light on the mood-contingent connectivity changes seen in the brain where previous findings in patient groups have been inconclusive or inconsistent, as well as begin to establish a profile of pathophysiology that may be responsible for the transdiagnostic experience of mood instability.

Ultimately, findings of neurofunctional impairments in the dynamic nature of brain connectivity in mood instability can more accurately uncover the core pathophysiological process of mood disorders. This is important for indicators of early diagnosis, prediction of episode onset and severity, and in the potential for discovery of better treatment response and novel targets.

5.2 Methods

The current chapter focuses on analyses and results from resting-state functional MRI (fMRI) data collected as part of the COMET study, over two time points. A summary of the wider methodology used in the collection of this data can be found in c*hapter 2*, *section 2.5.7*. A broader overview of the participants recruited in the study can be found in *chapter 2*, *section 2*, as well as overall sample characteristics in *section 3*. The remainder of this chapter will focus, thus, on presenting the particulars of the MRI data collected and the methods employed in the analysis of resting state fMRI data.

5.2.1 Participants

Out of the seventy-four participants who completed the COMET study, data from 66 participants were available to analyse in this chapter. Thirty-four of these participants were in the high MDQ group, and 32 in the low MDQ group. All participants provided resting-state fMRI and structural scans at two time points, resulting in 132 datasets for analysis.

Data from 8 of the remaining COMET sample (high MDQ n = 3; low MDQ n = 5) were not available for these analyses for two reasons: scanning error (n = 6) (including fewer volumes of data available and missing fieldmap data) and completion of only one scan (n = 2).

5.2.2 Procedure

Participants completed two MRI scans, the first between weeks 1 and 2 of the study (referred to from here on as “scan 1”) and the second between weeks 9 and 10 of the

study (referred to from here on as “scan 2”). If participants decided to complete their scan 1 on the same day as their screening visit, study researchers accompanied them from the Department of Psychiatry, Warneford Hospital, to the John Radcliffe Hospital for their MRI scan at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). For all other scheduling options at scan 1 and scan 2, researchers met with participants directly at OCMR.

Before participants entered the scanner, they were asked to remove all metallic and MRI unsafe objects from their person, and to change into metal-free clothing if necessary. A study researcher, trained as an MRI operator, confirmed MRI safety. If participants wore glasses, they were asked to wear contact lenses for each scan if available, or they were alternatively given prescription-matched MRI-safe goggles.

At both sessions, the resting-state scan was the first scan to be conducted. Please see *chapter 2*, *section 2.5.7.1* for further details of the order in which MRI scan sequences were conducted at each time point.

The duration from arrival at OCMR to departure was about 2 hours, including ~90 minutes in the MRI scanner.

5.2.3 Neuroimaging protocol

All scans were performed using a 3-Tesla Siemens TIM Trio Scanner (Siemens Medical Solutions, Bracknell, UK) with a 32-channel coil.

5.2.3.1 Structural MRI

Structural scans were acquired via T1-weighted images (TR = 3000ms, TE = 4.71ms, flip angle = 8º, field of view = 256mm, voxel dimension = 1 mm isotropic, acquisition time = 8 mins 48s). Participants were able to close their eyes during the scan, but were instructed not to fall asleep.

5.2.3.2 Resting-state fMRI[31]

Whole-brain resting-state functional imaging was conducted using a gradient-echo EPI sequence (TR = 2000ms, TE = 28ms, flip angle = 89º, field of view = 192mm, voxel dimension = 3.0 x 3.0 x 3.5mm, 180 volumes, acquisition time = 6 mins 04s). Participants were instructed to lay still, to keep their eyes open while looking at a black fixation cross on a white background, to blink normally, think of nothing in particular, and to not fall asleep. An eye-tracker camera was used to ensure that participants had their eyes open during the scan.

Images were distortion corrected by an acquired fieldmap (echos at 5.19ms and 7.65ms, TR = 488ms, flip angle = 60º).

5.2.4 Analysis

Data were analysed using FSL (FMRIB Software Library v6.0; https://fsl.fmrib.ox.ac.uk/fsl) (Jenkinson, Bannister, Brady, & Smith, 2002; Smith et al., 2004; Woolrich et al., 2009).

[31] Please see *chapter 2, section 2.2.4.7.1* for further details of the MRI protocol used, and *appendix 5.1* for full details of the resting-state fMRI protocol.

5.2.4.1 Pre-processing

FSL's Brain Extraction Tool BET (Smith, 2002) was used to extract the brain from the structural scans. Single subject resting state fMRI data were pre-processed and analysed using Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC version 3.15, FSL). Pre-processing was conducted to reduce structural variability in the data and to improve the validity of statistical analyses. Thus, the following steps were carried out for each subject[32]: (a) removal of non-brain structures using BET (Smith, 2002); (b) motion correction using FMRIB's Linear Image Registration Tool (McFLIRT) (Jenkinson et al., 2002); (c) distortion correction using fsl_prepare_fieldmap; (d) spatial smoothing using a Gaussian kernel of FWHM 5mm; (e) grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; and (f) high-pass temporal filtering cut-off = 150s (Gaussian-weighted least squares straight line fitting, with sigma = 75.0s). A strict denoising process was conducted with McFLIRT and any noise due to motion and physiological artefacts were removed. Additionally, specific resting-state pre-processing steps included (a) masking of non-brain voxels; (b) voxel-wise demeaning of the data; and (c) normalisation of the voxel-wise variance. Resting functional images were registered to their high resolution structural image using the high contrast functional image and Boundary-Based Registration through FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001). Resting functional images from scan 1 and scan 2 were registered to structural images from scan 1 for all participants in order to ensure consistency in analysis. Non-linear registration from structural to MNI (Montreal

[32] "Subject" here refers to all individual scans from all participants at both time points (scan 1 and scan 2) (*N* = 132).

Neurological Institute) standard space was then achieved using FNIRT non-linear registration (Andersson, Jenkinson, & Smith, 2007), resampling resolution = 2mm.

5.2.4.2 ICA analysis

Probabilistic ICA (Beckmann & Smith, 2004) using FSL's MELODIC was employed to analyse the resting-state fMRI data.

Pre-processed data were first whitened and projected onto a 91-dimensional subspace using probabilistic Principal Component Analysis (PCA), where the number of dimensions was estimated using the Laplace approximation to the Bayesian evidence of the model order (Beckmann & Smith, 2004). The whitened observations were decomposed into sets of vectors that describe signal variation across the temporal domain (time-courses) and across the spatial domain (maps) by optimising for non-Gaussian spatial source distributions using a fixed-point iteration technique (Hyvärinen, 1999). Estimated component maps were divided by the standard deviation of the residual noise and thresholded by fitting a mixture model to the histogram of intensity values (Beckmann & Smith, 2004).

ICA denoising was then conducted to denoise resting-state fMRI data using FMRIB's ICA-based Xnoisefier (FIX) via a two-step method. First, components were compared and labelled using a training dataset created from the related experimental medicine study of BD patients with mood instability randomised to lithium or placebo, OxLith (*N* = 21) (Saunders et al., 2016). Secondly, another training dataset was then created from 10 COMET participants in each group, at each time point (*n* = 40), all of whom were randomly selected using a random number generator. Manually labelling of

components was done by me and checked over by two independent researchers (Dr. Liliana Capitao and Dr. Cassandra Gould van Praag). A conservative approach was employed such that components we were unsure of were included (Griffanti et al., 2017).

Next, these pre-processed and cleaned data were then temporally concatenated across subjects in order to create a single 4D dataset. They were then decomposed using a group ICA so that large-scale patterns of functional connectivity, restrained to 25 components, could be identified across subjects (as described by Filippini et al., 2009). Identification of RSNs from these components was conducted in a three-step process, namely (a) visual inspection by me, Dr. Liliana Capitao, and Dr. Cassandra Gould van Praag; (b) comparison to previously published maps (Smith et al., 2009); and (c) Pearson spatial cross-correlation comparison with FIND Lab's 90 ROI atlas (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012).

Dual regression was then run in order to generate subject-specific versions of the spatial maps and associated time series, across all subjects, using the spatial maps created from the group-wise analysis. In this step, the group-wise set of spatial maps is regressed into each individual 4D space-time dataset and the resulting set of subject-specific time series are again regressed into the same 4D dataset files. Therefore, dual regression conducted two associated multiple regressions, firstly with spatial regressors, and secondly with temporal regressors. The outcome of this is a set of subject-specific spatial maps, corresponding to one per group-level spatial map.

A voxel-wise General Linear Model (GLM) based analysis was then employed to test for statistically significant differences between groups and time points. Nonparametric permutation testing (5000 permutations) via FSL's randomise permutation testing tool, Randomise, was used, and clusters were determined using Threshold-Free Cluster Enhancement (TFCE) and a family-wise-error corrected cluster significance threshold of $p < .05$.

5.2.4.3 Seed-based analysis

The denoised functional data from the ICA analysis was used in the seed-based analysis. Masks of the left and right amygdala, and insula were created from the probabilistic maps provided by the Harvard-Oxford Subcortical Structural Atlas within FSL.

Seed-based correlations were carried out for each participant using FMRI Expert Analysis Tool (FEAT v6.0). The timeseries derived from the mask corresponding to the relevant seed (i.e., left amygdala, right amygdala, or insula) was included as an explanatory variable (EV) to determine which other brain areas significantly correlated with this time course. Time series derived from white matter (WM) and cerebrospinal fluid (CSF) masks were included as confounding regressors.

Group FEAT analyses were then run for each seed, to determine whether group (high MDQ or low MDQ), time (scan 1 or scan 2), and group by time interaction affected functional connectivity with the seed. This analysis utilised FMRIB's Local Analysis of Mixed Effects (FLAME) (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Ripley, Brady, & Smith, 2001).

Statistical maps were thresholded using clusters determined by $Z > 3.1$ and a corrected cluster significance threshold of $p < .05$.

5.2.4.4 Scan-to-scan movement

In order to assess scan-to-scan movement, absolute mean displacement and relative mean displacement values were extracted for each participant ($n = 66$) at each scan session (scan 1 and scan 2). Absolute mean displacement is known to describe motion in a given volume with respect to a reference time point (i.e., middle volume in a time-series), providing useful information on gradual shifts in head position over time. Relative mean displacement at a given volume describes motion with respect to the subsequent time point, useful for identifying abrupt changes in head position. Each value (absolute and relative) is an average across all volumes, for each participant at each scan session.

A repeated measures ANOVA was conducted using SPSS (IBM Corp, 2017) to analyse the effect of group (high MDQ or low MDQ; the between-subjects factor), time (scan session; the within-subjects factor), and group by time interaction for absolute mean displacement and relative mean displacement.

As described in *section 5.2.4.1*, a strict denoising process was also conducted with McFLIRT during pre-processing, and any noise due to motion and physiological artefacts were removed. Thus, motion was not included as regressor, and censoring was not performed, as data denoising was completed at an individual level and the same denoising procedure was applied to all datasets.

5.3 Results

5.3.1 Demographics

	High MDQ (*n*=34)	Low MDQ (*n*=32)
Gender *[m:f]*	12:22	9:23
Handedness *[right:left]*	27:7	27:5
Age *[mean (SD)]*	24.32 (6.63)	25.16 (7.05)

Table 29: Demographic data for high and low MDQ groups.

Demographic data for the sixty-six participants whose resting-state fMRI data (across both time points) were analysed are shown in table 29. No statistically significant association between group and gender ($X(1) = 0.39$, $p = .532$) or handedness ($X(1) = 0.27$, $p = .601$) was found. Also, no significant difference in age, $t(64) = -0.49$, $p = .623$, between the groups was reported.

5.3.2 Scan-to-scan movement

	High MDQ (*n*=34)		Low MDQ (*n*=32)	
	Scan 1	*Scan 2*	*Scan 1*	*Scan 2*
Absolute mean displacement *[mean (SD)]*	0.31 (0.24)	0.29 (0.33)	0.28 (0.24)	0.43 (0.56)
Relative mean displacement *[mean (SD)]*	0.10 (0.07)	0.09 (0.09)	0.07 (0.04)	0.09 (0.08)

Table 30: Descriptive data of scan-to-scan movement values. Means are shown for absolute and relative mean displacement, with spread of data (standard deviation) in parentheses.

There was no significant main effect of group ($F(1, 64) = 0.46$, $p = .500$) or time (scan session) ($F(1, 64) = 1.73$, $p = .193$) in absolute mean displacement. There was also no significant group by time interaction, $F(1, 64) = 2.93$, $p = .092$ (fig. 31).

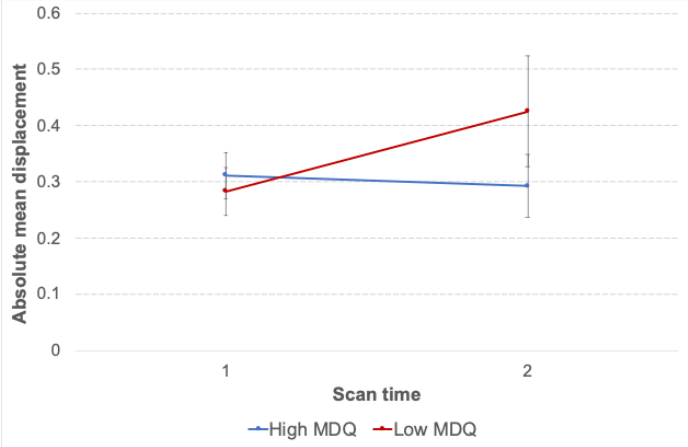


Figure 31: Absolute mean displacement by high MDQ and low MDQ participants at scan 1 and scan 2. Error bars represent ± 1 *SEM*.

There was no significant main effect of group ($F(1, 64) = 0.55$, $p = 0.463$) or time (scan session) ($F(1, 64) = 0.75$, $p = .390$) in relative mean displacement. There was also no significant group by time interaction, $F(1, 64) = 1.67$, $p = .202$ (fig. 32).

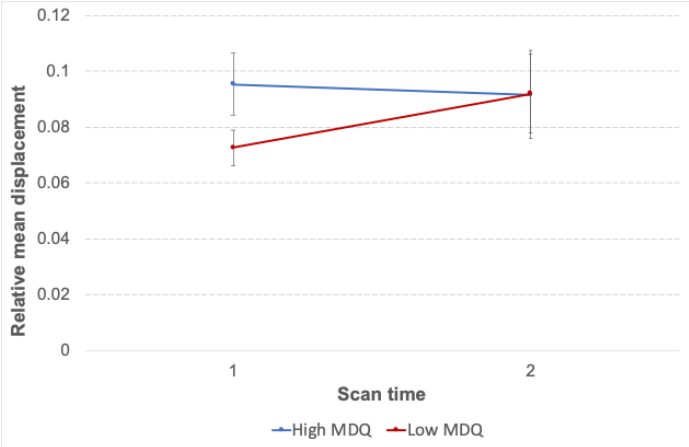


Figure 32: Relative mean displacement by high MDQ and low MDQ participants at scan 1 and scan 2. Error bars represent ± 1 *SEM*.

5.3.3 Overall resting state networks (RSNs)

5.3.3.1 Identification of RSNs

Independent Component Analysis (ICA) was restricted to 25 components, identified as depicting 14 individual RSNs encompassing the majority of grey matter (fig. 33).

RSNs corresponded with those described previously and known to show stability over time (Shirer et al., 2012; Smith et al., 2009). Using the same method, five noise components were identified, reflecting scanner artefacts, head motion, and physiological noise (Griffanti et al., 2017). Please see *appendix 5.2* for further details of the RSN identification process.

5.3.3.2 Group differences in RSNs

Table 31 shows the GLM models that were conducted in order to test for differences in the 14 RSNs identified. Across both time points, main effects of group and time were explored. Additionally, a main effect of group was investigated within each individual time point, as well as time within each group.

Using a combination of three model designs, as shown in table 27, no significant differences in RSNs between groups (high MDQ and low MDQ) and time (scan 1 and scan 2), as well as group by time interaction, was found.

Test variable		Contrasts
Overall	All scans	High MDQ vs. low MDQ Scan 1 vs. scan 2
Time	Scan 1 Scan 2	High MDQ vs. low MDQ
Group	High MDQ Low MDQ	Scan 1 vs. scan 2

Table 31: Analysis models. Contrasts including overall comparisons of group, time, and group by time interaction are shown.

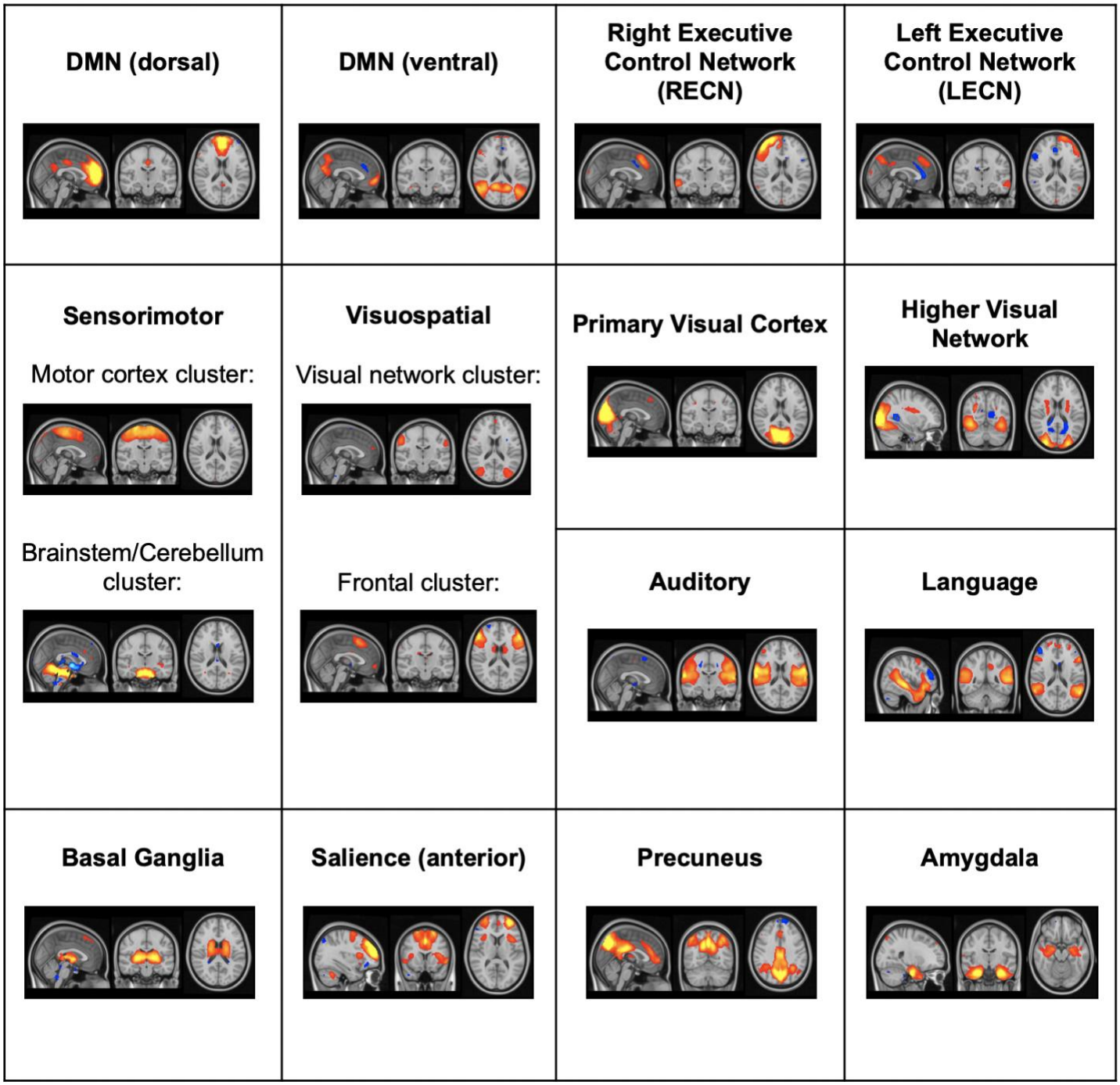


Figure 33: Axial, coronal and sagittal slices of the main resting state networks (RSNs) detected across all participants and all time points, overlaid onto the standard 1mm MNI brain. Noise components are not included.

5.3.4 Seed-based analysis

In addition to ICA analysis and identification of whole brain RSNs, anatomical ROI analysis was also conducted with seeds in the right and left amygdala, and insula.

5.3.4.1 Amygdala (right and left)

There was no significant overall effect of group (high MDQ vs. low MDQ), time (scan 1 vs. scan 2), or group by time interaction on functional connectivity with the right or left amygdala. Within this, there was also no significant main effect of time given group, or group given time, on functional connectivity with both of these seed regions.

In order to complement less stringent cluster-forming threshold analysis methods used in previous literature, current data was also analysed for $Z > 2.3$, $p < .05$. This analysis also yielded no significant effects. There was no overall main effect of group, time, or group by time interaction on functional connectivity with the right or left amygdala. There was also no main effect of time given group, or group given time, on functional connectivity with both of these seed regions.

5.3.4.2 Insula

There was no significant overall effect of group (high MDQ vs. low MDQ), time (scan 1 vs. scan 2), or group by time interaction on functional connectivity with the insula. Within this, there was also no significant main effect of time given group, or group given time, on functional connectivity with this seed regions.

In order to complement less stringent cluster-forming threshold analysis methods used in previous literature, current data was also analysed for $Z > 2.3$, $p < .05$. This analysis also yielded no significant effects. There was no overall main effect of group, time, or group by time interaction on functional connectivity with the insula. There was also no main effect of time given group, or group given time, on functional connectivity with this seed regions.

5.4 Discussion

To my knowledge, this is the first study to investigate the resting-state functional connectivity basis of mood instability. No differences in neural networks activated at rest were found between those who were in the high MDQ group compared to those in the low MDQ group. There was also no effect of repeat testing (time) in the current sample. Similarly, using a seed-based approach, there was no difference in specific connectivity with the emotion processing and regulation regions of the amygdala and insula between groups or across time. Despite reporting null results, current findings do begin to extend our understanding of the neural basis of mood disorders such as BD and MDD by suggesting patterns of mood-contingent neural variability, and thus offering a number of considerations for further study employing more sophisticated dynamic connectivity analyses to more accurately examine mood instability.

Using an independent components analysis (ICA) of static functional connectivity, RSNs were identified across high MDQ individuals and those in the low MDQ group, with no effect of scan session or time. Although this is in line with indistinguishable and consistent patterns of functional connectivity in RSNs found in euthymic BD patients and healthy controls (Syan et al., 2018), studies of such connectivity in patients with manic, mixed, or depressive episodes have shown varying results (Vargas et al., 2013). For instance, Öngür and colleagues (2010) reported differences in the extent of spatial connectivity in BD patients, whilst Liu and colleages (2012) found differences in regional homogeneity within the DMN of depressed BD patients. The reason for such varying results of RSN functional connectivity in BD plausibly lays in the differences in clinical states studied, such that the presence of a significant mood episode may account for the specific connectivity patterns with the DMN noted (Liu et

al., 2012; Öngür et al., 2010). Given that current findings in a large, subclinical, medication-naïve, and at-risk group follow a similar pattern to those seen in euthymic patients (Syan et al., 2018) suggests an overarching stability in networks across the high MDQ group. This presents interesting implications for further study considering the mechanisms by which DMN disruption may predict the onset of episodes, as well as the further dynamic properties that may instead characterise the neurobiological basis of BD.

Results from the seed-based analysis extend this. Whilst the amygdala and insula are known to be implicated in the development of mood disorders, particularly BD, and involved in its maintenance (Garrett & Chang, 2008), a more recent systematic review reported heterogenous patterns of functional connectivity with these regions, based on current mood episode (Vargas et al., 2013). Therefore, as patterns of functional connectivity with the amygdala and insula become more variable with the experience of clinical euthymia, it is not surprising that current static assessments in a subclinical group do not yield significant results. It may instead be that more nuanced techniques of exposing the underlying mechanisms of euthymia, a state we know is overwhelmingly characterised by mood instability, are better equipped at determining the nature of involvement of these finer-grained emotional processing and regulating regions. Given the wider need to account for the subtle and temporal variabilities that underlie mood instability, it is increasingly important that such null findings are used to motivate the need for more sensitive dynamic analyses.

Additionally, owing to the fact that this is the first study using neuroimaging methods in mood instability, warrants the need for further, more stringent investigation of these

putative functional connectivity patterns. Future studies could employ a similar mood monitoring and resting-state fMRI protocol in order to test this effect in more diverse samples of individuals with and without mood instability in order to fully understand the differences in underlying neural connectivity associated with mood instability, as well as to incorporate further temporally sensitive techniques such as more frequent fMRI scanning and testing over a longer time period, in order to tease apart the mechanism by which temporal dynamics in functional connectivity may be related both to mood instability and mood regulation. An additional consideration of how these patterns – of functional connectivity during both mood instability and across time – are modulated in patients with mood disorders characterised by instability, such as BD, can also aid us in better understanding the temporally distinct method of action of lithium and other mood stabilising treatments.

Using a data-driven ICA analysis of the resting-state fMRI data across two time points, a consistent set of RSNs were shown to be active in high MDQ and low MDQ individuals. Interestingly, these networks were also found to be stable when comparing two time points across a 10-week period, suggesting a pattern of stability highlighted using this approach. However, given that ICA is a static method of functional connectivity analysis that averages across time, it is possible that temporal variation in activation may have been missed. For instance, a consistent pattern of highly variable connectivity can be interpreted as a stable characteristic across time just as much as a consistent pattern of invariable connectivity. This potential for missed nuances in functional connectivity due to lowered sensitivity to temporally dynamic patterns using the current static methods is particularly pertinent in light of our aim of studying the oscillating nature of mood instability. Whilst it could also be that the

experience of mood instability in an otherwise healthy group, without widespread diagnoses or functional impairment, may have contributed to this finding of stability in networks across groups and time, the majority of evidence from mood disorder patient groups suggest that employing more sophisticated methods of functional connectivity analysis may aid in detecting more nuanced intricacies of mood instability.

For instance, we know from studies of dynamic functional connectivity in MDD that depression is associated with more variable patterns of connectivity in the insula and PFC, and within regions of the PFC, and that this is also highly correlated with the severity of depressive symptoms (Kaiser et al., 2016). Using a similar method, BD patients have been shown to have less variable patterns of connectivity between the medial PFC and PCC over time compared to healthy controls, and that this was associated with slower processing speed and reduced set-shifting (Nguyen et al., 2017). Whilst research using these dynamic techniques are otherwise currently minimal, taken together so far, they highlight patterns of disruption in dynamic functional connectivity that relate to patterns of mood and cognitive symptoms that seem to underlie the wider fluctuating experience of mood instability. The idea that such dynamic functional connectivity patterns also relate to cognitive symptoms, impairments that are similarly observed in task-based functional connectivity studies in MDD and BD (Panchal et al., 2019), also further lends itself to the proposal of a higher order imbalance in neural homeostatic mechanisms to regulate mood and related behavioural and cognitive outputs as being the core pathophysiological basis of mood instability. Whilst I am unable to investigate these distinct cognitive impairments and their relation to mood instability in the current thesis, it is important to consider the cognitive outcomes of this disruption, in addition to the clinical and

behavioural outcomes presented thus far, in order to fully understand the profile of mood instability.

Whilst the methods employed here are important in their novel use in building a neuroscientific profile of mood instability, a consideration of the influence of motion-based artefacts should be noted. In the current sample, high and low MDQ participants did not differ in the amount of both gradual and abrupt scan-to-scan movement they made, and there was also no difference across scan sessions. Strict denoising was also still completed as part of the pipeline for pre-processing the data. However, given that resting-state analysis is particularly sensitive to such artefacts, and that residual confounds of these artefacts are known to persist despite removal by specific pre-processing techniques (Cole, Smith, & Beckmann, 2010), future analyses could be further strengthened by both removing individual high-movement volumes via censoring (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012, 2013; Power et al., 2014), and including motion as a regressor in subsequent analyses. Thus, the employment of stricter motion corrective measures, both in pre-processing and in the main analysis of data, can help to overcome the negative influence of these artefacts across the resting-state time course, thus improving the accuracy of static networks and connectivity patterns identified.

Nevertheless, current findings are important given the often inconsistent and limited nature of results in static resting-state functional connectivity across mood disorders, and due to the fact that this is the first such study in mood instability. Current findings highlight the complexities involved in exploring the functional connectivity patterns of highly variable and fluctuating clinical symptoms, and warrants the need for further

investigation of the dynamic nature of underlying functional connectivity. The subsequent chapter aims to do just this using dynamic functional connectivity analysis methods. Whilst first building an account of whole brain functional connectivity patterns in those experiencing mood instability using traditional static functional connectivity analysis methods, I am now able to explore the dynamic intricacies of this connectivity in order to more sensitively detect the presence of disruptions in neural homeostatic mechanisms that may underlie mood instability and its related behavioural and cognitive outcomes.

Chapter 6 | Dynamic resting-state functional connectivity in mood instability

6.1 Introduction

As discussed in the previous chapter, little is currently understood of the pathophysiology of mood disorders such as BD and MDD. Whilst the analysis of resting-state neuroimaging data, or neural connectivity at rest, is gaining traction for its ability to inform us of the neurobiology of disorders outside of task demands, results are often inconsistent or contradictory (Vargas et al., 2013). The identification of mood instability, a dynamic and temporally oscillating phenomenon, as a core feature across these disorders, has led to the emerging focus on exploring the dynamic nature of functional connectivity. Thus, it is predicted that such dynamic investigations are more sensitive in uncovering the nuanced mechanisms of disruptions that are likely to underscore temporally fluctuating mood symptoms, compared to more traditional methods examining static functional connectivity changes.

When considering traditional methods of analysing resting-state functional connectivity data, for example whole-brain approaches such as independent components analysis (ICA) and regional techniques such as seed-based analysis, we are able to explore intrinsic brain organisation based on the assumption that functional connectivity is stationary during the entire scan period, or at least static during a given task or condition such as rest (Allen et al., 2014; Rashid, Damaraju, Pearlson, & Calhoun, 2014). This assumption, however, does not take into account the presence and potential of temporal variability given that spontaneous fluctuations are a hallmark of recordings of neural signals, developing over time scales spanning milliseconds and

tens of minutes (Allen et al., 2014). Additionally, considering that individuals are often engaged in different mental activities during these rest periods (that is, that mental activity is unconstrained) and that subtle modulations in cognitive load can change patterns of functional connectivity throughout the brain, including in DMN regions (Nguyen et al., 2017; Yan et al., 2009), highlights how a static view of functional connectivity which averages across neural connectivity during a scan period may be an oversimplification. Findings of fluctuations in functional connectivity over the course of an experiment using these traditional methods (Arieli, Sterkin, Grinvald, & Aertsen, 1996; Makeig, Debener, Onton, & Delorme, 2004; Onton & Makeig, 2006), and those that have highlighted the uncontrolled but recurring patterns of interactions among intrinsic networks at rest (Calhoun, Miller, Pearlson, & Adali, 2014) lend further support to this notion that moves away from a static consideration of functional connectivity and towards a more nuanced examination of dynamic and fluctuating connectivity across time, both in psychiatric and healthy samples (Hutchison et al., 2013)

Sliding window analysis is the most commonly used approach to investigate dynamic functional connectivity (dFNC) for its ability to capture dynamic phenomena of potential functional relevance (Hutchison et al., 2013). In this approach, data points within time windows of a fixed length (or TRs), often with tapered or weighted edges, are used to calculate functional connectivity correlations that are then shifted in time by a fixed number of data points, creating an overlap between successive windows. The outcome of this is a quantification of the time-varying behaviour, in the form of correlation coefficients, across the duration of the scan. Given that it is often difficult to interpret variability metrics since fluctuations present in a range of data including noise, initial studies employing the sliding window approach aimed to validate the

technique by exploring the relative amplitude of dynamic functional connectivity in regions known to be related to static functional connectivity analyses (Shen et al., 2013). Across a range of studies, it has been shown that regions with both unidirectional and bidirectional static connections (Abou-Elseoud et al., 2010) have increasingly stable dynamic functional connectivity profiles compared to those with no directional connections, often thought to be in regions outside of primary sensorimotor and higher-order networks (Gonzalez-Castillo et al., 2014, 2012). This validation sets the foundation for exploring related disruptions in stability markers during illness, particularly those that are characterised by symptomatic instabilities, such as mood disorders.

Before discussing the potential relevance this dFNC approach has to the study of mood disorders, however, it is important to acknowledge the limitations of such methods, particularly given that they are in their infancy. A concern often noted is that of the potential for noise, frequently caused by motion artefacts, to influence results from dFNC analyses. Given that most sources of noise are non-stationary in nature and, thus, less likely to be eliminated in pre-processing steps employed in static functional connectivity pipelines such as ICA, suggests the increased likelihood of an overamplification in results. Secondly, concerns around the size of windows, particularly in ensuring that they are large enough to allow robust estimations of functional connectivity, but small enough to detect potentially interesting fluctuations in connectivity (Hutchison et al., 2013; Sakoğlu et al., 2010), are noted. To date, a range of empirical evidence has addressed this and suggested window sizes of around 30 seconds as providing the most robust results by ensuring optimal balance between temporal and spatial resolution (Jones et al., 2012; Shirer et al., 2012), and has been

implemented in current analyses (see *Methods 2.4.2.2*). Together, these limitations are important to consider given the emerging use of this approach in the study of dynamic functional connectivity in psychiatric illness, and it is hoped that the advent of more stringent pre-processing techniques tailored specifically to these dynamic approaches may aid in circumventing the particular confounds these concerns may currently present in the interpretation of results.

Despite these concerns, initial studies employing these dFNC approaches in the study of clinical populations have provided interesting results highlighting significant patterns of dynamics across a range of disorders. For instance, patients with schizophrenia have been shown to exhibit decreased variability over time in the spatial configuration of the DMN, but increased variability in the coordinated connectivity of frontoparietal and temporal regions compared to healthy controls (Ma, Calhoun, Phlypo, & Adali, 2014). Additionally, patients with Alzheimer's disease show more persistent functional connectivity among anterior regions of the DMN such as the medial PFC (mPFC) than age-matched healthy controls (Jones et al., 2012), together highlighting that altered dFNC, particularly in regions of the DMN, may be an important dimension of the pathophysiology of psychiatric illness.

When considering these patterns in the pathophysiology of mood disorders, the results from studies employing static functional connectivity analyses have often informed us of the potential dynamic mechanisms at play. For instance, a recent meta-analysis of static resting-state functional connectivity in MDD also revealed increased connectivity in regions of the DMN, especially in the mPFC (Kaiser et al., 2015), and led to the prediction that this static connectivity pattern may be accompanied by decreased

dynamic connectivity, together reflecting the habit of inflexible, sustained attention to negative self-referential thoughts that are core to depressive rumination. Similarly, by building on evidence from static analyses that have shown abnormal connectivity between regions of the DMN and insula, known to be implicated in cognitive and emotional regulation, has led to the hypothesis of increased dynamic functional connectivity in DMN and prefrontal or insular regions. This latter prediction is particularly interesting given its consideration of dynamic variability in regions involved with regulatory mechanisms, suggesting a potential neural representation of homeostasis that may be influenced by mood instability.

In Kaiser and colleagues' (2016) study testing these predictions of dynamic functional connectivity in unmedicated MDD patients, results show that depression was characterised by decreased dynamic, or less variable, connectivity between mPFC and regions of the parahippocampal gyrus and DMN, highlighting an amplification of connectivity between regions thought to underlie negative biases in cognitive affective processing in MDD. Additionally, increased dynamic, or more variable, connectivity between the PFC and regions of the insula was found, such that variation increased as a function of the severity of recent rumination. Whilst again highlighting a mechanism of disruption in neural regions known to be involved in emotional regulation, these findings also begin to uncover abnormal patterns of fluctuating neural communication in MDD that are also involved in broader cognitive symptoms of the disorder.

In a similar study exploring the cognitive correlates of dFNC in BD, Nguyen and colleagues (2017) reported decreased variability in dynamic connectivity in the mPFC

and posterior cingulate cortex (PCC) regions of the DMN, despite the absence of differences in overall static connectivity strength between the mPFC and DMN in their sample of euthymic BD patients. Importantly, this increase in dynamic rigidity within the DMN was also associated with slower processing speed and reduced cognitive set-shifting, suggesting that the presence of reduced intranetwork flexibility is also a correlate of cognitive impairments in euthymic BD. When considering this finding in relation to the core feature of increased mood instability in BD, we are led to hypothesise that a reduction in network variability in a clinical sample characterised by increased symptomatic variability perhaps reflects an inability to flexibly switch between networks. This would be especially pertinent in a comparatively healthy sample where an increase in variability in dFNC could have otherwise reflected optimal adaptability to changing environmental and task demands (Nguyen et al., 2017).

This finding of lowered dynamic amplitude in BD has also been reported in a study of intrinsic regional differences in functional connectivity variability in schizophrenia and BD patients. Outside of differences in static or average whole-brain functional connectivity, Rashid and colleagues (2014) identified disease-specific dynamic differences such that all patients made fewer transitions across dynamic neural states, as well as showing connectivity variations in states involving the activation of frontal and frontoparietal regions, compared to healthy controls. Interestingly, the researchers commented on how these dynamic connectivity patterns were often modulated by diagnosis, such that patterns of connectivity were most starkly different in schizophrenia, followed by BD. Collectively, these differences in dynamic functional connectivity seemed to more accurately capture the subtleties and more nuanced differences in the clinical presentation of schizophrenia and BD, something that is

often missed in more traditional analyses of the static differences in connectivity that average across time periods and thus lose temporal specificity, and further highlights the importance of such dynamic methods in capturing the temporal basis of mood and related disorders.

Whilst we are able to contemplate the dynamic nature of functional connectivity that may underlie mood instability given that patterns of dynamic functional connectivity are often reported in mood disorders outside of specific or consistently identified static differences in connectivity, an exploratory approach will be taken in subsequent analyses. This is to account of the novel nature of the dFNC approach in the assessment of mood instability, and thus, to ensure that a whole brain approach is taken to investigate the nuances and complexities of both dynamic neural connectivity and dynamic mood instability. Such an approach will also ensure that the most comprehensive pathophysiological profile of mood instability is built, in order to motivate future more targeted and therapeutic studies. Therefore, by providing this first study of dynamic functional connectivity in mood instability, it is hoped that we may begin to uncover an overarching disruption in neural homeostatic mechanisms that are responsible for regulating mood instability and related behavioural patterns.

Analyses in the current chapter aim to build upon the foundation built in the previous chapter investigating whole-brain static functional connectivity in mood instability (*chapter 5*), by employing a sliding-window approach to investigate the particular dynamic nuances that more accurately capture this temporally oscillating phenomenon. In order to achieve this, two stages of analysis of resting-state fMRI data from the COMET study will be undertaken, namely: (a) sliding window approach to

explore dynamic variability and properties across time in high MDQ and low MDQ individuals; and (b) an investigation of the relationship between these dynamic neural properties and mood and circadian rest-activity patterns. It is hoped that such analyses can begin to capture the subtleties of mood instability and its related behavioural correlates in order to uncover the dynamic pathophysiological process of mood disorders, and the more nuanced targets for therapeutic intervention this may represent.

6.2 Methods

The current chapter focuses on analyses and results from resting-state functional MRI (fMRI) data collected as part of the COMET study, over two time points. A summary of the wider methodology used in the collection of this data can be found in *chapter 2*, *section 2.5.7*. A broader overview of the participants recruited in the study can be found in *chapter 2*, *section 2*, as well as overall sample characteristics in *section 3*. The remainder of this chapter will focus, thus, on presenting details of the methods employed in the dynamic analysis of rest-stating fMRI data.

6.2.1 Participants

Out of the seventy-four participants who completed the COMET study, data from 65 participants were available to analyse in this chapter. Thirty-three of these participants were in the high MDQ group, and 32 in the low MDQ group. All participants provided resting-state fMRI and structural scans at two time points, resulting in 130 datasets for analysis.

Data from the remaining 9 participants from the COMET sample (high MDQ n = 4; low MDQ n = 5) were not available for these analyses for two reasons: scanning error (n = 7) (including fewer volumes of data available and missing fieldmap data) and completion of only one scan (n = 2). A participant with fewer volumes of data (172 instead of 180) was further excluded in these analyses, yet included in static resting state analyses (see *chapter 5*, *section 5.2.1*) due to the fact that the current analysis package requires all data to be uniform.

6.2.2 Procedure

Please see *chapter 5*, *section 2.2*, for the MRI procedure used.

At both scan sessions, the resting-state fMRI scan sequence was conducted first. Please see *chapter 2*, *section 2.5.7.1* for further details of the order in which MRI sequences were conducted at each session.

6.2.3 Neuroimaging protocol

Please see *chapter 5*, *section 2.3* for the neuroimaging protocol used in the collection of resting-state fMRI and structural MRI data, as well as *appendix 5.1* for the full resting-state fMRI protocol.

6.2.4 Analysis

Data were pre-processed using FSL (FMRIB Software Library v6.0; https://fsl.fmrib.ox.ac.uk/fsl) (Jenkinson et al., 2002; Smith et al., 2004; M. W. Woolrich et al., 2009), and analysed using GIFT (Group ICA of fMRI Toolbox; http://mialab.mm.org/software/gift) (Calhoun, 2004). GIFT is a GUI application developed in MATLAB (The MathWorks Inc., 2010) that enables group inferences from fMRI data using Independent Component Analyses (ICA) and dynamic functional connectivity (dFNC) analysis using the windowed functional network connectivity (wFNC) approach.

6.2.4.1 Pre-processing

Please see *chapter 5*, *section 2.4.1* for details of the pipeline and methods used in the pre-processing of resting-state fMRI data.

6.2.4.2 Dynamic functional connectivity analysis (dFNC)

Please see figure 34 for an overview of the analyses conducted in this chapter.

In order for the data to be appropriately structured and formatted for dFNC, it was necessary to conduct static ICA in the GIFT toolbox. The settings for this ICA were matched to those applied by the FSL MELODIC toolbox where possible.

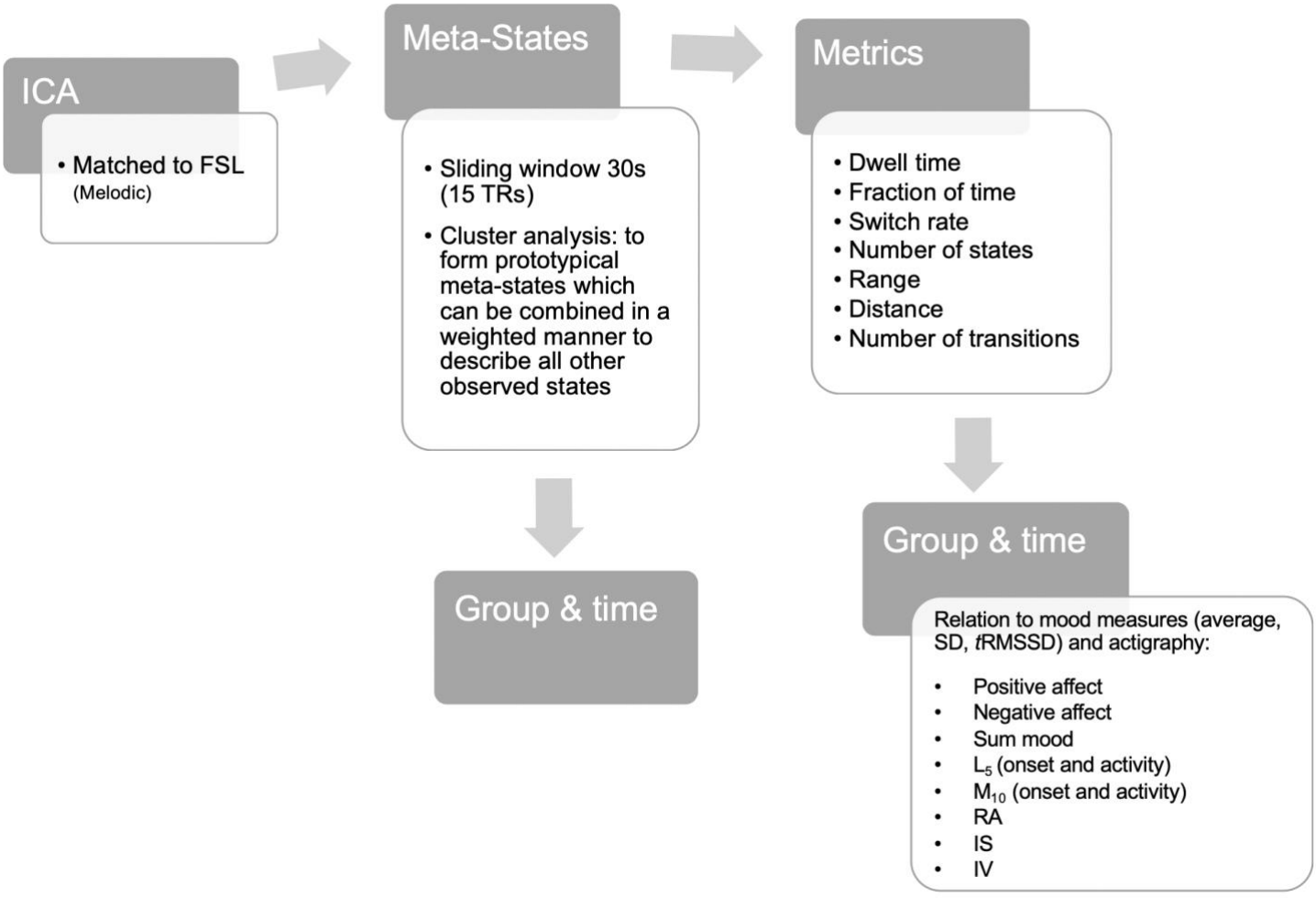


Figure 34: Flow chart of dFNC analysis steps conducted on COMET resting-state fMRI data.

6.2.4.2.1 Decomposition into resting state networks (RSNs)

After pre-processing, group independent components analysis (GICA), conducted through the GIFT toolbox, was run on the resting-state fMRI data from all participants across all scan sessions (*N* = 130), resulting in a decomposed set of 25 statistically independent spatial components with common time course profiles. Of these 25 components, 12 intrinsic resting-state networks (RSNs) were identified using a similar method to that outlined in *chapter 5*, *section 2.4.2*. Identification of these RSNs was conducted using Pearson Spatial cross-correlation comparison of FIND Lab's 90 ROI atlas (Shirer et al., 2012).

Please see *appendix 6.1* for details of the RSN identification process.

Spatio-temporal regression was used to obtain subject-specific spatial maps and time courses. Subject-specific RSN time courses were detrended, orthogonalized with respect to motion parameters, despiked by replacing outlier time points with 3rd order spline fit to cleaner neighbouring points, and filtered using a 5th order Butterworth filter with a passband of .01 to .15 Hz (Miller et al., 2016).

6.2.4.2.2 Windowed Functional Network Connectivity (wFNCs)

Windowed segments of intrinsic RSN time courses were calculated by using a tapered rectangular window of length 15 TR (30 seconds), advancing 1 TR at each step. Windowed functional network connectivity (wFNC) was then conducted by computing pairwise correlations between each of these windowed segments. In line with previous

research (Miller et al., 2016), an L^1 constraint on the inverse covariance matrix using the G-LASSO framework (Friedman, Hastie, & Tibshirani, 2008) was applied, with regularisation parameter optimised subject-wise by evaluating the log-likelihood of each subject's unseen data in a cross-validation framework.

6.2.4.2.3 Basis Correlation Patterns (CPs) to identify meta-states

Using clustering algorithms, patterns of connectivity in each window were clustered to form prototypical meta-states which can be combined in a weighted manner to describe all other observed states (Yu et al., 2013). Here MATLAB's (The MathWorks Inc., 2010) implementation of k-means clustering (Allen et al., 2014) was used in order to separate out the set of wFNCs into clusters whose centroids are treated as basis correlation patterns (see fig. 40 in *Results 3.2.1*). The elbow criterion of the cluster validity index was used to determine the number of clusters to be four, which is calculated as the ratio between within-cluster distances to between-cluster distance (Rashid et al., 2014). Thus, observed wFNCs are replaced by the prototype states that they most resemble, enabling connectivity dynamics to be described as a process of moving from one of these summary states, or meta-states, to another.

6.2.4.2.4 Dynamic functional connectivity (dFNC) metrics

After identification of meta-states, global metrics of connectivity dynamism were also obtained, for all participants at each scan session (N = 130). These metrics correspond to number of states occupied, switch rate between states, range of states occupied, the overall distance travelled across states, and the number of transitions between states made. Markers of time spent in each of the four meta-states were also provided,

corresponding to dwell time and fraction of time. Please see table 32 for further details of these metrics and markers.

Metric	Description
Number of states	The number of distinct meta-states occupied during each scan session.
Switch rate	The frequency by which participants switch from one meta-state to another.
Range	The range of meta-states occupied, or the largest distance between occupied meta-states.
Distance	The total distance travelled by each participant through the state space.
Number of transitions	The number of times participants transition from one meta-state to another.
Dwell time	The amount of time a participant remains in one of the four meta-states once they occupy it.
Fraction of time	The time a participant spends in each of the four meta-states, as a fraction of overall time.

Table 32: Description of dynamic functional connectivity metrics.

6.2.5 Meta-state coupling across groups

After distinct meta-states were identified, the GIFT toolbox conducted meta-state composition differences (MSCD) tests in order to investigate group differences in coupling within each of the four meta-states, over all scan sessions (scan 1 and scan 2) and individually at scan 1 and scan 2.

6.2.6 dFNC metrics across time

In order to investigate the effect of time, or scan session, on dynamic functional connectivity metrics, as well as to visualise this potential interaction across groups,

repeated measures ANOVAs were conducted using SPSS (IBM Corp, 2017). The effect of group (high MDQ or low MDQ; the between-subjects factor), time (scan session; the within-subjects factor), and group by time interaction for number of states, switch rate, range, distance, number of transitions, dwell time and fraction of time (individually for each of the four meta-states) was analysed.

6.2.7 Correlational analyses of dFNC metrics and mood instability

6.2.7.1 dFNC metrics and mood

Correlational analyses were conducted using SPSS (IBM Corp, 2017) to test the relationship between dynamic functional connectivity metrics (as measured by number of states, switch rate, range, distance, number of transitions, and dwell time and fraction of time across all four meta-states) and overall daily mood[33] (as measured by positive affect and negative affect). Change in dFNC metrics across time was used as the variable of interest, such that metric values at scan 1 were subtracted from the metric values at scan 2 to find the difference. These analyses were also run on both average and variability – as measured by the standard deviation (SD) and *t*RMSSD – measures of daily mood, in order for the relationship between dynamic functional connectivity and mood experiences and instability to be explored.

[33] Please see *chapter 3, section 2* for a full description of daily mood measures collected in the COMET study.

6.2.7.2 dFNC metrics and rest-activity patterns

Correlational analyses were also employed, via SPSS (IBM Corp, 2017), to test the relationship between dynamic functional connectivity metrics (again as measured by number of states, switch rate, range, distance, number of transitions, and dwell time and fraction of time across all four meta-states) and overall summary data for rest-activity variables[34] (L_5 onset, L_5 activity, M_{10} onset, M_{10} activity, RA, IS, and IV). Again, change in dFNC metrics across time was used as the variable of interest. These analyses will begin to shed light on the relationship between dynamic functional connectivity and rest-activity pattern disruptions known to be symptomatic of mood instability and mood disorders.

[34] Please see *chapter 4, section 2* for a full description of the rest-activity measures collected as part of the COMET study.

6.3 Results

6.3.1 Demographics

	High MDQ (*n*=33)	Low MDQ (*n*=32)
Gender *[m:f]*	12:21	9:23
Handedness *[right:left]*	26:7	27:5
Age *[mean (SD)]*	24.33 (6.74)	25.16 (7.05)

Table 33: Demographic data for high and low MDQ groups.

Demographic data for the sixty-five participants whose resting-state fMRI data (across both time points) were analysed are shown in table 33. No statistically significant association between group and gender ($X(1) = 0.50$, $p = .478$) or handedness ($X(1) = 0.34$, $p = .562$) was found. Also, no significant difference in age ($t(63) = -0.48$, $p = .632$) between the groups was reported.

6.3.2 Meta-states

6.3.2.1 Identification of meta-states

Four distinct meta-states were identified across all participants and all scan sessions (scan 1 and scan 2) (fig. 35). Meta-states were labelled via visual inspection by me and Dr Cassandra Gould van Praag: highly interconnected (meta-state 1), DMN (meta-state 2), sensorimotor (meta-state 3), and low connectivity (meta-state 4).

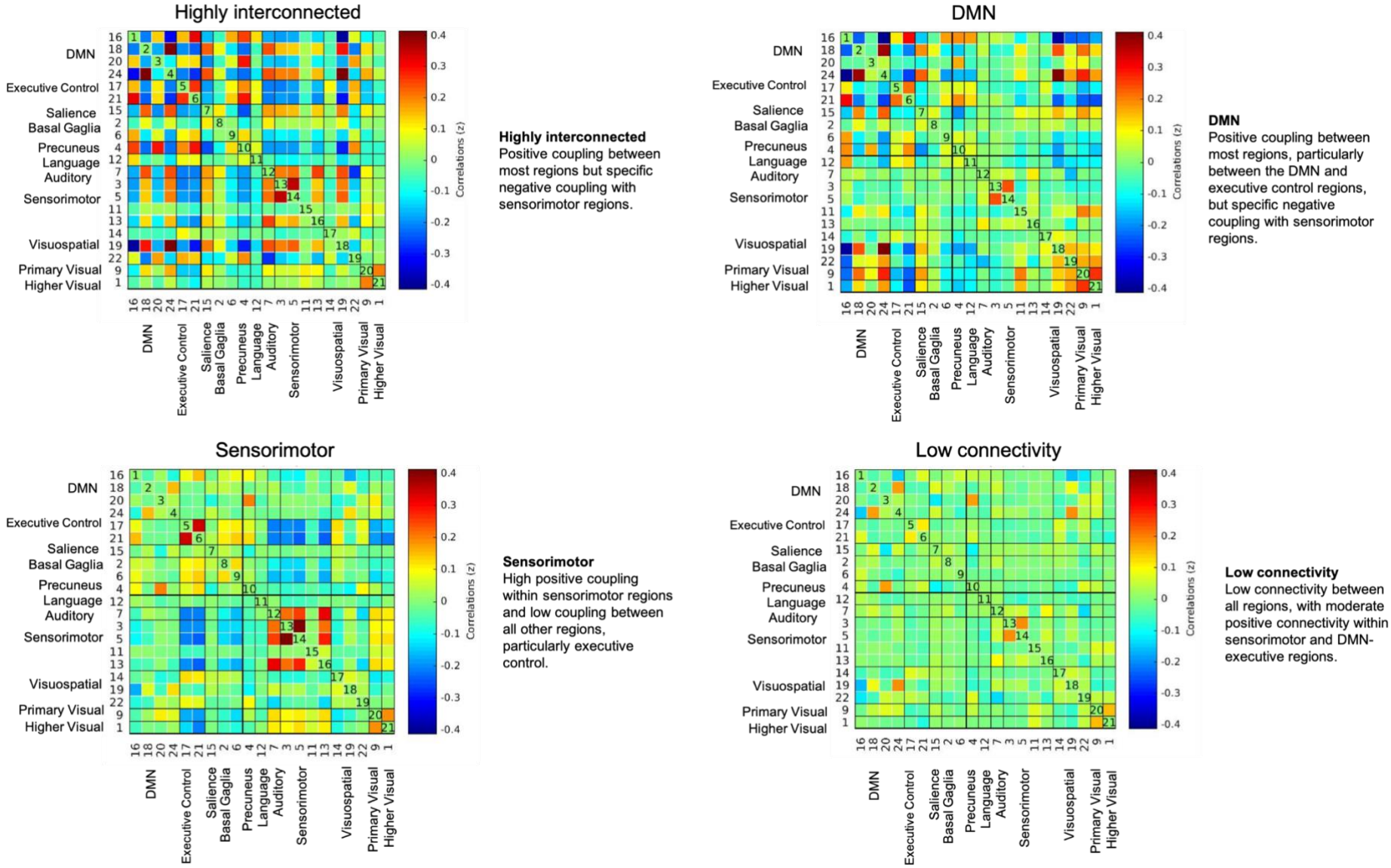


Figure 35: Meta-states identified across all participants and all scan sessions. Group specific centroids of the meta-states (state 1 to state 4) are obtained from k-means clustering (k = 4).

6.3.2.2 Meta-state coupling between groups

Meta-state	*p*
Overall	
Highly interconnected	.758
DMN	.095
Sensorimotor	.985
Low connectivity	.805
Scan 1	
Highly interconnected	.387
DMN	.970
Sensorimotor	.289
Low connectivity	.937
Scan 2	
Highly interconnected	.144
DMN	.079
Sensorimotor	.757
Low connectivity	.781

Table 34: A comparison of meta-state coupling between groups, across all scan sessions/time points and individually at scan 1 and scan 2. Meta-state composition differences (MSCD) p-values are shown.

As can be seen in table 34, no differences in coupling between groups within each of the four meta-states were found. This was noted across meta-states for all scans, and at scan 1 and scan 2 individually.

6.3.3 Dynamic functional connectivity (dFNC) metrics

6.3.3.1 Descriptive statistics

Metric		High MDQ	Low MDQ
		Mean (SD)	*Mean (SD)*
Number of states		33.83 (6.08)	30.39 (7.15)
Switch rate		66.33 (7.05)	61.41 (7.86)
Range		9.89 (1.04)	9.64 (1.13)
Distance		87.79 (12.57)	81.19 (14.26)
Number of transitions		12.33 (3.67)	12.22 (2.87)
Dwell time	*Highly interconnected*	8.10 (5.11)	8.06 (5.57)
	DMN	8.93 (4.85)	8.70 (5.27)
	Sensorimotor	5.83 (3.64)	9.65 (6.61)
	Low connectivity	21.37 (17.96)	21.62 (20.10)
Fraction of time	*Highly interconnected*	0.17 (0.15)	0.15 (0.12)
	DMN	0.19 (0.13)	0.18 (0.14)
	Sensorimotor	0.10 (0.08)	0.19 (0.15)
	Low connectivity	0.54 (0.19)	0.48 (0.17)

Table 35: Dynamic functional connectivity metrics, or markers of variability, in resting-state functional connectivity. Overall averages and standard deviations for the high MDQ and low MDQ groups are shown.

Table 35 shows descriptive statistics for each of the seven dynamic functional connectivity metrics (number of states, switch rate, range, distance, number of transitions, dwell time, and fraction of time), averaged across the two scan sessions.

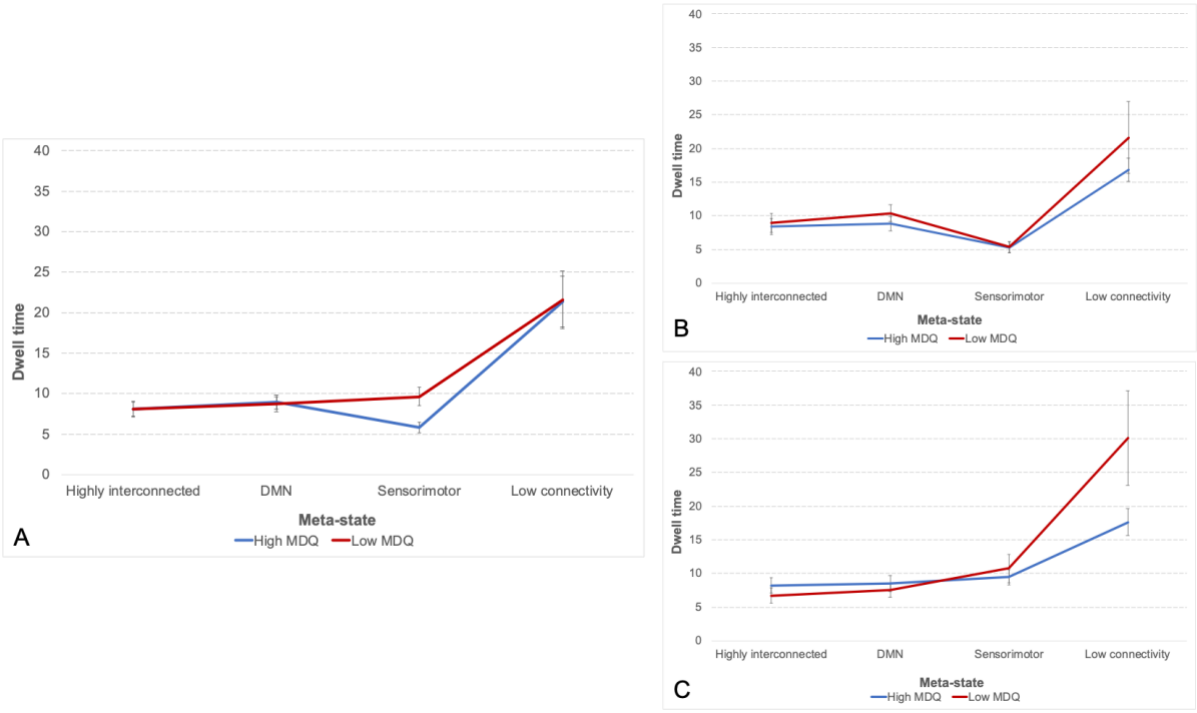


Figure 36: Dwell time across all four meta-states for high MDQ and low MDQ participants. Error bars represent ± 1 *SEM*. (A) dwell time across all scans; (B) at scan 1; (C) at scan 2.

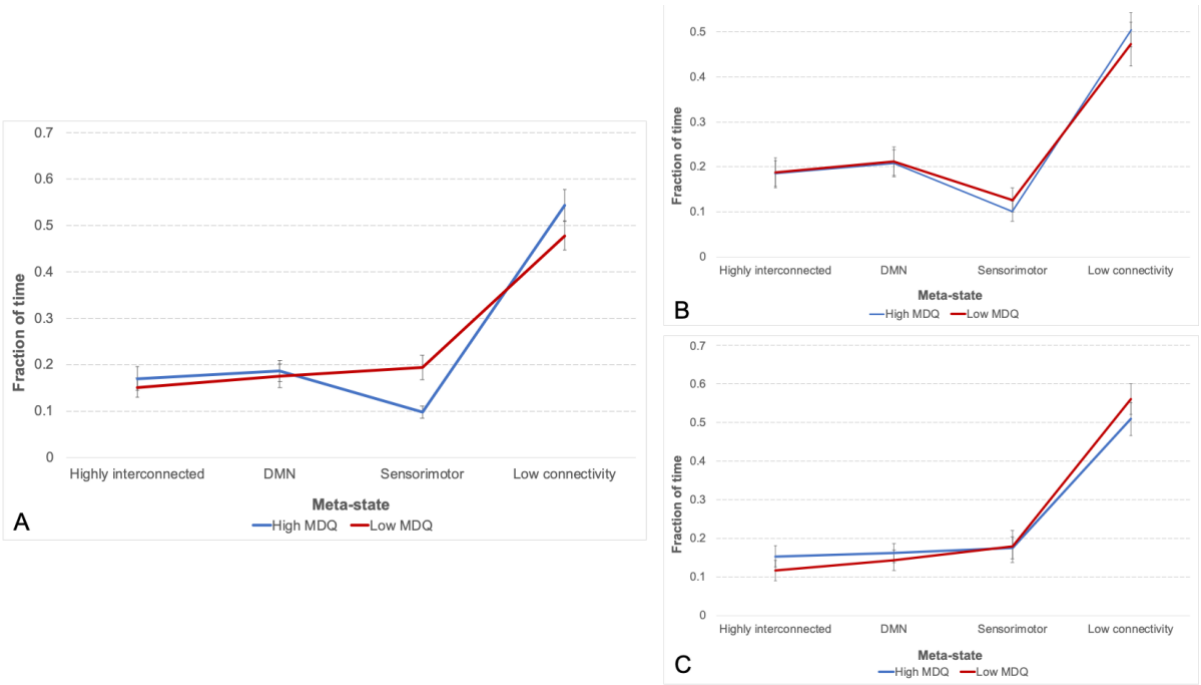


Figure 37: Fraction of time spent in all four meta-states for high MDQ and low MDQ participants. Error bars represent ± 1 *SEM*. (A) fraction of time spent in states across all scans; (B) at scan 1; (C) at scan 2.

6.3.3.2 dFNC metrics across time

6.3.3.2.1 Number of states

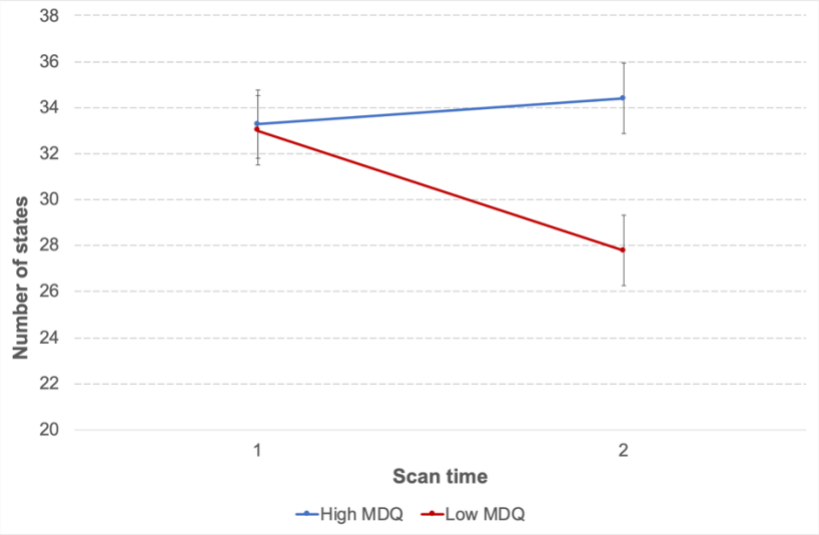


Figure 38: Number of states occupied by high MDQ and low MDQ participants, across both scan 1 and scan 2. Error bars represent ± 1 *SEM*.

There was a significant main effect of group, such that individuals in the high MDQ group occupied more of the four meta-states identified compared to those in the low MDQ group, $F(1, 63) = 4.38$, $p = .040$ (fig. 38). There was no significant main effect of time (scan session), $F(1, 63) = 2.24$, $p = .139$.

Results, however, revealed a significant group by time interaction, $F(1, 63) = 5.36$, $p = .024$, such that both groups differed in this pattern across time. Individuals in the low MDQ group occupied fewer meta-states at scan 2 than scan 1, compared to those in the high MDQ group (fig. 38).

6.3.3.2.2 Switch rate

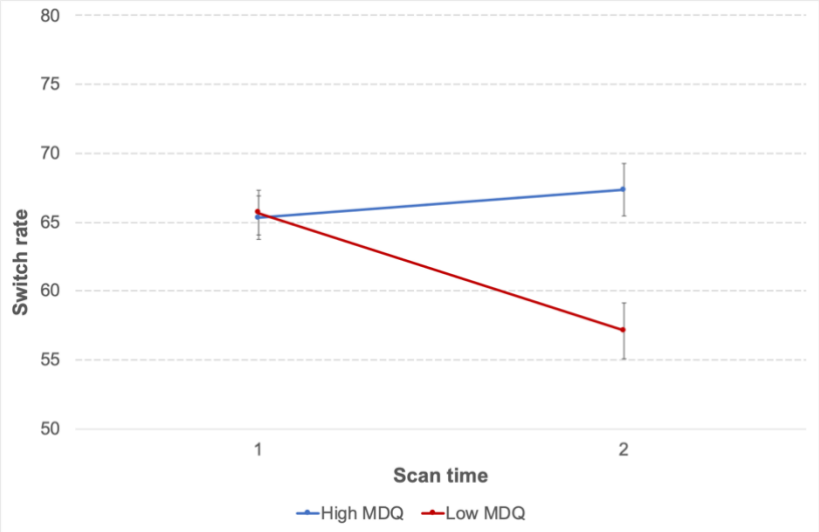


Figure 39: Rate of change between states, or switch rate, across scans 1 and 2, for high MDQ and low MDQ participants. Error bars represent ± 1 *SEM*.

There was a significant main effect of group, such that individuals in the high MDQ group had a higher rate of change between the four states than those in the low MDQ group, $F(1, 63) = 7.08$, $p = .010$ (fig. 39). There was no significant main effect of time (scan session), $F(1, 63) = 3.58$, $p = .063$.

Results revealed a significant group by time interaction, $F(1, 63) = 9.27$, $p = .003$, such that individuals in the low MDQ group had a lower switch rate at scan 2 over scan 1, compared to those in the high MDQ group (fig. 39).

6.3.3.2.3 Range

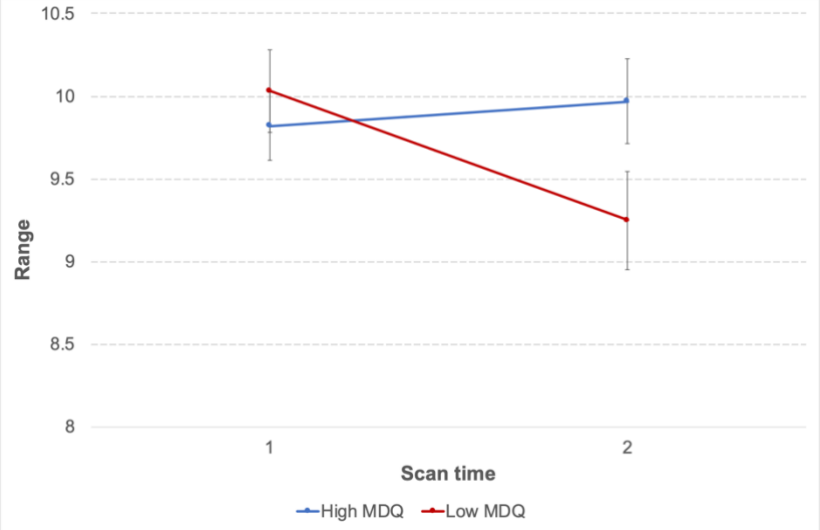


Figure 40: State span, or range, across scan 1 and scan 2 for high MDQ and low MDQ participants. Error bars represent ± 1 *SEM*.

There was no significant main effect of group ($F(1, 63) = .88$, $p = .351$) or time (scan session) ($F(1, 63) = 1.72$, $p = .194$) on range. There was also no significant group by time interaction, $F(1, 63) = 3.78$, $p = .056$ (fig. 40).

6.3.3.2.4 Distance

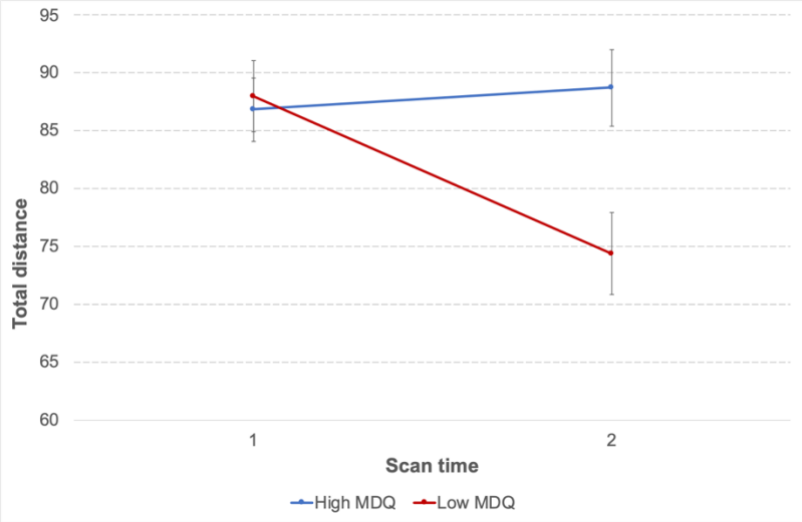


Figure 41: Total distance across meta-states travelled by high MDQ and low MDQ participants at scan 1 and scan 2. Error bars represent ± 1 *SEM*.

Results revealed no significant main effect of group, $F(1, 63) = 3.93$, $p = .052$, and no significant main effect of time (scan session), $F(1, 63) = 3.82$, $p = .055$.

There was a significant group by time interaction, $F(1, 63) = 6.65$, $p = .012$, such that individuals in the low MDQ group travelled a shorter distance between meta-states at scan 2 over scan 1, compared to those in the high MDQ group (fig. 41).

6.3.3.2.5 Number of transitions

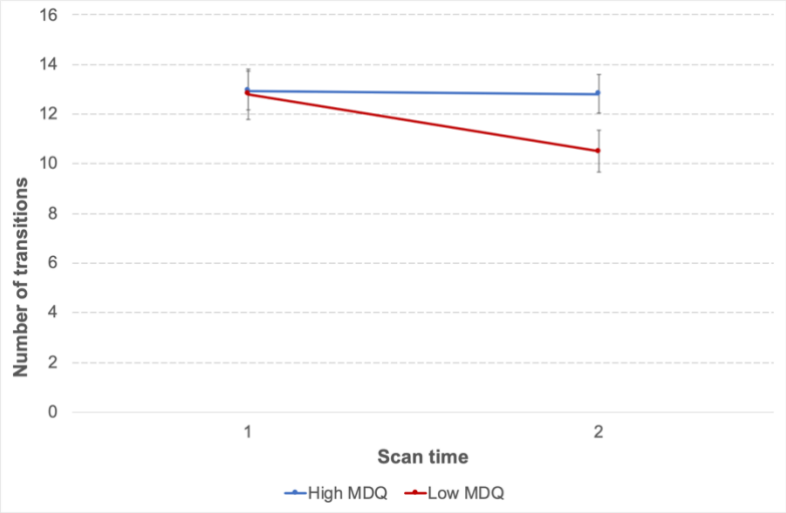


Figure 42: Number of transitions between meta-states made by the high MDQ and low MDQ groups, across scan 1 and scan 2. Error bars represent ± 1 *SEM*.

There was no significant main effect of group ($F(1, 63) = 2.32$, $p = .133$) or time (scan session) ($F(1, 63) = 1.83$, $p = .181$). There was also no significant group by time interaction, $F(1, 63) = 1.48$, $p = .228$ (fig. 42).

6.3.3.2.6 Dwell time

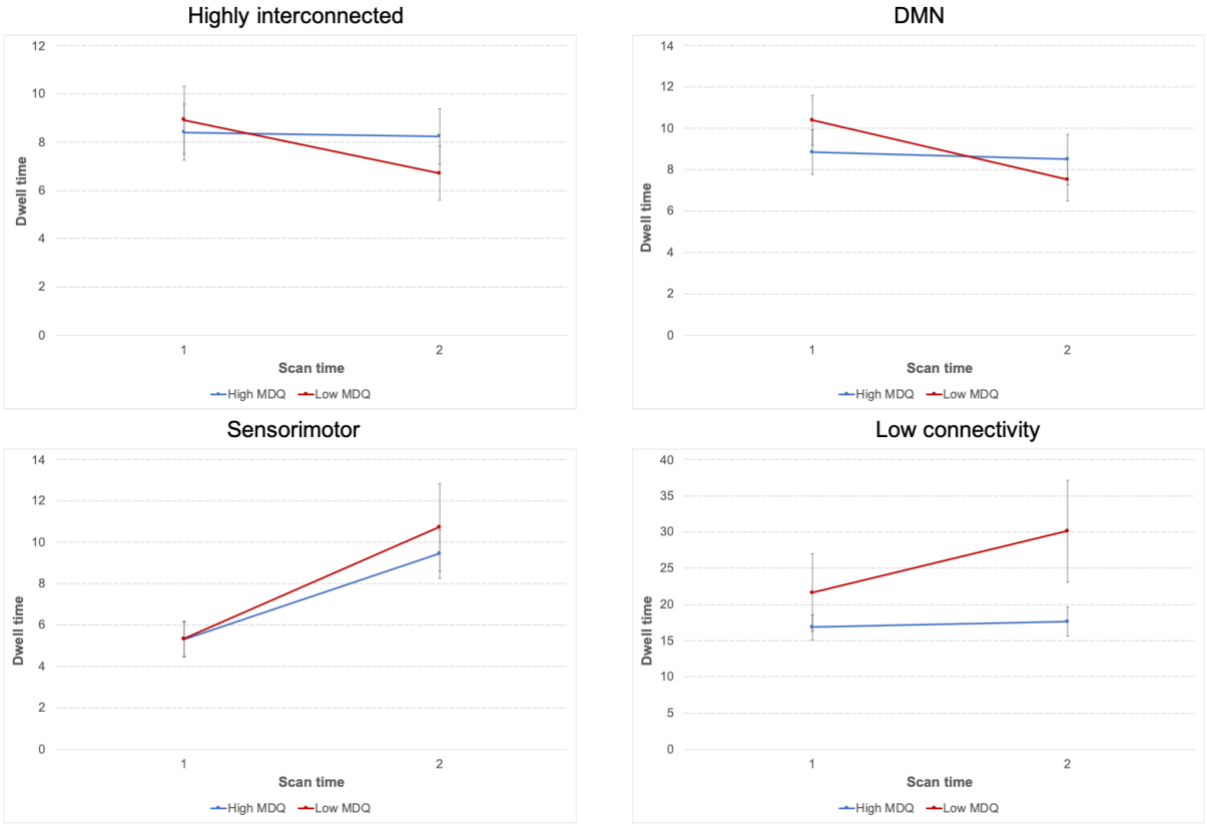


Figure 43: Dwell time within the four meta-states at scan 1 and scan 2, for high MDQ and low MDQ groups. Error bars represent ± 1 *SEM*.

Within the highly interconnected meta-state, there was no significant main effect of group ($F(1, 63) = 0.15$, $p = .701$) or time (scan session) ($F(1, 63) = 1.20$, $p = .278$) on dwell time. There was also no significant group by time interaction, $F(1, 63) = 0.89$, $p = .350$.

Within the DMN meta-state, there was no significant main effect of group ($F(1, 63) = 0.05$, $p = .825$) or time (scan session) ($F(1, 63) = 2.63$, $p = .110$) on dwell time. There was also no significant group by time interaction, $F(1, 63) = 1.63$, $p = .206$.

Within the sensorimotor meta-state, there was no significant main effect of group (F(1, 63) = 0.21, p = .645) on dwell time. There was, however, a significant main effect of time (scan session), F(1, 63) = 14.23, p < .001, such that all participants regardless of group had greater dwell time in this meta-state at scan 2 over scan 1. Results revealed no significant group by time interaction, F(1, 63) = 0.26, p = .614.

Within the low connectivity meta-state, there was no significant main effect of group (F(1, 63) = 3.53, p = .065) or time (scan session) (F(1, 63) = 1.08, p = .302) on dwell time. There was also no significant group by time interaction, F(1, 63) = 0.75, p = .390.

6.3.3.2.7 Fraction of time

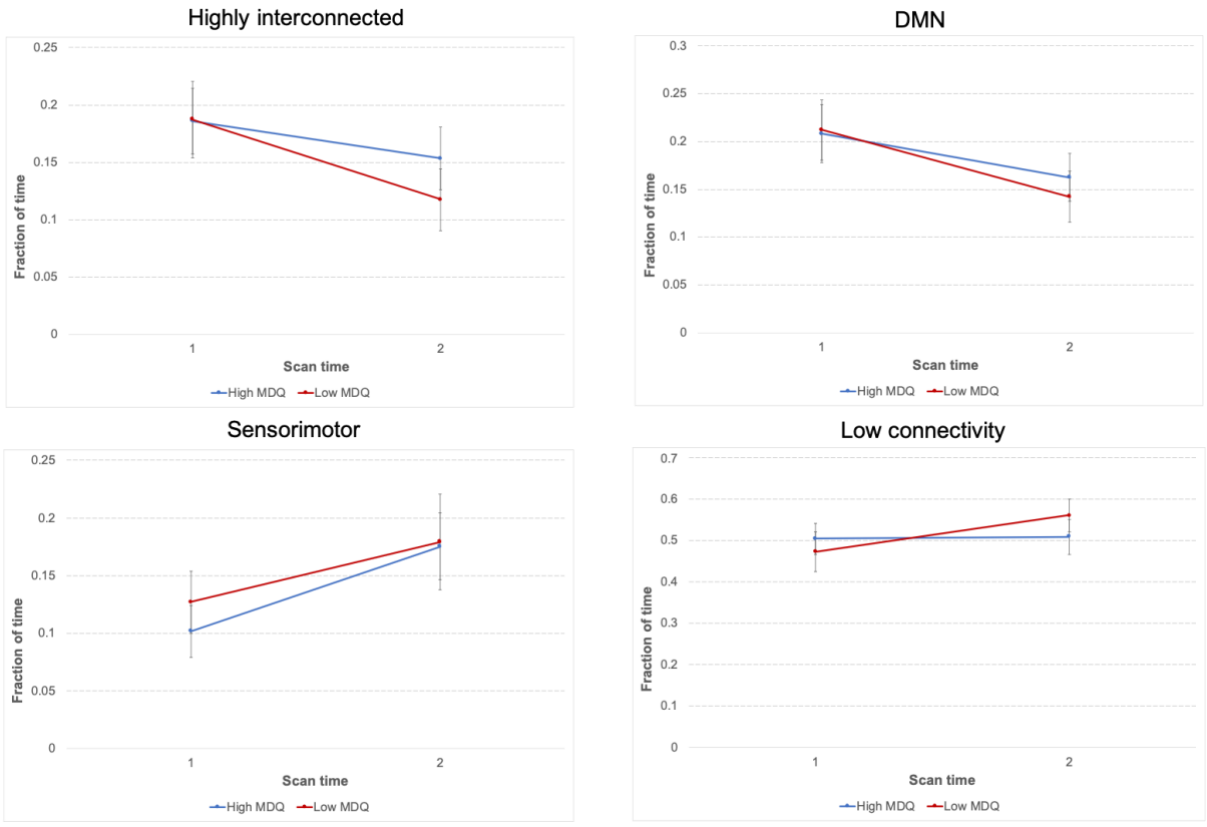


Figure 44: Fraction of time spend in all four meta-states at scan 1 and scan 2, for high MDQ and low MDQ groups. Error bars represent ± 1 *SEM*.

Within the highly interconnected meta-state, there was no significant main effect of group (F(1, 63) = 0.27, p = .605) on fraction of time spent in the meta-state. There was, however, a significant main effect of time (scan session), F(1, 63) = 4.48, p = .038, such that all participants, regardless of group, spent a smaller fraction of time in this meta-state at scan 2 over scan 1. Results revealed no significant group by time interaction, F(1, 63) = 0.60, p = .442.

Within the DMN meta-state, there was no significant main effect of group (F(1, 63) = 0.06, p = .815) on fraction of time spend in the meta-state. Again however, there was a significant main effect of time (scan session), F(1, 63) = 7.00, p = .010, such that all participants, regardless of group, spent a smaller fraction of time in this meta-state at scan 2 over scan 1. Results revealed no significant group by time interaction, F(1, 63) = 0.30, p = 586.

Within the sensorimotor meta-state, there was no significant main effect of group, F(1, 63) = 0.22, p = .643, on fraction of time spent in the meta-state. However, there was a significant main effect of time (scan session), F(1, 63) = 4.45, p = .039, such that all participants, regardless of group, spent a greater fraction of time in this meta-state at scan 2 over scan 1. Results revealed no significant group by time interaction, F(1, 63) = 0.13, p = .722.

Within the low connectivity meta-state, there was no significant main effect of group (F(1, 63) = 0.05, p = .822) or time (scan session) (F(1, 63) = 1.47, p = .230) on fraction of time spent in this state. There was also no significant group by time interaction, F(1, 63) = 1.18, p = .281.

6.3.4 Exploratory relationship between dFNC metrics and mood

6.3.4.1 dFNC metrics and mood

		Number of states		Switch rate		Range		Distance		Number of transitions	
		High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
Positive affect	*Average*	**.36***	-.15	**.41***	-.26	.28	-.16	**.40***	-.26	.26	-.18
	SD	**-.42***	.03	-.24	.09	-.17	-.11	-.31	.10	-.24	-.12
	tRMSSD	-.25	-.07	-.02	.13	-.12	-.22	-.08	.03	-.11	-.18
Negative affect	*Average*	-.32	.12	-.11	.05	**-.45****	.19	-.17	-.04	-.34	-.14
	SD	-.32	.26	-.27	.21	**-.42***	.12	-.32	.17	**-.35***	-.01
	tRMSSD	**-.36***	.24	**-.37***	.26	**-.49****	-.00	**-.37***	.23	-.34	-.00

Table 36: Pearson Product-Moment correlation coefficients of dynamic functional connectivity markers (number of states, switch rate, range, distance, and number of transitions) and overall daily mood (positive affect and negative affect). Absolute and variability (standard deviation (SD) and *t*RMSSD) markers of mood are shown.

* $p < .05$, ** $p < .01$

As demonstrated in table 36, high MDQ participants had more significant associations between dynamic functional connectivity metrics and mood[35]. For example, Fishers Z test to test significance of the difference between two correlation coefficients revealed that absolute positive affect was positively associated with a greater number of states occupied ($z = 2.03$, $p = .042$), greater rate of switching between states ($z = 2.69$, $p = .007$), and greater distance travelled across states ($z = 2.66$, $p = .008$) in the high MDQ group (fig. 45).

[35] Please see *chapter 3* for a full description and discussion of the mood measures.

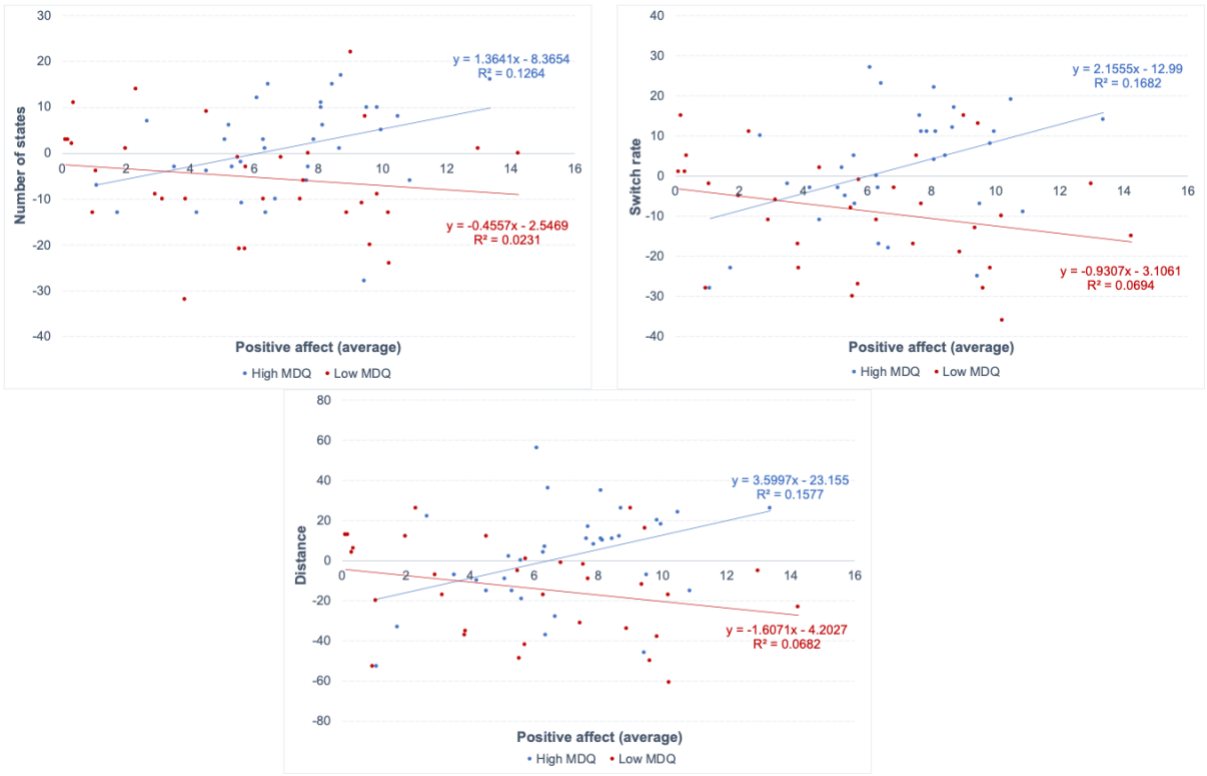


Figure 45: Relationship between positive affect (average) and number of states, switch rate, and distance in high and low MDQ groups.

Negative affect was particularly negatively associated with the range of states occupied, such that as absolute and variability (as measured by both SD and *t*RMSSD) in negative affect increased, the range of meta-states occupied decreased in the high MDQ group (average: z = -2.60, p = .009; SD: z = -2.18, p = .029; *t*RMSSD: z = -2.06, p = .039). Variability in negative affect in the high MDQ group was also negatively associated with the number of states occupied (z = -2.39, p = .017), switch rate between states (z = -2.51, p = .012), and distance travelled across states (z = -2.39, p = .017). Thus, as variability in negative affect increased, high MDQ participants occupied fewer states, had a lower rate of switches between states, and travelled a shorter distance across states (fig. 46).

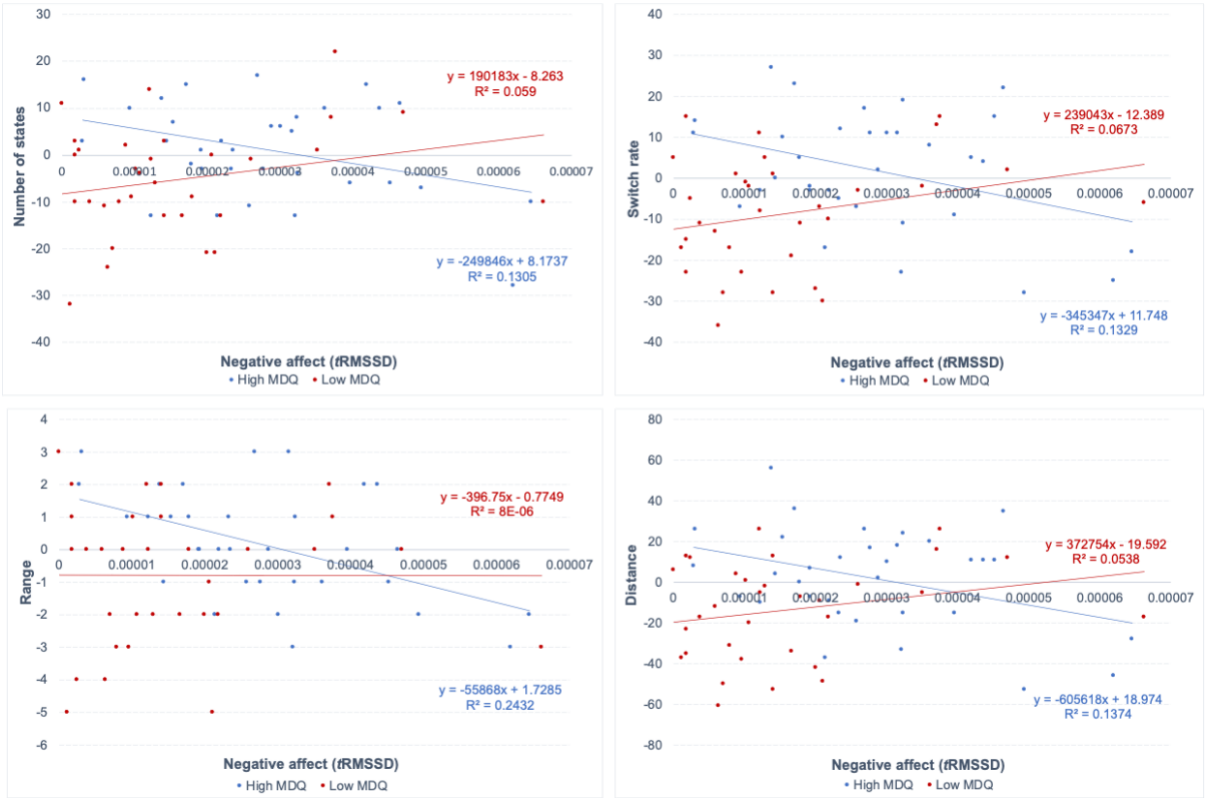


Figure 46: Relationship between variability in negative affect (as measured by tRMSSD) and number of states, switch rate, range, and distance in high and low MDQ groups.

6.3.4.2 Dwell time and mood

		Dwell time							
		Highly interconnected		DMN		Sensorimotor		Low connectivity	
		High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
Positive affect	*Average*	.30	.34	-.21	.32	.17	.11	-.30	-.12
	SD	**-.37***	**.48****	-.09	.05	.34	-.12	.22	.01
	tRMSSD	-.25	.31	-.11	.15	**.37***	.00	.11	.11
Negative affect	*Average*	-.05	.11	-.12	.13	.07	.24	.30	.21
	SD	-.13	.34	-.01	.13	.06	-.01	**.35***	.01
	tRMSSD	-.15	**.38***	-.08	.18	.04	-.04	**.35***	-.13

Table 37: Pearson Product-Moment correlation coefficients of dwell time markers across meta-states (highly interconnected, DMN, sensorimotor, and low connectivity) and overall daily mood (positive affect and negative affect). Absolute and variability (standard deviation (SD) and *t*RMSSD) markers of mood are shown. * $p < .05$, ** $p < .01$

As can be seen from table 37, high MDQ participants had greater associations between dwell times across the meta-states compared to low MDQ participants, excluding the DMN state which did not show any significant association with mood in either of the groups. Variability in positive affect was negatively associated with dwell time in the highly interconnected meta-state for the high MDQ group, such that as variability in positive affect increased in the high MDQ group, dwell time in the highly interconnected state decreased. Instead, low MDQ participants showed a positive association between variability in positive affect and dwell time in the highly interconnected state, such that as variability in positive affect increased in low MDQ participants, dwell time in this state also increased. Fishers Z test revealed that this difference was significant ($z = -3.5$, $p = .001$).

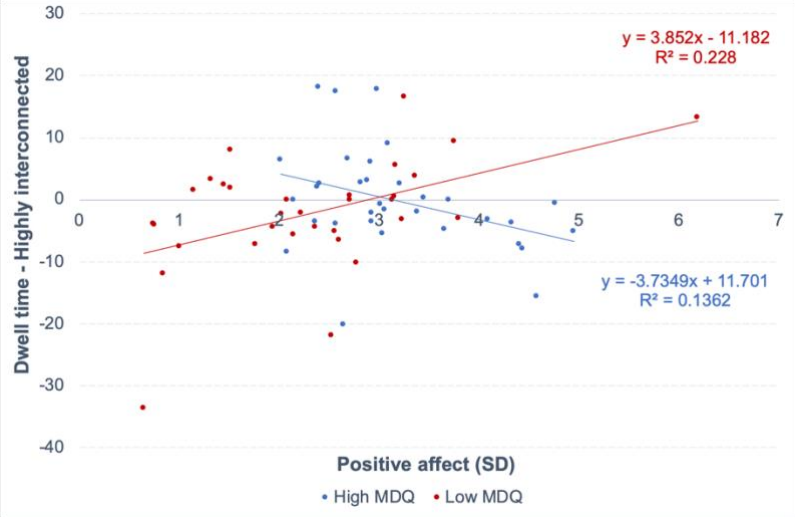


Figure 47: Relationship between variability in positive affect (as measured by SD) and dwell time in the highly interconnected state in high and low MDQ groups.

In low MDQ participants, variability in negative affect was positively associated with dwell time in the highly interconnected state (z = -2.12, p = .034) such that as variability in negative affect increased in these participants, dwell time in the highly interconnected state also increased.

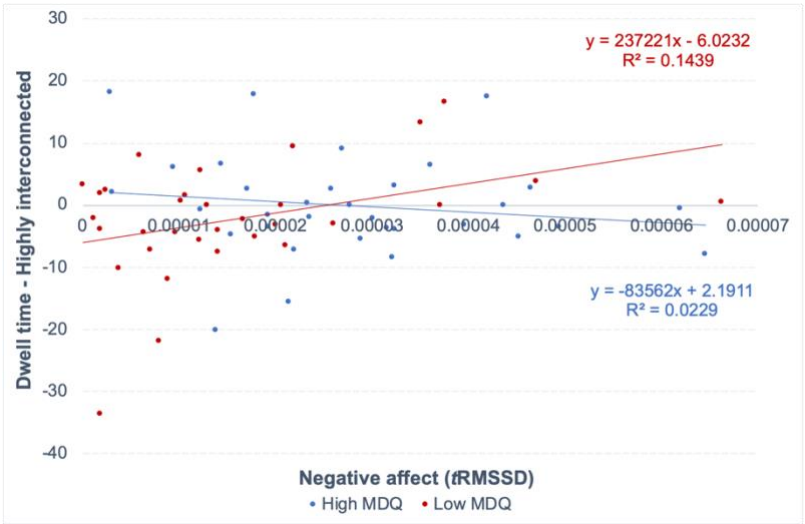


Figure 48: Relationship between variability in negative affect (as measured by tRMSSD) and dwell time in the highly interconnected state in high and low MDQ groups.

6.3.4.3 Fraction of time and mood

		Fraction of time							
		Highly interconnected		DMN		Sensorimotor		Low connectivity	
		High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
Positive affect	*Average*	.16	.156	-.06	**.44***	.23	.11	-.24	**-.41***
	SD	**-.52****	.26	-.31	.26	**.40***	-.10	.27	-.20
	tRMSSD	-.28	.22	-.28	.33	**.37***	-.14	.11	-.18
Negative affect	*Average*	-.30	.16	-.15	.17	.07	-.09	.25	-.10
	SD	**-.41***	**.38***	-.31	.16	.05	-.17	.31	-.16
	tRMSSD	-.32	**.35***	-.21	.14	.06	-.08	.31	-.21

Table 38: Pearson Product-Moment correlation coefficients of fraction of time markers across meta-states (highly interconnected, DMN, sensorimotor, and low connectivity) and overall daily mood (positive affect and negative affect). Absolute and variability (standard deviation (SD) and *t*RMSSD) markers of mood are shown. * $p < .05$, ** $p < .01$

As can be seen from table 38, mood was associated with fraction of time spent in the meta-states across both groups, but only for the low MDQ group in the DMN state. Within positive affect, Fishers Z tests revealed that variability was negatively associated with fraction of time spent in the highly interconnected state ($z = -3.24$, $p = .001$) and positively associated with fraction of time spent in the sensorimotor state (SD: $z = 2.01$, $p = .044$; *t*RMSSD: $z = 2.03$, $p = .042$) for high MDQ participants, such that as variability in positive affect increased in these participants, they also spent a lower fraction of time overall in the highly interconnected state (fig. 49) and a greater fraction of time overall in the sensorimotor state (fig. 50). For low MDQ participants, absolute positive affect was positively associated with fraction of time spent in the DMN state ($z = -2.04$, $p = .041$), such that they spent a greater fraction of time in this state as their positive affect increased.

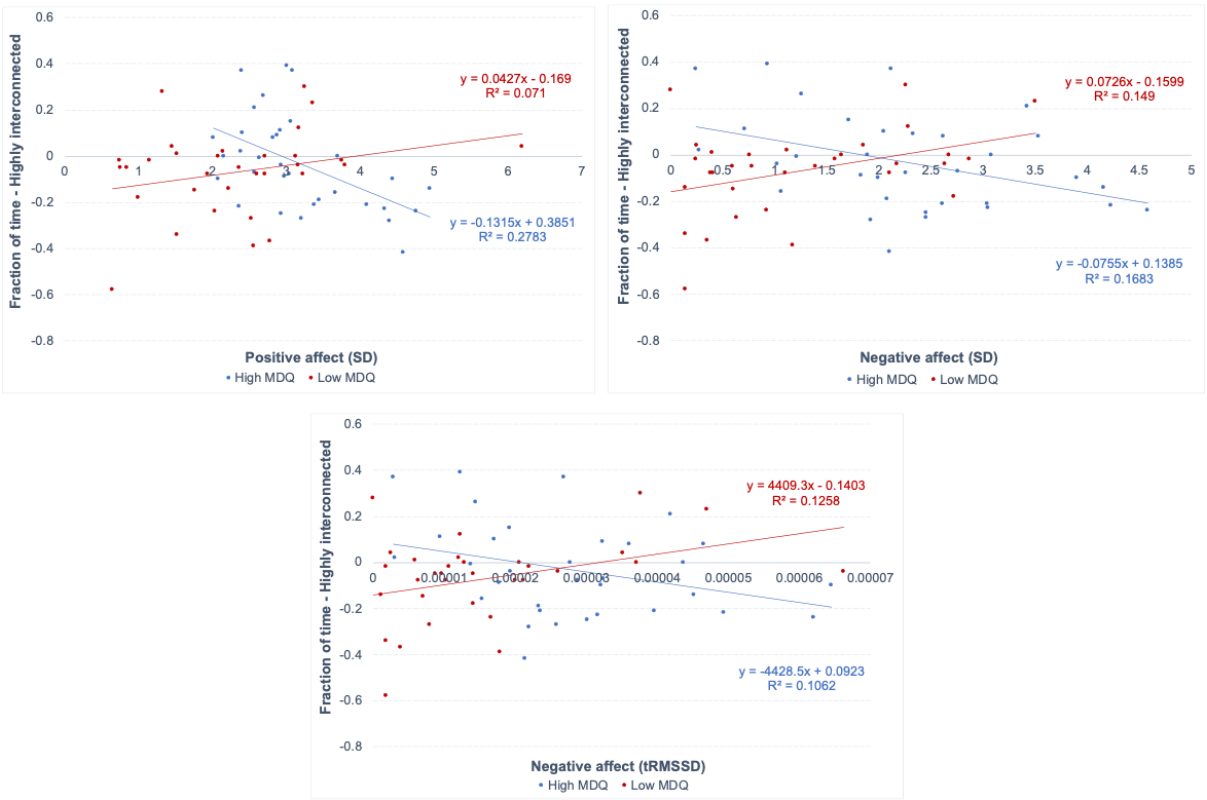


Figure 50: Relationship between variability in positive and negative affect (as measured by SD and tRMSSD) and fraction of time in the highly interconnected state in high and low MDQ groups.

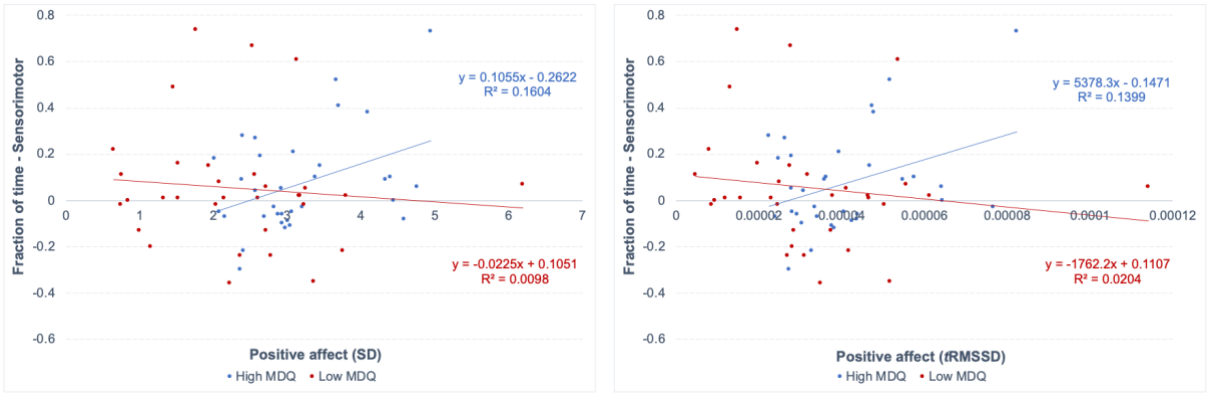


Figure 49: Relationship between variability in positive affect (as measured by SD and tRMSSD) and fraction of time in the sensorimotor state in high and low MDQ groups.

Variability in negative affect was negatively associated with fraction of time spent in the highly interconnected state in high MDQ participants (fig. 49), such that as variability in negative affect increased, fraction of time spent in the highly interconnected state decreased. Conversely, increased variability in the low MDQ group was associated with increased fraction of time spent in this state. Fishers Z test revealed that this difference was significant between the groups (SD: z = -3.21, p = .001; tRMSSD: z = -2.68, p = .007).

It should be noted that effect sizes across all correlational analyses with mood markers (tables 36, 37, and 38) ranged from weak to moderate. Also, significant results did not survive a Bonferroni adjusted alpha level of .001 across comparisons.

6.3.5 Exploratory relationship between dFNC metrics and rest-activity patterns

6.3.5.1 dFNC metrics and rest-activity patterns

		Number of states		Switch rate		Range		Distance		Number of transitions	
		High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
L_5	*Onset*	-.17	.18	-.18	-.01	-.03	.25	-.15	.05	-.03	.10
	Activity	.08	-.06	-.01	-.02	.25	-.13	.02	-.09	.07	-.00
M_{10}	*Onset*	.03	-.14	-.27	-.10	.18	-.01	-.24	.05	-.04	.03
	Activity	.13	**-.40***	.33	-.26	.21	-.28	.29	-.32	.14	**-.43***
RA		.00	-.26	.19	-.16	-.05	-.14	.13	-.16	-.01	-.27
IS		.16	-.01	.08	-.09	-.03	.32	.13	.02	.30	-.09
IV		-.02	-.34	.24	-.37	.09	-.35	.16	**-.42***	-.11	-.30

Table 39: Pearson Product-Moment correlation coefficients of dynamic functional connectivity markers (number of states, switch rate, range, distance, and number of transitions) and overall rest-activity markers (L5 onset, L5 activity, M10 onset, M10 activity, relative amplitude (RA), interdaily stability (IS), and intradaily variability (IV)).
* $p < .05$, ** $p < .01$

As demonstrated in table 39, associations between rest-activity parameters[36] and dynamic functional connectivity metrics were only seen in the low MDQ group. Fishers Z tests revealed that low MDQ participants had negative associations between M_{10} activity and number of states occupied ($z = 2.13$, $p = .033$) and number of transitions between states made ($z = 2.31$, $p = .021$), as well as with IV and total distance across states travelled ($z = 2.34$, $p = .019$). Thus, as activity during the day increased in low MDQ participants, the number of states they occupied and number of transitions they made between states decreased (fig. 51); and as low MDQ participants experienced

[36] Please see *chapter 4* for a full description and discussion of the rest-activity measures.

increased fragmentation in rest-activity rhythms, the total distance they travelled across states decreased (fig. 52).

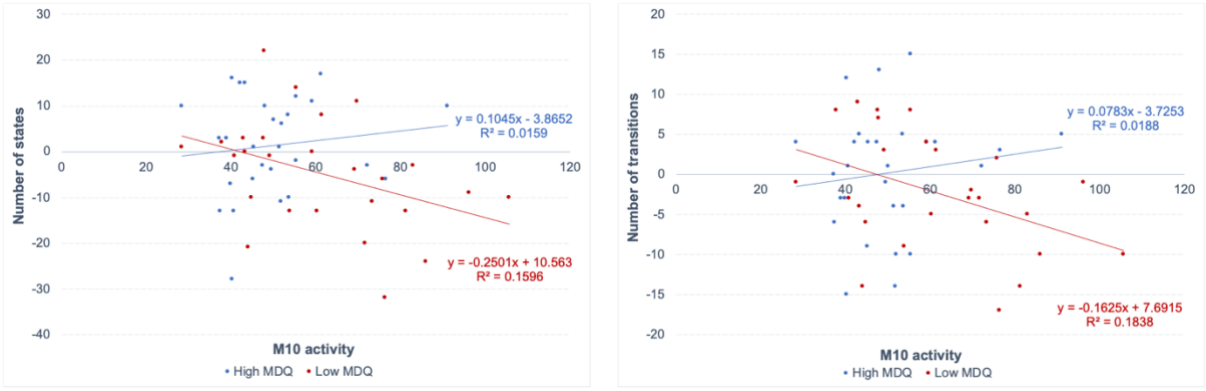


Figure 51: Relationship between M10 activity and number of states and number of transitions in high and low MDQ groups.

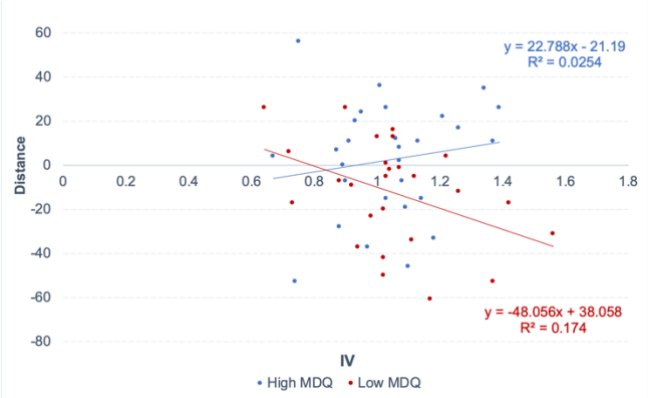


Figure 52: Relationship between IV and distance in high and low MDQ groups.

6.3.5.2 Dwell time and rest-activity patterns

		Dwell time							
		Highly interconnected		DMN		Sensorimotor		Low connectivity	
		High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
L_5	*Onset*	-.14	.09	-.23	**.54****	-.01	.02	.10	-.11
	Activity	-.08	.04	.04	.24	.05	.04	-.03	.05
M_{10}	*Onset*	-.07	.11	**.42***	**-.41***	-.20	-.13	.08	.08
	Activity	-.10	.04	.33	-.06	.32	.04	-.26	.22
RA		.02	-.08	.09	-.33	.15	.06	-.09	.08
IS		.05	**.44***	-.08	-.20	**-.38***	-.17	-.27	-.02
IV		.02	-.31	-.13	-.07	**.41***	**.47***	.11	.13

Table 40: Pearson Product-Moment correlation coefficients of dwell time markers across meta-states (highly interconnected, DMN, sensorimotor, and low connectivity) and overall rest-activity markers (L5 onset, L5 activity, M10 onset, M10 activity, relative amplitude (RA), interdaily stability (IS), and intradaily variability (IV)).

* $p < .05$, ** $p < .01$

As can be seen from table 40, in the DMN state, high MDQ participants had a positive association with M_{10} onset and dwell time, whereas low MDQ participants had a negative association between these variables ($z = 3.39$, $p = .001$) (fig. 53, right). Thus, as the onset of daytime activity increased in the high MDQ group so did dwell time in the DMN state, whereas dwell time decreased in the low MDQ group. However, L_5 onset was positively associated with dwell time in the DMN state in low MDQ participants ($z = -3.22$, $p = .001$) (fig. 53, left), such that as onset in sleep/night-time activity increased so did dwell time in the DMN state.

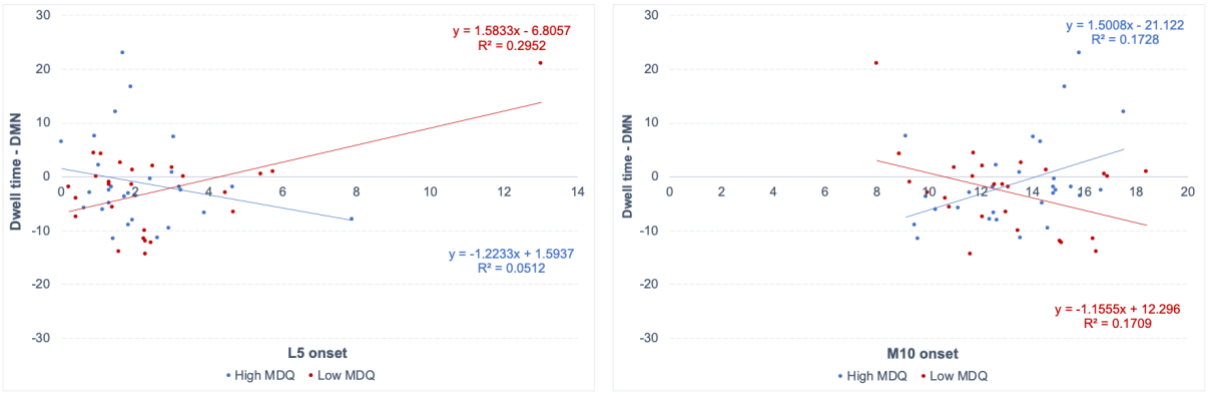


Figure 53: Relationship between L5 onset and M10 onset and dwell time in the DMN state in high and low MDQ groups.

6.3.5.3 Fraction of time and rest-activity patterns

		Fraction of time							
		Highly interconnected		DMN		Sensorimotor		Low connectivity	
		High MDQ	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*	*High MDQ*	*Low MDQ*
L_5	*Onset*	-.07	.13	-.16	.23	-.06	-.02	.19	-.18
	Activity	-.07	.03	.16	.19	-.01	-.09	-.05	-.05
M_{10}	*Onset*	-.25	.03	**.48****	-.23	-.31	-.14	.10	.22
	Activity	-.03	-.16	.08	-.21	**.41***	-.11	-.34	.29
RA		.05	-.19	-.09	-.32	.19	.06	-.12	.23
IS		.23	.29	.19	-.06	-.28	-.13	-.05	-.03
IV		-.02	-.31	-.35	.10	**.46***	.29	-.12	-.11

Table 41: Pearson Product-Moment correlation coefficients of fraction of time markers across meta-states (highly interconnected, DMN, sensorimotor, and low connectivity) and overall rest-activity markers (L5 onset, L5 activity, M10 onset, M10 activity, relative amplitude (RA), interdaily stability (IS), and intradaily variability (IV)).

* $p < .05$, ** $p < .01$

As demonstrated in table 41, fraction of time was associated with rest-activity markers in the high MDQ group only. High MDQ participants had positive associations between M_{10} onset and fraction of time spent in the DMN state ($z = 2.91$, $p = .004$) (fig. 54, left), and between M_{10} activity and fraction of time spent in the sensorimotor state ($z = 2.10$,

p = .036) (fig. 54, right). Thus, as high MDQ participants had a greater onset in daytime activity, the fraction of time they spent in the DMN state increased. Also, as their daytime activity increased, the fraction of time they spent in the sensorimotor state also increased.

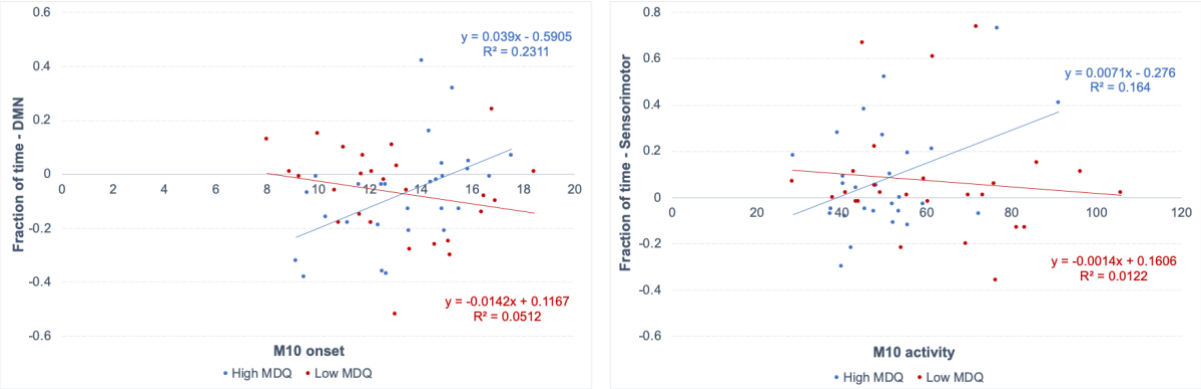


Figure 54: Relationship between M10 onset and fraction of time spent in the DMN state (left) and M10 activity and fraction of time spent in the sensorimotor state (right) in high and low MDQ groups.

It should also be noted that effect sizes across all correlational analyses with rest-activity markers (tables 39, 40, and 41) ranged from weak to moderate. Again, significant results did not survive a Bonferroni adjusted alpha level of .001 across comparisons.

6.3.6 Exploratory relationship between dFNC metrics with mood and rest-activity patterns: a summary

6.3.6.1 dFNC metrics

	Number of states	Switch rate	Range	Distance	Number of transitions
Mood	+ positive affect (average)	+ positive affect (average)	– negative affect (average)	+ positive affect (average)	
	– negative affect (variability)	– negative affect (variability)	– negative affect (variability)	– negative affect (variability)	
Rest-activity	– M_{10} activity			– IV	– M_{10} activity

Table 42: Summary table showing significant positive and negative correlations between dynamic functional connectivity metrics with mood and rest-activity markers.

– : high MDQ; – : low MDQ.

6.3.6.2 Dwell time

	Dwell time			
	Highly interconnected	DMN	Sensorimotor	Low connectivity
Mood	– positive affect (variability)			
	+ positive affect (variability)			
	+ negative affect (variability)			
Rest-activity		+ M_{10} onset		
		– M_{10} onset		
		+ L_5 onset		

Table 43: Summary table showing significant positive and negative correlations between dwell time markers with mood and rest-activity markers. – : high MDQ; – : low MDQ.

6.3.6.3 *Fraction of time*

	Fraction of time			
	Highly interconnected	DMN	Sensorimotor	Low connectivity
Mood	– positive affect (variability)	+ positive affect (average)	+ positive affect (variability)	
	– negative affect (variability)			
	+ negative affect (variability)			
Rest-activity		+ M_{10} onset	+ M_{10} activity	

Table 44: Summary table showing significant positive and negative correlations between fraction of time markers with mood and rest-activity markers. – : high MDQ; – : low MDQ.

6.4 Discussion

Dynamic functional connectivity (dFNC) patterns were identified in high MDQ individuals. Despite the sliding window approach identifying a comparative level of activation within four distinct resting meta-states across participants and time, groups differed across a range of dynamic properties in functional connectivity. In particular, low MDQ individuals occupied fewer states overall at the second scan session compared to the first, whilst high MDQ individuals remained just as highly changeable. When assessing the relationship between these dynamic properties with mood and circadian rest-activity patterns, we were able to uncover differential patterns of functional connectivity as a function of mood instability. Together, these results further the evidence for dFNC found in previous studies in mood disorders such as BD and MDD, as well as begin to highlight how disruptions in these dynamic connections persist outside of diagnosis and particular functional impairment, and thus may represent an overarching impairment in neural homeostatic mechanisms to regulate mood and related behaviours.

Using the sliding window approach to investigate dFNC, I was able to establish four robust meta-states across all participants and time points, namely: (a) a highly interconnected state; (b) the DMN; (c) a sensorimotor state; and (d) a state of low connectivity. Whilst differences between groups and time were not found in the degree of neural coupling within these meta-states, the fact that they were distinctly identified across the COMET sample of otherwise healthy, medication-naïve individuals presents interesting implications. For instance, the DMN has long been identified as a core network activated during rest and mind wandering (Buckner, Andrews-Hanna, & Schacter, 2008) and so is most often identified in resting-state fMRI studies. However,

when delving into mental activity, or mind-wandering, during rest, individuals are often noted to engage in self-referential thoughts as well as working memory encoding (Sormaz et al., 2018), highlighting the engagement of the prefrontal cortex (PFC), cingulate cortex, and hippocampal regions of the DMN. In the case of mood disorders, we know that abnormal DMN functioning is associated with symptoms of rumination in MDD (Cha et al., 2015), particularly reflected in hyperconnectivity between the subgenual cingulate cortex and posterior cingulate cortex. Whilst there are fewer studies of DMN functioning in BD, consistent findings of an association between disruptions in this network and increased symptoms of both BD mania (Öngür et al., 2010; Vargas et al., 2013) and BD depression (Liu et al., 2012) have been reported. Together with the knowledge that DMN regions often project to limbic structures involved in emotional processing and regulation (Mohan et al., 2016), these findings suggest an integral role of the DMN in modulating healthy cognition, a process which is often impaired in mood disorders.

In a similar vein, the identification of a sensorimotor state also presents interesting implications given the interaction between sensory and motor modalities and mood disorders (Canbeyli, 2010). For instance, exposure to light is known to alleviate depressive symptoms of both seasonal (Avery, 1998; Lewy, Kern, Rosenthal, & Wehr, 1982; Rosenthal et al., 1984) and non-seasonal (Even, Schröder, Friedman, & Rouillon, 2008; Kripke, 1998; Mackert, Volz, Stieglitz, & Müller-Oerlinghausen, 1991) mood disorders. Additionally, evidence of a negative affective bias in visual processing, particularly involving reduced connectivity in the anterior cingulate cortex and insula to positively-valanced images, and between the insula and hippocampus to negatively-valanced images in MDD has been reported (Lee et al., 2007). Combined

with the fact that auditory stimulation, often through music is known to regulate mood (Kemper & Danhauer, 2005), as well as the presence of symptoms such as disrupted appetite and physical behaviour throughout the course of mood disorders, it has become increasingly evident that sensorimotor modalities, across their neural, clinical, and behavioural representations, are core to the experience of disrupted mood. Whilst we did not observe group differences in connectivity within the sensorimotor and DMN states in the current study, the fact that these regions are identified as core functional meta-states, as well as the finding of distinct dynamic properties in the functional connectivity across these states in high MDQ individuals, suggests their integral involvement in the underlying neurobiological basis of temporally dynamic mood instability.

When focusing on the dynamic metrics, or properties, of functional connectivity identified in this analysis, a number of distinct and important observations were made. Whilst low MDQ individuals occupied fewer states and made fewer changes between states across scan sessions, demonstrating a learning-like curve of habituation in dynamics or perhaps regulation as a result of daily mood monitoring, high MDQ individuals remained just as highly changeable in their functional connectivity across time. This differential pattern further supports findings of dynamic rigidity in BD patients (Nguyen et al., 2017) by demonstrating that a consistent pattern of highly changeable dynamics between neural states are also a reflection of reduced internetwork flexibility when comparing to an otherwise healthy pattern of regulation across time.

This lack of habituation or regulation across time in high MDQ individuals, who remain just as highly changeable in dynamics, also bears hallmarks of an anxious nature.

Given that the high MDQ group were also found to report significantly greater levels of anxiety, as well as increased variability in anxious symptoms, across the 10-week study period (see *chapter 2, section 3*), suggests that this pattern of highly changeable and inflexible functional connectivity may be a neural underpinning of a related highly activated clinical state. Whilst the current study focused on investigating individuals with risk of mood disorders, and did not directly assess the relationship between anxiety symptoms and dFNC, the fact that anxiety disorders are a common comorbidity (Kaufman & Charney, 2000; Regier, Rae, Narrow, Kaelber, & Schatzberg, 1998), share a similar profile of cognitive and behavioural impairment, and are associated with many of the neural networks implicated in BD and MDD, for instance within the PFC, insula, and amygdala (Baur, Hänggi, Langer, & Jäncke, 2013), suggests that they may share a similar pattern of dynamic neural disruption. Future studies could investigate this more clearly by extending the current study in patients distinguished by BD, MDD, and anxiety disorder diagnoses, in order to tease apart the differences in neural connectivity that may underscore their clinical presentation.

All participants, regardless of group, spent a greater amount of time in the sensorimotor meta-state, as measured by dwell time and fraction of overall time. When combining this with the finding that a smaller fraction of time was spent in the highly interconnected and DMN state across scan sessions, suggests a pattern of neural activation that may have moved away from a more cognitive-loaded state of self-referential thought and memory encoding (Sormaz et al., 2018) to one that emphasised sensory inputs from the environment. Whilst this activation could reflect the conscious appraisal of a salient MRI scanner environment, a novel and unfamiliar experience for most people, the fact that this marker of time was significantly

associated with sensorimotor neural networks presents interesting implications when considering it alongside differences in dynamic metrics. Given that all participants spent more time in this sensorimotor state, yet high MDQ participants occupied a greater number of states and made an increased number of switches between states, suggests a pattern of dynamic functional instability that may be related to the engagement of sensorimotor regions. Given, also, that we know that sensorimotor modalities are implicated in the clinical presentation of mood disorders, and offer targets for therapeutic relief, further suggests that a rigid pattern of instability in the maintenance of neural connections across this state and with projections to others, may be a hallmark of the particular neural homeostatic mechanism that underlies mood instability.

Analyses of a relationship between dFNC properties and measures of mood began to highlight a neural underpinning of mood instability in the high MDQ group. Overall group differences in the number of meta-states occupied and the rate of switching between states was particularly strengthened by increasing positive affect, and attenuated by increased variability in negative affect, in high MDQ participants. Thus, as high MDQ individuals became more stable in mood, they were able to show more flexible patterns of functional connectivity, although this pattern became more rigid as they became more unstable in negative mood. Whilst this result is preliminary in nature and should be further examined in order to investigate how mood changeability may impact the differences in dynamic connectivity across time that were also observed, it does lend further support to the notion of increased rigidity and inflexible patterns of neural communications in mood disorders, particularly during periods of depression marked by rumination and negative biases (Kaiser et al., 2016). Therefore, it could be

that mechanisms of positive mood work to promote more flexible and variable functional connections between brain regions, but it is the further mechanism by which this is maintained and habituated across longer periods of time that may protect against more severe forms of mood instability that we see in BD. Despite its exploratory nature, this interpretation can present particularly significant implications for our current understanding of the temporally dynamic process of mood instability, and its reflection in a number of cyclic behavioural and cognitive patterns.

Furthering this relationship, the amount of time spent in distinct meta-states was modulated by mood. As high MDQ participants showed more mood instability, across the domains of positive affect and negative affect, they spent a smaller fraction of time in the highly interconnected state; but as low MDQ participants became more variable in mood, they instead dwelled for longer in this state. This suggests that engagement of the highly interconnected state, or activation across a broader range of brain regions, may act as a resilience or protective factor against mood instability. Given that the high MDQ group was found to show significant symptoms of negative mood indicative of a depressive episode across analyses in this thesis, further suggests that this overall relationship between mood instability and lowered whole brain communication may be more representative of an inflexible pattern of functional connectivity reflecting dampened affect. Future studies should aim to tease apart the effect that may be a representation of MDD depression rather than of BD, by exploring dFNC across groups of BD and MDD patients with characteristic mood instability.

Although the relationship between dFNC markers and rest-activity variables were less consistent, results begin to highlight a potential protective feature of associated

dynamic neural connectivity. For instance, low MDQ individuals occupied fewer meta-states and made fewer transitions between states as their daytime activity levels increased. Given that daytime activity was found to be significantly different between the groups (see *chapter 4*), such that high MDQ individuals moved less during the day than low MDQ individuals and that this was modulated by absolute and variability in mood, suggests that a stable level of neural functional connectivity may represent a protective feature in regulating the circadian rest-activity disruptions noted with fluctuating mood. Similarly, greater daytime activity was associated with increased time spent in the sensorimotor state in high MDQ individuals only, perhaps demonstrating an interaction in these neural regions to both control and regulate circadian rest-activity patterns. Whilst this is in line with previous findings of an association between instability in circadian rest-activity markers and abnormalities in connections between the dorsolateral PFC and somatosensory regions such as the supramarginal gyri (McKenna, Drummond, & Eyler, 2014), subsequent research should aim to further examine this potential cyclical relationship between mood instability, circadian rest-activity patterns, and dynamic functional connectivity using more sensitive measurement techniques such as polysomnography and melatonin secretion, in combination with actigraphy and dFNC fMRI methods.

While results of a relationship between properties of dFNC with markers of mood and circadian rest-activity patterns provide an informative basis to consider the wide-ranging implications of a disruption in neural homeostasis, a number of limitations should be noted. Firstly, due to the number of variables used to measure each component and thus, the number of comparisons being made, the likelihood of erroneous inferences due to multiple comparisons increases. In particular, this can

lead to false positives, or type I errors. However, when using the Bonferroni correction (Bland & Altman, 1995; Dunn, 1961) for multiple comparisons, significant associations did not survive. Therefore, current results of a relationship with mood and circadian rest-activity patterns are exploratory in nature and should be interpreted with caution. More direct assessments of these putative associations should be carried out in the future, perhaps with the addition of interventions such as mood regulating therapies or behavioural interventions, in order for the translational outputs of neural dynamics to be better understood. Additionally, the novel nature of the wider approach of dFNC should also be acknowledged. Whilst it provides an interesting and more nuanced method of exploring the complexities of psychiatric phenomenon, particularly in the case of a temporally sensitive and dynamic process such as mood instability, the interpretations of these dynamic properties are still in their infancy. It is hoped that further research will aid us in more accurately navigating this approach by providing further validations of dFNC outputs, as well as building more comprehensive analysis pipelines, in order for mood instability and other such phenomenon to be investigated.

Nevertheless, current results have elucidated important patterns of dynamic functional connectivity that underlie mood instability, over and above the absence of disruptions in static functional connectivity (see *chapter 5*). High MDQ individuals have been shown to have significantly distinct profiles of functional connectivity highlighting not only an instability in communication between core regions, but also a pattern of inflexibility or rigidity in dynamic patterns across time which may represent overarching disruptions in habituation or regulation. As this is the first study, to my knowledge, to explore such dynamic connectivity in mood instability across time, results are preliminary in nature and should be further built upon and validated. However, current

results provide a critical basis of evidence emphasising the need to consider the dynamic pathophysiological mechanisms that underlie the temporally dynamic process of mood instability. Such pathophysiology, involving holistic disruptions in neural homeostatic mechanisms to regulate mood and related clinical, behavioural, and cognitive outcomes, are thus able to better inform us of illness onset (be it BD or MDD), symptom severity, and treatment targets.

Chapter 7 | Discussion

The aim of this doctoral research was to build a translational neuroscience profile of mood instability in order to establish its underlying pathophysiological circuits. In particular, both behavioural dimensions and neural systems were considered so as to explore the symptomatic correlates of a potential disruption in neural homeostatic mechanisms to regulate mood and related behaviours. Additionally, special consideration was given to the temporal dynamics of each domain such that the oscillating nature of mood instability could be sensitively captured. As the first such investigation into the underlying mechanisms of mood instability, this research can begin to advance our understanding of the mood disorders for which it is characteristic, particularly BD and MDD. It is hoped that a more nuanced assessment of the temporal dynamics of this phenomenon will aid in both better understanding the method of action of lithium and other mood stabilising and antidepressant drug treatments, as well as in developing better suited targets for novel therapeutic intervention.

7.1 Summary

7.1.1 Identifying mood instability

Using a longitudinal and remote monitoring method, significant mood instability was identified in high MDQ individuals as measured by the Mood Disorder Questionnaire (MDQ). These participants were more variable in positive affect and negative affect over a 10-week period, and also reported greater symptoms of depression, mania, and anxiety. Whilst further supporting the idea that the MDQ may be a sensitive tool for capturing mood instability in the general population – rather than strictly

vulnerability to BD – high MDQ individuals were also found to be significantly lower in mood. In addition to a greater number of MDD diagnoses (5 out of 9, 13.5% of the total group) compared to BD diagnoses (3 out of 9, 8.1% of the total group), increased levels of negative affect – or low mood – was found to distinguish those meeting diagnostic criteria from those who did not in the high MDQ group, regardless of the category of diagnosis. Although I am not able to tease apart the distinct BD and MDD mechanisms at play in the current thesis, these findings lend further support to observations of increased diagnostic overlap between the disorders (Ghaemi et al., 1999), as well as the notion that mood instability may be a transdiagnostic marker across mood disorders (Patel et al., 2015; Thompson et al., 2011). Nevertheless, analyses in *chapter 3* were able demonstrate the ability of both the MDQ and daily remote monitoring techniques to capture longitudinally oscillating mood in a subclinical sample, laying the foundations for subsequent investigations of the dynamic behavioural correlates and neural underpinnings of mood instability.

7.1.2 Capturing disruptions in circadian rest-activity patterns

Thus, the subsequent chapter aimed to investigate the behavioural correlates of this instability, as measured by circadian rest-activity patterns. High MDQ individuals had significantly lower circadian relative amplitude, a differentiation marker of daytime and night-time activity, driven by decreased movement or activity during the day. When assessing this relationship with concurrent mood monitoring, I was able to uncover a pattern of temporal association such that the high MDQ and low MDQ groups showed differential patterns of modulation between mood instability and circadian relative amplitude. Building on this, high MDQ individuals also showed a significantly different

pattern of association between mood instability in both positive and negative affect and night-time activity, outside of distinct group differences in this circadian measure. Combined with the finding of a differential relationship between daytime activity and mood instability in the positive affect domain, current results point to the importance of a regulatory mechanism – in this case, circadian relative amplitude to account for both daytime and night-time activity – and its relationship with mood instability. Together, this study was able to extend previous research of at-risk-to BD groups (e.g. Bullock & Murray, 2014; Rock, Goodwin, Harmer, & Wulff, 2014) by further confirming the persistence of circadian rest-activity disruptions outside of distinct diagnoses and in a sub-clinical group, albeit with differences in the particular factors underlying this difference.

In their actigraph study over a two week period, Rock and colleagues (2014) found that high MDQ individuals had increased patterns of movement or activity during sleep, whilst I instead found a pattern of decreased daytime activity in the absence of sleep disruptions. Whilst these patterns often present hand-in-hand, that is that restless sleep can cause changes in daytime movement, the fact that the current study investigated these patterns over a longer 10-week scale suggests that a cumulative decrease in activity may be a key correlate of mood instability. Combined with findings of a distinct modulation in these circadian patterns by mood instability, supporting Bullock & Murray's (2014) results of lower levels of circadian relative amplitude as a function of depression in their at-risk-to BD group, current findings seem to further highlight the presence of depression in the current sample. Given that psychomotor retardation, lack of energy, and feelings of fatigue are core symptoms of MDD along with low mood, it therefore seems that the current high MDQ group were showing two

indications of depression, namely (a) absolute low mood; and (b) lower levels of movement or activity during the day. Again, although we are unable to disentangle the specific nature of this potentially depressive experience, the fact that mood instability affects these behavioural disruptions over and above diagnoses of BD or MDD suggests a common underlying mechanism of instability. Together, this further warrants the need for exploring the underlying pathophysiological basis of mood instability and its related behavioural disruptions, in order to elucidate the shared neural homeostatic mechanisms that may be susceptible to imbalance.

7.1.3 The neural basis of mood instability: static and dynamic functional connectivity

The second half of my empirical work aimed to explore the neural profile of mood instability. To do this, I first intended to build a profile of the whole brain connectivity patterns that may underlie the distinct mechanisms of mood instability and its specific associations with emotional processing and regulation regions such as the amygdala and insula (*chapter 5*), before going on to explore the particular dynamic mechanisms by which nuances in connectivity may relate to the temporally dynamic experience of mood instability (*chapter 6*). When addressing this first part, no differences between groups or time (that is, repeat testing) in neural networks activated at rest were found. This is in line with evidence from euthymic BD patients and healthy controls, which has generally reported the absence of functional connectivity differences in resting-state networks (RSNs) (Syan et al., 2018), and further lends support to the finding of varying degrees of neural disruption in BD modulated by mood and distinct mood episodes (Vargas et al., 2013). Similarly, seed-based analyses using the amygdala and insula as regions of interest (ROIs) showed no differences in specific connectivity

between the groups or across time. These results are in line with previous research which has often reported inconsistent and heterogenous results of resting state connectivity in mood disorders (Vargas et al., 2013), and also further highlights the difficulties in applying a static method to the analysis of a highly variable and finer-grained symptom, thought to be reflected in dynamic neural connectivity. This becomes ever more important to understand when considering that mood instability, or oscillating patterns of mood, is characteristic of a number of mood disorders including BD and MDD, and so understanding the nature of its pathophysiology may hold the key for transforming its treatment. Thus, these findings further warrant the need for additional investigation of the dynamic nature of such underlying functional connectivity in order to more precisely uncover its pathophysiology.

Therefore, and despite limited differences in functional connectivity found using these static measures, distinct dynamic properties were uncovered. A comparative level of activation within four independent meta-states (that is, (a) highly interconnected; (b) DMN; (c) sensorimotor; and (d) low connectivity) was identified between groups, and across time. However, low MDQ individuals occupied fewer states and made fewer changes between states over time, while high MDQ individuals remained just as highly changeable. This difference in dynamics between the groups, such that low MDQ individuals seemed to show a pattern of habituation or regulation in functional connectivity over time, further suggests a pattern of dynamic rigidity in high MDQ individuals. Therefore, a consistent pattern of highly changeable dynamics across time in these individuals may be further evidence of a reduction in internetwork flexibility (Nguyen et al., 2017) when compared to an otherwise healthy pattern of regulation across time.

When assessing the modulation of these dynamic patterns by mood instability, it appeared that a mechanism of mood elevation could work to promote more flexible and variable functional connections between brain regions. However, the method by which this pattern is maintained and regulated across longer periods of time may protect against more severe forms of mood instability that is seen in mood disorders such as BD and MDD. Thus, this preliminary finding using the novel sliding window approach to investigate dynamic functional connectivity suggests a system controlling neural balance may be key – and that an imbalance in temporally dynamic connectivity may account for mood instability. Further, high MDQ individuals were found to spend a lower amount of time in the highly interconnected state as their mood instability increased, yet the opposite pattern was observed in low MDQ individuals. The implications of this finding are two-fold. Firstly, it suggests that the engagement of a wider range of brain regions may act as a protective, or resilience, factor signalling a healthy pattern of neural flexibility. Secondly, and combined with previous findings of an overall depressed state in the high MDQ group as shown by lowered overall mood (*chapter 3*) and less daytime activity (*chapter 4*), it suggests that a general relationship between diminished whole brain communication may be more representative of an inflexible pattern of functional connectivity reflecting dampened affect, something that is also reported in studies of functional connectivity in MDD marked by rumination and negative biases (Kaiser et al., 2016).

When extending this investigation by considering the relationship between dynamic functional connectivity properties and circadian rest-activity patterns, results begin to further highlight a set of protective or resilience features. For instance, those in the low

MDQ group occupied fewer meta-states and changed between states less often as their daytime activity levels increased. Considering that daytime activity was lower overall in the high MDQ group, and shared particular association with mood instability (*chapter 4*), this suggests that a more stable profile of dynamic connectivity may represent a protective feature in regulating the circadian rest-activity disruptions noted with mood instability.

Overall, both strands of study into the resting-state functional connectivity profile of mood instability have elucidated patterns of dynamic functional connectivity that underlie this instability, over and above the absence of static differences. In particular, high MDQ individuals have significantly distinct profiles of functional connectivity highlighting not only an instability in communication between core regions, but also a pattern of inflexibility or rigidity in dynamic patterns across time that may represent overarching disruptions in regulation. Additionally, frequent indications of a protective or resilience mechanism – for instance, in specific associations between dynamic properties and circadian rest-activity patterns – further emphasises the role that an imbalance in neural homeostatic mechanisms has to play in the maintenance of mood instability.

7.2 Implications

Findings in the current thesis provide important implications for our understanding of mood instability and its relation to mood disorders such as BD and MDD. By identifying longitudinal mood instability in a sample distinguished by a positive MDQ screen, and demonstrating the circadian rest-activity patterns of disruptions associated with such

instability, we are able to present a more scientifically grounded representation of mood instability, which has otherwise only been shown in observational studies of clinical groups over shorter timescales. Additionally, not only does this consideration of the associated dynamic behavioural outcomes of mood instability provide insights for interventions that target behavioural changes, they have also begun to highlight the overarching involvement of disruptions in neural mechanisms which may cause both the symptoms of mood instability and behavioural disruptions.

Such longitudinal monitoring of mood and rest-activity patterns may aid in identifying those who go on to show functional impairment and thus, may also predict illness onset. Extending this to the longitudinal study of mood and related behavioural instabilities in patient groups can also aid in informing patients and clinicians alike, of the worsening of symptoms and the need for hospital admission or mood stabiliser prescriptions (Patel et al., 2015). While I am currently unable to tease apart the nature of mood disorder presented here, further such monitoring could shed light on the trajectories to BD and MDD that may manifest.

Conversely, current results also begin to elucidate potential resilience factors or protective features that may impact the progression of mood instability to mood disorders. For instance, 75% of the high MDQ group did not meet diagnostic criteria for any axis I disorder (see *chapter 2*) suggesting that mood instability by itself, during this time period, was not enough to cause significant illness. Additionally, previous research has shown the benefits of exercise as an adjunct treatment for mood disorders (e.g. Hearing et al., 2016) that can work to regulate mood by reducing symptoms of depression and increasing positive affect (Bartholomew et al., 2005).

This combination is particularly important to consider given that high MDQ individuals were shown to have lowered levels of activity in the day, particularly affected by mood instability, and that flexible patterns of dynamic functional connectivity seemed to reflect a healthy relationship with daytime activity in low MDQ individuals. Therefore, this cyclic relationship between mood instability, circadian rest-activity patterns, and resting-state patterns of functional connectivity not only presents implications for the progression of mood instability to mood disorder, but also of the protective features that may be at play both in low MDQ individuals, and in those in the high MDQ group who do not go on to show functional impairment or necessarily meet diagnostic criteria.

Together, these implications can inform us of better treatment targets. For example, I have discussed the potential for exercise to alleviate mood symptoms and regulate affect, given that circadian rest-activity patterns are closely related to mood disorders and mood instability. However, by further elucidating the neural profile of mood instability and its related behavioural outcomes, we are able to begin to understand the nature and method of action of lithium and other established and novel mood stabilising medications. Owing to the fact that mood instability is considered a core feature of the clinical presentation of BD, often outside of the varying nature of depressive and manic episodes, a holistic approach of investigating the translational neuroscience basis of mood instability such as this one may aid in determining the potential ability for lithium to regulate the neural mechanisms that may cause mood and related instabilities. In a similar vein, considering this neural basis as a target for the development of novel therapeutic targets can also aid in improving treatment options and clinical outcomes for patients with mood disorders characterised by such instability.

7.3 Further Directions

7.3.1 Experimental medicine interventions

Based on these wider implications, and given that this is the first such study to investigate the associated behavioural and neural profile of mood instability, future work could begin to investigate the effects of intervention on this phenomenon. The Oxford Lithium Trial (OxLith) is a current study which aims to do just this, employing a similar methodology to that of the COMET study in investigating the clinical, cognitive, behavioural, neural, and biochemical effects of lithium carbonate in BD (Saunders et al., 2016). It is hoped that such a study can begin to understand the propensity for lithium to target and help regulate mood instability and associated symptoms. By additionally investigating the effects of this mood stabilising treatment on neural functioning, it can also further elucidate the particular networks and neural dynamics that are core to the symptom of mood instability in disordered mood, as opposed to those that may instead be protective. Such an assessment of the longitudinal effects of lithium on mood instability could then be extended to the consideration of novel and non-pharmacological treatments, in order to both develop better suited treatment options, and to fully account for the wide-ranging symptomatic consequences of mood instability.

7.3.2 Further validating novel methodologies

On a more nuanced level, and as discussed in individual chapters, future work should also validate current findings, particularly given the largely novel set of methodologies used. For instance, while the use of actigraph devices present a beneficial and low intensity technique for the measurement of longitudinal and fine-grained data, their output of proxy markers can be considered problematic for its derivative nature (McGowan et al., 2019). Future studies could therefore complement current work by employing the use of additional circadian measures such as melatonin secretion, polysomnography, and sleep diaries. Furthermore, the validity of the novel analysis of dynamic functional connectivity via the sliding window approach should be extended. Owing to the importance of such neuroimaging analysis methods for a range of psychiatric disorders, and the translational implications they present, it is hoped that current work emphasising distinctions in dynamic properties in mood instability will contribute to this process.

7.3.3 Cognitive impairments associated with mood instability

Moreover, and in line with the RDoC framework of investigating psychiatric illness in terms of varying degrees of dysfunction in general psychological and biological systems (Insel et al., 2010), future work should also address the temporally dynamic nature of cognitive impairments that may present as a consequence of mood instability. This is particularly important given that we know of distinct and marked disruptions in cognitive functioning in mood disorders and during mood instability (e.g. Broome, He, Iftikhar, Eyden, & Marwaha, 2015; Eldar & Niv, 2015) (see *chapter 1*), as well as the established cognitive neuropsychological hypothesis of antidepressant action (Harmer, Goodwin, & Cowen, 2009) that posits a direct action of mood

stabilising treatment on cognitive functioning before clear regulation in mood is observed. While I am unable to experimentally address the cognitive nature of mood instability in the current thesis, it is hoped that analysis of the cognitive data collected in the COMET study will further add to the profile built here. Ultimately, it is expected that mood instability will be reflected in an overarching disruption in neural homeostatic mechanisms that are responsible for regulating mood and related behavioural and cognitive symptoms.

7.4 Strengths and limitations

Despite the advances made in understanding mood instability in the current thesis, it is important to note a number of limitations. For instance, and as further discussed in *chapter 2*, questions remain around the use of the MDQ, a screening tool for BD (Hirschfeld et al., 2000), in the identification of mood instability. Whilst this tool was able to accurately detect mood instability in those in the current sample who screened in (the high MDQ group), we are unable to conclusively attribute that to the sensitivity of the MDQ. As well as assessing functional impairment, the MDQ is known to account more heavily for symptoms of hypomania and mania, and while the current high MDQ group were significantly more unstable in positive affect compared to the low MDQ group, they were also overwhelmingly lower in absolute negative mood. Thus, it remains to be seen whether other screening measures, independently and together with the MDQ, such as the Affect Lability Scale (ALS) (Oliver & Simons, 2004) and Affective Intensity Measure (AIM) (Solhan et al., 2009), could also sensitively predict longitudinal mood instability, whilst also giving an indication of the affective domain that may be more implicated. This is particularly vital to understand when applying the

current findings to the management of symptoms in mood disorders, given that mood instability is characteristic of both BD and MDD, both of which are known to share significant diagnostic overlap. Therefore, the advent or repurposing of a tool adept at both identifying mood instability and sensitively predicting the course of illness – be it mania indicative of BD, or depression indicative of either MDD or BD – can further aid in administering early therapeutic interventions and preventing worsening of outcomes.

In a similar vein, whilst the majority of high MDQ participants did not meet diagnostic criteria for a DSM-IV axis I disorder, a number did, with a range of heterogenous comorbidities. As noted in *chapter 3*, these individuals were significantly lower in absolute negative mood than the rest of the high MDQ group. However, and due to the small sample size, we were unable to ascertain whether these differences persist outside of mood monitoring, and whether those who met diagnostic criteria also had differing patterns of circadian and functional connectivity which may have differentially affected current results. Future research could address this by further parcellating the high MDQ group into those who do and do not meet diagnostic criteria, in order to determine the components of a disrupted homeostatic mechanism that are involved with, and even responsible for, worsening symptoms, functional impairment, and the progression of illness.

Although the 10-week study period, incorporating daily measures of mood and minute-by-minute changes in activity, was beneficial in its ability to both longitudinally monitor symptoms and capture finer-grained fluctuations in mood, we were unable to assess the outcomes of the mood instability identified. While the high MDQ group showed

significant levels of mood instability, they also showed indications of being in an overall low or depressed state – through both their absolute mood scores and lowered levels of daytime activity. It therefore may have been that 10-weeks of monitoring was able to detect mood instability, but was not long enough to track the progression of absolute mood changes. This is particularly important given that depressive episodes in BD are known to last between 2 and 3 months (Frankle et al., 2002) and thus, further monitoring for a longer period of time would have shed light on whether this mood instability reported over 10 weeks was part of the BD depressive phenotype, more prolonged periods of MDD depression, or disordered mood in its own right. Similarly, whilst we were able to detect dynamic patterns of functional connectivity related to mood instability, in the absence of static changes, results began to highlight the complex nature of association whereby the persistent, or rigid, nature of dynamic functional connectivity over time seemed to be characteristic of the high MDQ group. Although this analysis was exploratory in nature, more frequent scanning over a longer period of time, providing finer-grained snapshots at functional connectivity, may have helped to elucidate the mechanism of dynamic rigidity noted in the high MDQ group.

To my knowledge, analyses in *chapter 4* are the first to assess the longitudinal relationship between circadian rest-activity patterns and mood instability in groups distinguished by scores on the MDQ. Despite uncovering interesting patterns implicating the regulatory role of both daytime and night-time activity in mood instability, the current linear mixed effects models were unable to determine the cause and effect nature of this relationship. Thus, it remains to be seen whether increased levels of mood instability over time lead to the lowering of circadian relative amplitude in the high MDQ group, or instead whether disruptions in these patterns precede mood

instability. Future studies could aim to extend these results by including activity-based interventions – such as social rhythm therapy, known to help regulate and manage chaotic daily rhythms in BD (Frank et al., 2005; Frank, Swartz, & Kupfer, 2000) – into a longitudinal randomised controlled trial design in order to tease apart the directionality of this relationship, if any, and further inform us of the underlying homeostatic mechanism at play.

Building on this, while the novel and exploratory nature of dynamic functional connectivity analyses have uncovered interesting patterns of association with mood instability for the first time, the infancy of these methods is noted. Despite the advantages of resting state functional connectivity analyses in comparison to task-based functional connectivity, namely test-retest reliability (Cao et al., 2014; M. L. Elliott et al., 2020; Noble et al., 2019; Zuo & Xing, 2014), a number of physiological- (such as movement) and sample- (such as those with and without diagnoses) based factors may have influenced current results, outside of the strict pre-processing pipelines used, given their dynamic nature. Future research could begin to address this by both extending and replicating current static and dynamic analyses in studies of mood instability (for example, OxLith (Saunders et al., 2016)), as well as working with the most updated and advanced resting state analysis techniques as they are developed (Noble et al., 2019).

A number of overall strengths are also important to consider. The oscillating nature of mood infers that mood instability is a temporally sensitive and dynamic phenomenon. Thus, it is vital that assessments of this phenomenon are able to capture this temporally dynamic course. The current COMET study, and the individual analysis

methods employed in this thesis, aimed to do just this. For example, the current sample were monitored for a period of 10 weeks, using daily remote measures of mood, cognition, and activity. While the use of remote technological devices eased participation burden and ensured the real-time monitoring of symptoms, the ability for this method to capture high-quality and fine-grained data is noted. Adding particularly to the strengths of this study and associated analyses in this thesis, such high-quality and fine-grained data has allowed for the more nuanced study of dynamic changes in symptoms - from a consideration of seconds in the sliding-window approach of dynamic functional connectivity, to the minute-by-minute method of actigraphy monitoring, and day-by-day to week-by-week assessment of mood. Taken together, this methodology particularly highlights the ability and significance of big data research in psychiatry, allowing the concurrent investigation of dynamic changes in psychological and biological systems. This is of particular importance in the study of complex psychiatric phenomena such as mood instability, and highlights the merits of technologically advanced, mathematically nuanced, and objective measures of psychological experience, further supporting the RDoC framework outlined by the National Institute of Mental Health (NIMH).

However, longitudinal scientific investigation can only take us so far and thus, I was unable to ascertain whether the marked state of depression observed in the high MDQ group showing mood instability was a marker of BD, MDD, or separate to current diagnostic distinctions. It may have been that 10 weeks of monitoring captured a depressive episode of BD, or instead reflected the state of euthymia. However, given that individuals met criteria for MDD more frequently than BD, mood instability - regardless of initially being captured by a BD screening tool assessing manic

symptoms - may be just as importantly a feature of depression, outside of the particular diagnostic criteria this may fall into. Although further follow up of the participants may have demonstrated the potentially distinct trajectories of mood disorder that progress from this initial state of depression, this current facet of the research again supports the efforts outlined in the RDoC framework that offer new approaches to understanding psychiatric disorders. Therefore, by focusing less on the distinct diagnostic categories that mood instability may lead to, or be a feature of, findings lend further support to the notion of mood instability as a transdiagnostic marker that may integrate various types of information – including behavioural outcomes, cognitive functioning, and neural circuitry – to inform us of the nature of mood disorders.

7.5 Conclusion

Led by the need to improve clinical outcomes for patients with mood disorders, the aim of this thesis was to begin to build a profile of the translational neuroscientific nature of mood instability. In doing so, I was able to identify longitudinal mood instability in a sub-clinical and medication-naïve group of high MDQ individuals showing. Secondly, I uncovered distinct patterns of circadian rest-activity disruptions in these individuals, such that the effect of oscillating mood on circadian relative amplitude – combining facets of both daytime and night-time activity - distinguished those in the high MDQ group from those in the low MDQ group. Finally, I was able to explore the functional connectivity patterns that underlie this instability such that high MDQ individuals were represented in highly volatile patterns of dynamic functional connectivity that persisted over time, reflecting a rigid pattern of internetwork flexibility in mood instability. These dynamic mechanisms were also shown to be associated

with subtleties in mood and circadian rest-activity patterns such that the cyclic nature of dynamic functional connectivity presented trajectories for both the worsening of mood instability and protective features against it. Overall, as the first study to investigate the wide-ranging characteristics of dynamic mood instability, the doctoral research presented in this thesis has uncovered the beginnings of an overarching disruption in neural homeostatic mechanisms that are responsible for regulating mood and related clinical, behavioural, and cognitive outcomes. These exciting findings provide a valuable foundation for continued research into mood instability, in the hope of transforming our current understanding of mood disorders and improving clinical outcomes.

References

Abler, B., Greenhouse, I., Ongur, D., Walter, H., & Heckers, S. (2008). Abnormal reward system activation in mania. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *33*(9), 2217–2227. https://doi.org/10.1038/sj.npp.1301620

Abou-Elseoud, A., Starck, T., Remes, J., Nikkinen, J., Tervonen, O., & Kiviniemi, V. (2010). The effect of model order selection in group PICA. *Human Brain Mapping*, *31*(8), 1207–1216. https://doi.org/10.1002/hbm.20929

Admon, R., & Pizzagalli, D. A. (2015). Dysfunctional reward processing in depression. *Current Opinion in Psychology*, *4*, 114–118. https://doi.org/10.1016/j.copsyc.2014.12.011

Akil, H., Brenner, S., Kandel, E., Kendler, K. S., King, M. C., Scolnick, E., … Zoghbi, H. Y. (2010, March 26). The future of psychiatric research: Genomes and neural circuits. *Science*, Vol. 327, pp. 1580–1581. https://doi.org/10.1126/science.1188654

Allen, E. A., Damaraju, E., Plis, S. M., Erhardt, E. B., Eichele, T., & Calhoun, V. D. (2014). Tracking whole-brain connectivity dynamics in the resting state. *Cerebral Cortex*, *24*(3), 663–676. https://doi.org/10.1093/cercor/bhs352

Altman, E., Hedeker, D., Peterson, J. L., & Davis, J. M. (1997). The altman self-rating Mania scale. *Biological Psychiatry*, *42*(10), 948–955. https://doi.org/10.1016/S0006-3223(96)00548-3

Altman, E., Hedeker, D., Peterson, J. L., & Davis, J. M. (2001). A comparative evaluation of three self-rating scales for acute mania. *Biological Psychiatry*, Vol. 50, pp. 468–471. https://doi.org/10.1016/S0006-3223(01)01065-4

American Psychiatric Association (APA). (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Anand, A., Li, Y., Wang, Y., Lowe, M. J., & Dzemidzic, M. (2009). Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. *Psychiatry Research - Neuroimaging*, *171*(3), 189–198. https://doi.org/10.1016/j.pscychresns.2008.03.012

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., … Lowe, M. J. (2005). Activity and connectivity of brain mood regulating circuit in depression: A functional magnetic resonance study. *Biological Psychiatry*, *57*(10), 1079–1088. https://doi.org/10.1016/j.biopsych.2005.02.021

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007). Non-linear registration aka spatial normalisation. In *FMRIB Technical Report TRO7JA2*. Retrieved from http://fmrib.medsci.ox.ac.uk/analysis/techrep/tr07ja2/tr07ja2.pdf

Angst, J., Gamma, a, & Endrass, J. (2003). Risk factors for the bipolar and depression spectra. *Acta Psychiatrica Scandinavica. Supplementum*, *108*(418), 15–19. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12956808

Anticevic, A., Brumbaugh, M. S., Winkler, A. M., Lombardo, L. E., Barrett, J., Corlett, P. R., … Glahn, D. C. (2013). Global prefrontal and fronto-amygdala dysconnectivity in bipolar i disorder with psychosis history. *Biological Psychiatry*, *73*(6), 565–573. https://doi.org/10.1016/j.biopsych.2012.07.031

Apple Inc. (n.d.). Retrieved from https://www.apple.com/uk/

Arieli, A., Sterkin, A., Grinvald, A., & Aertsen, A. (1996). Dynamics of ongoing activity: Explanation of the large variability in evoked cortical responses. *Science*, *273*(5283), 1868–1871. https://doi.org/10.1126/science.273.5283.1868

Avery, D. H. (1998, October 1). A turning point for seasonal affective disorder and

light therapy research? *Archives of General Psychiatry*, Vol. 55, pp. 863–864. https://doi.org/10.1001/archpsyc.55.10.863

Baayen, R. H., Davidson, D. J., & Bates, D. M. (2008). Mixed-effects modeling with crossed random effects for subjects and items. *Journal of Memory and Language*, *59*(4), 390–412. https://doi.org/10.1016/j.jml.2007.12.005

Baldessarini, R. J., Tondo, L., Vázquez, G. H., Undurraga, J., Bolzani, L., Yildiz, A., … Tohen, M. (2012). Age at onset versus family history and clinical outcomes in 1,665 international bipolar-I disorder patients. *World Psychiatry*, *11*(1), 40–46. https://doi.org/10.1016/j.wpsyc.2012.01.006

Bardram, J. E., Frost, M., Szántó, K., Faurholt-Jepsen, M., Vinberg, M., & Kessing, L. V. (2013). Designing mobile health technology for bipolar disorder: A field trial of the MONARCA system. *Conference on Human Factors in Computing Systems - Proceedings*, 2627–2636. https://doi.org/10.1145/2470654.2481364

Bardram, J. E., Frost, M., Szántó, K., & Marcu, G. (2012). The MONARCA self-assessment system - A persuasive personal monitoring system for bipolar patients. *IHI'12 - Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium*, 21–30. https://doi.org/10.1145/2110363.2110370

Bartholomew, J. B., Morrison, D., & Ciccolo, J. T. (2005). Effects of acute exercise on mood and well-being in patients with major depressive disorder. *Medicine and Science in Sports and Exercise*, *37*(12), 2032–2037. https://doi.org/10.1249/01.mss.0000178101.78322.dd

Basco, M. R., & Rush, A. J. (2005). *Cognitive-behavioral therapy for bipolar disorder*. Guilford Press.

Bates, D., Mächler, M., Bolker, B. M., & Walker, S. C. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1).

https://doi.org/10.18637/jss.v067.i01

Baur, V., Hänggi, J., Langer, N., & Jäncke, L. (2013). Resting-state functional and structural connectivity within an insula-amygdala route specifically index state and trait anxiety. *Biological Psychiatry*, *73*(1), 85–92. https://doi.org/10.1016/j.biopsych.2012.06.003

Beats, B. C., Sahakian, B. J., & Levy, R. (1996). Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychological Medicine*, *26*(3), 591–603. https://doi.org/10.1017/s0033291700035662

Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2003). General multilevel linear modeling for group analysis in FMRI. *NeuroImage*, *20*(2), 1052–1063. https://doi.org/10.1016/S1053-8119(03)00435-X

Beckmann, C. F., & Smith, S. M. (2004). Probabilistic Independent Component Analysis for Functional Magnetic Resonance Imaging. *IEEE Transactions on Medical Imaging*, *23*(2), 137–152. https://doi.org/10.1109/TMI.2003.822821

Berntson, G. G., Lozano, D. L., & Chen, Y. J. (2005). Filter properties of root mean square successive difference (RMSSD) for heart rate. *Psychophysiology*, *42*(2), 246–252. https://doi.org/10.1111/j.1469-8986.2005.00277.x

Bertocci, M. A., Hanford, L., Manelis, A., Iyengar, S., Youngstrom, E. A., Gill, M. K., … Phillips, M. L. (2019). Clinical, cortical thickness and neural activity predictors of future affective lability in youth at risk for bipolar disorder: initial discovery and independent sample replication. *Molecular Psychiatry*, *24*(12), 1856–1867. https://doi.org/10.1038/s41380-018-0273-4

Bilderbeck, A. C., Atkinson, L. Z., Geddes, J. R., Goodwin, G. M., & Harmer, C. J. (2017). The effects of medication and current mood upon facial emotion recognition: findings from a large bipolar disorder cohort study. *Journal of*

Psychopharmacology, *31*(3), 320–326. https://doi.org/10.1177/0269881116668594

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine*, *34*(4), 537–541. https://doi.org/10.1002/mrm.1910340409

Bland, J. M., & Altman, D. G. (1995). Multiple significance tests: The Bonferroni method. *BMJ*, *310*(6973), 170. https://doi.org/10.1136/bmj.310.6973.170

Blumberg, H. P., Leung, H. C., Skudlarski, P., Lacadie, C. M., Fredericks, C. A., Harris, B. C., … Peterson, B. S. (2003). A functional magnetic resonance imaging study of bipolar disorder: State- and trait-related dysfunction in ventral prefrontal cortices. *Archives of General Psychiatry*, *60*(6), 601–609. https://doi.org/10.1001/archpsyc.60.6.601

Boivin, D. B. (2000). Influence of sleep-wake and circadian rhythm disturbances in psychiatric disorders. *Journal of Psychiatry and Neuroscience*, *25*(5), 446–458.

Boland, E. M., & Alloy, L. B. (2013, February 1). Sleep disturbance and cognitive deficits in bipolar disorder: Toward an integrated examination of disorder maintenance and functional impairment. *Clinical Psychology Review*, Vol. 33, pp. 33–44. https://doi.org/10.1016/j.cpr.2012.10.001

Bonsall, M. B., Wallace-Hadrill, S. M. A., Geddes, J. R., Goodwin, G. M., & Holmes, E. A. (2012). Nonlinear time-series approaches in characterizing mood stability and mood instability in bipolar disorder. *Proceedings of the Royal Society B: Biological Sciences*, *279*(1730), 916–924. https://doi.org/10.1098/rspb.2011.1246

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive endophenotypes of bipolar

disorder: A meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of Affective Disorders*, Vol. 113, pp. 1–20. https://doi.org/10.1016/j.jad.2008.06.009

Bourne, C., Bilderbeck, A., Drennan, R., Atkinson, L., Price, J., Geddes, J. R., & Goodwin, G. M. (2015, August). Verbal learning impairment in euthymic bipolar disorder: BDI v BDII. *Journal of Affective Disorders*, Vol. 182, pp. 95–100. https://doi.org/10.1016/j.jad.2015.04.021

Bradley, B. P., Mogg, K., & Lee, S. C. (1997). Attentional biases for negative information in induced and naturally occurring dysphoria. *Behaviour Research and Therapy*, *35*(10), 911–927.

Bromundt, V., Köster, M., Georgiev-Kill, A., Opwis, K., Wirz-Justice, A., Stoppe, G., & Cajochen, C. (2011). Sleep - Wake cycles and cognitive functioning in schizophrenia. *British Journal of Psychiatry*, *198*(4), 269–276. https://doi.org/10.1192/bjp.bp.110.078022

Broome, M. R., He, Z., Iftikhar, M., Eyden, J., & Marwaha, S. (2015). Neurobiological and behavioural studies of affective instability in clinical populations: A systematic review. *Neuroscience and Biobehavioral Reviews*, *51*, 243–254. https://doi.org/10.1016/j.neubiorev.2015.01.021

Broome, M. R., Saunders, K. E. A., Harrison, P. J., & Marwaha, S. (2015). Mood instability: significance, definition and measurement. *The British Journal of Psychiatry*, *207*(4), 283–285. https://doi.org/10.1192/bjp.bp.114.158543

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008, March). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, Vol. 1124, pp. 1–38. https://doi.org/10.1196/annals.1440.011

Bullock, B., & Murray, G. (2014). Reduced amplitude of the 24 hour activity rhythm: A biomarker of vulnerability to bipolar disorder? *Clinical Psychological Science*, *2*(1), 86–96. https://doi.org/10.1177/2167702613490158

Bundesen, C. (1990). A Theory of Visual Attention. *Psychological Review*, *97*(4), 523–547.

Bundesen, C. (1998). A computational theory of visual attention. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *353*(1373), 1271–1281. https://doi.org/10.1098/rstb.1998.0282

Bunney, W. E., & Bunney, B. G. (2000). Molecular clock genes in man and lower animals: Possible implications for circadian abnormalities in depression. *Neuropsychopharmacology*, *22*(4), 335–345. https://doi.org/10.1016/S0893-133X(99)00145-1

Burt, T., Prudic, J., Peyser, S., Clark, J., & Sackeim, H. (2000). Learning and Memory in Bipolar and Unipolar Major Depression: Effects of Aging. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*.

Burton, C., McKinstry, B., Szentagotai Tătar, A., Serrano-Blanco, A., Pagliari, C., & Wolters, M. (2013). Activity monitoring in patients with depression: A systematic review. *Journal of Affective Disorders*. https://doi.org/10.1016/j.jad.2012.07.001

Buyukdura, J. S., McClintock, S. M., & Croarkin, P. E. (2011, March 30). Psychomotor retardation in depression: Biological underpinnings, measurement, and treatment. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, Vol. 35, pp. 395–409. https://doi.org/10.1016/j.pnpbp.2010.10.019

Calhoun, V. D. (2004). *Group ICA of fMRI Toolbox (GIFT)*.

Calhoun, V. D., Miller, R., Pearlson, G., & Adali, T. (2014, October 22). The Chronnectome: Time-Varying Connectivity Networks as the Next Frontier in

fMRI Data Discovery. *Neuron*, Vol. 84, pp. 262–274. https://doi.org/10.1016/j.neuron.2014.10.015

Canbeyli, R. (2010, March 5). Sensorimotor modulation of mood and depression: An integrative review. *Behavioural Brain Research*, Vol. 207, pp. 249–264. https://doi.org/10.1016/j.bbr.2009.11.002

Cao, H., Plichta, M. M., Schäfer, A., Haddad, L., Grimm, O., Schneider, M., … Tost, H. (2014). Test-retest reliability of fMRI-based graph theoretical properties during working memory, emotion processing, and resting state. *NeuroImage*, *84*, 888–900. https://doi.org/10.1016/j.neuroimage.2013.09.013

Cerullo, M. A., Adler, C. M., Delbello, M. P., & Strakowski, S. M. (2009). The functional neuroanatomy of bipolar disorder. *International Review of Psychiatry*, *21*(4), 314–322. https://doi.org/10.1080/09540260902962107

Cha, D., Michele, F., Soczynska, J., Woldeyohannes, H., Kaidanovich-Beilin, O., Carvalho, A., … McIntyre, R. (2015). The Putative Impact of Metabolic Health on Default Mode Network Activity and Functional Connectivity in Neuropsychiatric Disorders. *CNS & Neurological Disorders - Drug Targets*, *13*(10), 1750–1758. https://doi.org/10.2174/1871527313666141130205024

Chanen, A. M., Jovev, M., Djaja, D., McDougall, E., Yuen, H. P., Rawlings, D., & Jackson, H. J. (2008). Screening for borderline personality disorder in outpatient youth. *Journal of Personality Disorders*, *22*(4), 353–364. https://doi.org/10.1521/pedi.2008.22.4.353

Chen, C. H., Lennox, B., Jacob, R., Calder, A., Lupson, V., Bisbrown-Chippendale, R., … Bullmore, E. (2006). Explicit and implicit facial affect recognition in manic and depressed states of bipolar disorder: A functional magnetic resonance imaging study. *Biological Psychiatry*, *59*(1), 31–39.

https://doi.org/10.1016/j.biopsych.2005.06.008

Chepenik, L. G., Raffo, M., Hampson, M., Lacadie, C., Wang, F., Jones, M. M., … Blumberg, H. P. (2010). Functional connectivity between ventral prefrontal cortex and amygdala at low frequency in the resting state in bipolar disorder. *Psychiatry Research - Neuroimaging*, *182*(3), 207–210. https://doi.org/10.1016/j.pscychresns.2010.04.002

Christodoulou, T., Lewis, M., Ploubidis, G. B., & Frangou, S. (2006). The relationship of impulsivity to response inhibition and decision-making in remitted patients with bipolar disorder. *European Psychiatry*, *21*(4), 270–273. https://doi.org/10.1016/j.eurpsy.2006.04.006

Chun, M. M., & Jiang, Y. (1998). Contextual Cueing: Implicit Learning and Memory of Visual Context Guides Spatial Attention. *Cogn. Psychol.*, *36*(1), 28–71. https://doi.org/10.1006/cogp.1998.0681

Cole, D. M., Smith, S. M., & Beckmann, C. F. (2010). Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. *Frontiers in Systems Neuroscience*, Vol. 4. https://doi.org/10.3389/fnsys.2010.00008

Correll, C. U., Penzner, J. B., Frederickson, A. M., Richter, J. J., Auther, A. M., Smith, C. W., … Cornblatt, B. A. (2007). Differentiation in the preonset phases of schizophrenia and mood disorders: Evidence in support of a bipolar mania prodrome. *Schizophrenia Bulletin*, *33*(3), 703–714. https://doi.org/10.1093/schbul/sbm028

Craig, A. D. (2009, January). How do you feel - now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, Vol. 10, pp. 59–70. https://doi.org/10.1038/nrn2555

Damasio, A., & Carvalho, G. B. (2013, February 18). The nature of feelings:

Evolutionary and neurobiological origins. *Nature Reviews Neuroscience*, Vol. 14, pp. 143–152. https://doi.org/10.1038/nrn3403

Delvecchio, G, Sugranyes, G., & Frangou, S. (2013). Evidence of diagnostic specificity in the neural correlates of facial affect processing in bipolar disorder and schizophrenia: A meta-analysis of functional imaging studies. *Psychological Medicine*, *43*(3), 553–569. https://doi.org/10.1017/S0033291712001432

Delvecchio, Giuseppe, Fossati, P., Boyer, P., Brambilla, P., Falkai, P., Gruber, O., … Frangou, S. (2012). Common and distinct neural correlates of emotional processing in Bipolar Disorder and Major Depressive Disorder: A voxel-based meta-analysis of functional magnetic resonance imaging studies. *European Neuropsychopharmacology*, *22*(2), 100–113. https://doi.org/10.1016/j.euroneuro.2011.07.003

Diener, E., Larsen, R. J., Levine, S., & Emmons, R. A. (1985). Intensity and Frequency. Dimensions Underlying Positive and Negative Affect. *Journal of Personality and Social Psychology*, *48*(5), 1253–1265. https://doi.org/10.1037/0022-3514.48.5.1253

Dunn, O. J. (1961). Multiple Comparisons among Means. *Journal of the American Statistical Association*, *56*(293), 52–64. https://doi.org/10.1080/01621459.1961.10482090

Duque, A., & Vázquez, C. (2015). Double attention bias for positive and negative emotional faces in clinical depression: Evidence from an eye-tracking study. *Journal of Behavior Therapy and Experimental Psychiatry*, *46*, 107–114. https://doi.org/10.1016/j.jbtep.2014.09.005

Ebner-Priemer, U. W., Kuo, J., Kleindienst, N., Welch, S. S., Reisch, T., Reinhard, I., … Bohus, M. (2007). State affective instability in borderline personality disorder

assessed by ambulatory monitoring. *Psychological Medicine*, *37*(7), 961–970. https://doi.org/10.1017/S0033291706009706

Ekman, P., & Friesen, W. V. (1971). Constants across cultures in the face and emotion. *Journal of Personality and Social Psychology*, *17*(2), 124–129.

Eldar, E., & Niv, Y. (2015). Interaction between emotional state and learning underlies mood instability. *Nature Communications*, *6*, 6149. https://doi.org/10.1038/ncomms7149

Eldar, E., Rutledge, R. B., Dolan, R. J., & Niv, Y. (2016). Mood as Representation of Momentum. *Trends in Cognitive Sciences*, *20*(1), 15–24. https://doi.org/10.1016/j.tics.2015.07.010

Elliott, M. L., Knodt, A. R., Ireland, D., Morris, M. L., Poulton, R., Ramrakha, S., … Hariri, A. R. (2020). What Is the Test-Retest Reliability of Common Task-Functional MRI Measures? New Empirical Evidence and a Meta-Analysis. *Psychological Science*, *31*(7), 792–806. https://doi.org/10.1177/0956797620916786

Elliott, R., Sahakian, B. J., Herrod, J. J., Robbins, T. W., & Paykel, E. S. (1997). Abnormal response to negative feedback in unipolar depression: evidence for a diagnosis specific impairment. *Journal of Neurology, Neurosurgery & Psychiatry*, *63*(1), 74–82. https://doi.org/10.1136/jnnp.63.1.74

Elliott, R., Zahn, R., Deakin, J. F. W., & Anderson, I. M. (2011). Affective cognition and its disruption in mood disorders. *Neuropsychopharmacology*, *36*(1), 153–182. https://doi.org/10.1038/npp.2010.77

Erickson, K., Drevets, W. C., Clark, L., Cannon, D. M., Bain, E. E., Zarate, C. A., … Sahakian, B. J. (2005). Mood-congruent bias in affective Go/No-Go performance of unmedicated patients with major depressive disorder. *American*

Journal of Psychiatry, *162*(11), 2171–2173. https://doi.org/10.1176/appi.ajp.162.11.2171

Eshel, N., & Roiser, J. P. (2010). Reward and punishment processing in depression. *Biological Psychiatry*, *68*(2), 118–124. https://doi.org/10.1016/j.biopsych.2010.01.027

Esliger, D. W., Rowlands, A. V., Hurst, T. L., Catt, M., Murray, P., & Eston, R. G. (2011). Validation of the GENEA accelerometer. *Medicine and Science in Sports and Exercise*, *43*(6), 1085–1093. https://doi.org/10.1249/MSS.0b013e31820513be

Espie, C. a, Kyle, S. D., Hames, P., Gardani, M., Fleming, L., & Cape, J. (2014). The Sleep Condition Indicator: a clinical screening tool to evaluate insomnia disorder. *BMJ Open*, *4*(3), e004183. https://doi.org/10.1136/bmjopen-2013-004183

EuroQol Group. (1990). EuroQol--a new facility for the measurement of health-related quality of life. *Healthy Policy*, *16*(3), 199–208.

Even, C., Schröder, C. M., Friedman, S., & Rouillon, F. (2008, May). Efficacy of light therapy in nonseasonal depression: A systematic review. *Journal of Affective Disorders*, Vol. 108, pp. 11–23. https://doi.org/10.1016/j.jad.2007.09.008

Faurholt-Jepsen, M., Frost, M., Busk, J., Christensen, E. M., Bardram, J. E., Vinberg, M., & Kessing, L. V. (2019). Differences in mood instability in patients with bipolar disorder type I and II: a smartphone-based study. *International Journal of Bipolar Disorders*, *7*(1). https://doi.org/10.1186/s40345-019-0141-4

Faurholt-Jepsen, M., Vinberg, M., Christensen, E. M., Frost, M., Bardram, J., & Kessing, L. V. (2013). Daily electronic self-monitoring of subjective and objective symptoms in bipolar disorder--the MONARCA trial protocol (MONitoring,

treAtment and pRediCtion of bipolAr disorder episodes): a randomised controlled single-blind trial. *BMJ Open*, *3*(7). https://doi.org/10.1136/bmjopen-2013-003353

Faurholt-Jepsen, M., Vinberg, M., Frost, M., Christensen, M. M., Bardram, J., & Kessing, V. V. (2014). Daily electronic monitoring of subjective and objective measures of illness activity in bipolar disorder using smartphones- the MONARCA II trial protocol: A randomized controlled single-blind parallel-group trial. *BMC Psychiatry*, *14*(1). https://doi.org/10.1186/s12888-014-0309-5

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., … Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE-ε4 allele. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(17), 7209–7214. https://doi.org/10.1073/pnas.0811879106

Fornito, A., Malhi, G. S., Lagopoulos, J., Ivanovski, B., Wood, S. J., Saling, M. M., … Yücel, M. (2008). Anatomical abnormalities of the anterior cingulate and paracingulate cortex in patients with bipolar I disorder. *Psychiatry Research - Neuroimaging*, *162*(2), 123–132. https://doi.org/10.1016/j.pscychresns.2007.06.004

Foster, R. G., Peirson, S. N., Wulff, K., Winnebeck, E., Vetter, C., & Roenneberg, T. (2013). Sleep and Circadian Rhythm Disruption in Social Jetlag and Mental Illness. *Progress in Molecular Biology and Translational Science*, *119*, 325–346. https://doi.org/10.1016/B978-0-12-396971-2.00011-7

Frank, E., Kupfer, D. J., Thase, M. E., Mallinger, A. G., Swartz, H. A., Fagiolini, A. M., … Monk, T. (2005). Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Archives of General Psychiatry*,

62(9), 996–1004. https://doi.org/10.1001/archpsyc.62.9.996

Frank, E., Swartz, H. A., & Kupfer, D. J. (2000, September 15). Interpersonal and social rhythm therapy: Managing the chaos of bipolar disorder. *Biological Psychiatry*, Vol. 48, pp. 593–604. https://doi.org/10.1016/S0006-3223(00)00969-0

Frankle, W. G., Perlis, R. H., Deckersbach, T., Grandin, L. D., Gray, S. M., Sachs, G. S., & Nierenberg, A. A. (2002). Bipolar depression: Relationship between episode length and antidepressant treatment. *Psychological Medicine*, *32*(8), 1417–1423. https://doi.org/10.1017/S0033291702006165

Friedman, J., Hastie, T., & Tibshirani, R. (2008). Sparse inverse covariance estimation with the graphical lasso. *Biostatistics*, *9*(3), 432–441. https://doi.org/10.1093/biostatistics/kxm045

García-Blanco, A. C., Perea, M., & Livianos, L. (2013). Mood-congruent bias and attention shifts in the different episodes of bipolar disorder. *Cognition & Emotion*, *27*(6), 1114–1121. https://doi.org/10.1080/02699931.2013.764281

Garrett, A., & Chang, K. (2008). The role of the amygdala in bipolar disorder development. *Development and Psychopathology*, Vol. 20, pp. 1285–1296. https://doi.org/10.1017/S0954579408000618

Ghaemi, S. N., Sachs, G. S., Chiou, A. M., Pandurangi, A. K., & Goodwin, K. (1999). Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *Journal of Affective Disorders*, *52*(1–3), 135–144.

Glenn, T., & Monteith, S. (2014). New Measures of Mental State and Behavior Based on Data Collected From Sensors, Smartphones, and the Internet. *Current Psychiatry Reports*, Vol. 16. https://doi.org/10.1007/s11920-014-0523-3

Gogolla, N. (2017, June 19). The insular cortex. *Current Biology*, Vol. 27, pp. R580–

R586. https://doi.org/10.1016/j.cub.2017.05.010

Golier, J. A., Yehuda, R., Schmeidler, J., & Siever, L. J. (2001). Variability and severity of depression and anxiety in post traumatic stress disorder and major depressive disorder. *Depression and Anxiety*, *13*(2), 97–100. https://doi.org/10.1002/da.1022

Gonzalez-Castillo, J., Handwerker, D. A., Robinson, M. E., Hoy, C. W., Buchanan, L. C., Saad, Z. S., & Bandettini, P. A. (2014). The spatial structure of resting state connectivity stability on the scale of minutes. *Frontiers in Neuroscience*, *8*(8 JUN), 138. https://doi.org/10.3389/fnins.2014.00138

Gonzalez-Castillo, J., Saad, Z. S., Handwerker, D. A., Inati, S. J., Brenowitz, N., & Bandettini, P. A. (2012). Whole-brain, time-locked activation with simple tasks revealed using massive averaging and model-free analysis. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(14), 5487–5492. https://doi.org/10.1073/pnas.1121049109

Goodwin, G. M. (2003, June). Evidence-based guidelines for treating bipolar disorder: Recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology*, Vol. 17, pp. 149–173. https://doi.org/10.1177/0269881103017002003

Goodwin, G. M. (2009, June). Evidence-based guidelines for treating bipolar disorder: Revised second edition-recommendations from the British association for psychopharmacology. *Journal of Psychopharmacology*, Vol. 23, pp. 346–388. https://doi.org/10.1177/0269881109102919

Gordijn, M. C. M., Beersma, D. G. M., Bouhuys, A. L., Reinink, E., & Van den Hoofdakker, R. H. (1994). A longitudinal study of diurnal mood variation in depression; characteristics and significance. *Journal of Affective Disorders*,

31(4), 261–273. https://doi.org/10.1016/0165-0327(94)90102-3

Gotlib, I. H., Kasch, K. L., Traill, S., Joormann, J., Arnow, B. A., & Johnson, S. L. (2004). Coherence and specificity of information-processing biases in depression and social phobia. *Journal of Abnormal Psychology*, *113*(3), 386–398. https://doi.org/10.1037/0021-843X.113.3.386

Gotlib, I. H., Krasnoperova, E., Yue, D. N., & Joormann, J. (2004). Attentional Biases for Negative Interpersonal Stimuli in Clinical Depression. *Journal of Abnormal Psychology*, *113*(1), 127–135. https://doi.org/10.1037/0021-843X.113.1.121

Gotlib, I. H., Sivers, H., Gabrieli, J. D. E., Whitfield-Gabrieli, S., Goldin, P., Minor, K. L., & Canli, T. (2005). Subgenual anterior cingulate activation to valenced emotional stimuli in major depression. *Neuroreport*, *16*(16), 1731–1734.

Gottschalk, A., Bauer, M. S., & Whybrow, P. C. (1995). Evidence of Chaotic Mood Variation in Bipolar Disorder. *Archives of General Psychiatry*, *52*(11), 947–959. https://doi.org/10.1001/archpsyc.1995.03950230061009

Gray, J., Venn, H., Montagne, B., Murray, L., Burt, M., Frigerio, E., … Young, A. H. (2006). Bipolar patients show mood-congruent biases in sensitivity to facial expressions of emotion when exhibiting depressed symptoms, but not when exhibiting manic symptoms. *Cognitive Neuropsychiatry*, *11*(6), 505–520. https://doi.org/10.1080/13546800544000028

Griffanti, L., Douaud, G., Bijsterbosch, J., Evangelisti, S., Alfaro-Almagro, F., Glasser, M. F., … Smith, S. M. (2017). Hand classification of fMRI ICA noise components. *NeuroImage*, *154*, 188–205. https://doi.org/10.1016/j.neuroimage.2016.12.036

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *Journal of*

Personality and Social Psychology, *85*(2), 348–362. Retrieved from http://doi.apa.org/getdoi.cfm?doi=10.1037/0022-3514.85.2.348

Gruber, J., Miklowitz, D. J., Harvey, A. G., Frank, E., Kupfer, D., Thase, M. E., … Ketter, T. A. (2011). Sleep matters: Sleep functioning and course of illness in bipolar disorder. *Journal of Affective Disorders*, *134*(1–3), 416–420. https://doi.org/10.1016/j.jad.2011.05.016

Halahakoon, D. C., Kieslich, K., O'Driscoll, C., Nair, A., Lewis, G., & Roiser, J. P. (2020). Reward Processing Behavior in Depressed Participants Relative to Healthy Volunteers: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2020.2139

Haldane, M., Cunningham, G., Androutsos, C., & Frangou, S. (2008). Structural brain correlates of response inhibition in Bipolar Disorder I. *Journal of Psychopharmacology*, *22*(2), 138–143. https://doi.org/10.1177/0269881107082955

Hamet, P., & Tremblay, J. (2006, October 1). Genetics of the sleep-wake cycle and its disorders. *Metabolism: Clinical and Experimental*, Vol. 55, pp. S7–S12. https://doi.org/10.1016/j.metabol.2006.07.006

Hamilton, J. P., & Gotlib, I. H. (2008). Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biological Psychiatry*, *63*(12), 1155–1162. https://doi.org/10.1016/j.biopsych.2007.12.015

Hamilton, M. (1967). Development of a Rating Scale for Primary Depressive Illness. *British Journal of Social and Clinical Psychology*, *6*(4), 278–296. https://doi.org/10.1111/j.2044-8260.1967.tb00530.x

Harmer, C. J., Goodwin, G. M., & Cowen, P. J. (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug

action. *British Journal of Psychiatry*, Vol. 195, pp. 102–108. https://doi.org/10.1192/bjp.bp.108.051193

Harmer, C. J., Grayson, L., & Goodwin, G. M. (2002). Enhanced recognition of disgust in bipolar illness. *Biological Psychiatry*, *51*(4), 298–304. https://doi.org/10.1016/S0006-3223(01)01249-5

Harmer, C. J., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., … Cowen, P. J. (2009). Effect of acute antidepressant administration on negative affective bias in depressed patients. *American Journal of Psychiatry*, *166*(10), 1178–1184. https://doi.org/10.1176/appi.ajp.2009.09020149

Harvey, A. G., Schmidt, D. A., Scarnà, A., Semler, C. N., & Goodwin, G. M. (2005). Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *American Journal of Psychiatry*, *162*(1), 50–57. https://doi.org/10.1176/appi.ajp.162.1.50

Harvey, P. D. (2007). Cognitive impairments in major depression and bipolar disorders. *Psychiatry (Edgmont (Pa. : Township))*, *4*(1), 12–14. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2922383&tool=pmcentrez&rendertype=abstract

Hearing, C. M., Chang, W. C., Szuhany, K. L., Deckersbach, T., Nierenberg, A. A., & Sylvia, L. G. (2016). Physical Exercise for Treatment of Mood Disorders: A Critical Review. *Current Behavioral Neuroscience Reports*, *3*(4), 350–359. https://doi.org/10.1007/s40473-016-0089-y

Helbing, J., Draschkow, D., & Võ, M. L. H. (2020). Search superiority: Goal-directed attentional allocation creates more reliable incidental identity and location memory than explicit encoding in naturalistic virtual environments. *Cognition*, *196*. https://doi.org/10.1016/j.cognition.2019.104147

Henry, C, Mitropoulou, V., New, a S., Koenigsberg, H. W., Silverman, J., & Siever, L. J. (2001). Affective instability and impulsivity in borderline personality and bipolar II disorders: similarities and differences. *Journal of Psychiatric Research*, *35*(6), 307–312. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11684137

Henry, Chantal, Van den Bulke, D., Bellivier, F., Roy, I., Swendsen, J., M'Baïlara, K., … Leboyer, M. (2008). Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. *Psychiatry Research*, *159*(1–2), 1–6. https://doi.org/10.1016/j.psychres.2005.11.016

Hibar, D P, Westlye, L. T., Doan, N. T., Jahanshad, N., Cheung, J. W., Ching, C. R. K., … Andreassen, O. A. (2018). Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. *Molecular Psychiatry*, *23*(4), 932–942. https://doi.org/10.1038/mp.2017.73

Hibar, Derrek P., Stein, J. L., Renteria, M. E., Arias-Vasquez, A., Desrivières, S., Jahanshad, N., … Medland, S. E. (2015). Common genetic variants influence human subcortical brain structures. *Nature*, *520*(7546), 224–229. https://doi.org/10.1038/nature14101

Hildebrand, M., Van Hees, V. T., Hansen, B. H., & Ekelund, U. (2014). Age group comparability of raw accelerometer output from wrist-and hip-worn monitors. *Medicine and Science in Sports and Exercise*, *46*(9), 1816–1824. https://doi.org/10.1249/MSS.0000000000000289

Hirschfeld, R. M. A. (2002). The Mood Disorder Questionnaire: A simple, patient-rated screening instrument for bipolar disorder. *Primary Care Companion to the Journal of Clinical Psychiatry*, *4*(1), 9–11. https://doi.org/10.4088/pcc.v04n0104

Hirschfeld, R. M. A. (2007). Screening for bipolar disorder. In *American Journal of*

Managed Care (Vol. 13).

Hirschfeld, R. M. A. (2010). The mood disorder questionnaire: its impact on the field [corrected]. *Depression and Anxiety*, *27*(7), 627–630. https://doi.org/10.1002/da.20697

Hirschfeld, R. M. a, Calabrese, J. R., Weissman, M. M., Reed, M., Davies, M. a, Frye, M. a, … Wagner, K. D. (2003). Screening for bipolar disorder in the community. *The Journal of Clinical Psychiatry*, *64*(1), 53–59. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15163245

Hirschfeld, R. M., Holzer, C., Calabrese, J. R., Weissman, M., Reed, M., Davies, M., … Hazard, E. (2003). Validity of the mood disorder questionnaire: A general population study. *American Journal of Psychiatry*, *160*(1), 178–180. https://doi.org/10.1176/appi.ajp.160.1.178

Hirschfeld, R. M., Williams, J. B., Robert Spitzer, D. L., Calabrese, J. R., Flynn, L., Paul Keck, B. E., … Zajecka, J. (2000). Development and Validation of a Screening Instrument for Bipolar Spectrum Disorder: The Mood Disorder Questionnaire. *Am J PsychiatryAm J Psychiatry*, *15711*(157), 1873–1875. https://doi.org/10.1176/appi.ajp.157.11.1873

Holmes, A. J., & Pizzagalli, D. A. (2011). *Control : Relationship to Subclinical Measures of Depression*. *7*(1), 68–76. https://doi.org/10.1037/1528-3542.7.1.68.Task

Hutchison, R. M., Womelsdorf, T., Allen, E. A., Bandettini, P. A., Calhoun, V. D., Corbetta, M., … Chang, C. (2013). Dynamic functional connectivity: Promise, issues, and interpretations. *NeuroImage*, *80*, 360–378. https://doi.org/10.1016/j.neuroimage.2013.05.079

Hwang, J., Lyoo, I. K., Dager, S. R., Friedman, S. D., Oh, J. S., Lee, J. Y., …

Renshaw, P. F. (2006). Basal ganglia shape alterations in bipolar disorder. *The American Journal of Psychiatry*, *163*(2), 276–285. https://doi.org/10.1176/appi.ajp.163.2.276

Hyvärinen, A. (1999). Fast and robust fixed-point algorithms for independent component analysis. *IEEE Transactions on Neural Networks*, *10*(3), 626–634. https://doi.org/10.1109/72.761722

IBM Corp. (2017). *IBM SPSS Statistics for Windows*. Retrieved from https://www.ibm.com/uk-en/products/spss-statistics

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., … Wang, P. (2010). Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

Japee, S., Holiday, K., Satyshur, M. D., Mukai, I., & Ungerleider, L. G. (2015). A role of right middle frontal gyrus in reorienting of attention: A case study. *Frontiers in Systems Neuroscience*, *9*(MAR), 23. https://doi.org/10.3389/fnsys.2015.00023

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage*, *17*(2), 825–841. https://doi.org/10.1006/nimg.2002.1132

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*(2), 143–156. https://doi.org/10.1016/S1361-8415(01)00036-6

Johnson, S. L. (2005). Life events in bipolar disorder: Towards more specific models. *Clinical Psychology Review*, *25*(8), 1008–1027. https://doi.org/10.1016/j.cpr.2005.06.004

Jones, D. T., Vemuri, P., Murphy, M. C., Gunter, J. L., Senjem, M. L., Machulda, M.

M., … Jack, C. R. (2012). Non-stationarity in the “resting brain’s” modular architecture. *PLoS ONE*, *7*(6), e39731. https://doi.org/10.1371/journal.pone.0039731

Jones, S. H., Hare, D. J., & Evershed, K. (2005). Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. *Bipolar Disorders*, *7*(2), 176–186. https://doi.org/10.1111/j.1399-5618.2005.00187.x

Joormann, J., & Gotlib, I. H. (2007). Selective attention to emotional faces following recovery from depression. *Journal of Abnormal Psychology*, *116*(1), 80–85. https://doi.org/10.1037/0021-843X.116.1.80

Kaiser, R. H., Andrews-Hanna, J. R., Spielberg, J. M., Warren, S. L., Sutton, B. P., Miller, G. A., … Banich, M. T. (2015). Distracted and down: Neural mechanisms of affective interference in subclinical depression. *Social Cognitive and Affective Neuroscience*, *10*(5), 654–663. https://doi.org/10.1093/scan/nsu100

Kaiser, R. H., Whitfield-Gabrieli, S., Dillon, D. G., Goer, F., Beltzer, M., Minkel, J., … Pizzagalli, D. A. (2016). Dynamic Resting-State Functional Connectivity in Major Depression. *Neuropsychopharmacology*, *41*(7), 1822–1830. https://doi.org/10.1038/npp.2015.352

Kaufman, J., & Charney, D. (2000, January 1). Comorbidity of mood and anxiety disorders. *Depression and Anxiety*, Vol. 12, pp. 69–76. https://doi.org/10.1002/1520-6394(2000)12:1+<69::AID-DA9>3.0.CO;2-K

Kemper, K. J., & Danhauer, S. C. (2005, March). Music as therapy. *Southern Medical Journal*, Vol. 98, pp. 282–288. https://doi.org/10.1097/01.SMJ.0000154773.11986.39

King, R. (2002). Cognitive therapy of depression. Aaon Beck, John Rush, Brian Shaw, Gary Emery. New York: Guilford, 1979. *The Australian and New Zealand*

Journal of Psychiatry, *36*(2), 272–275. https://doi.org/10.1046/j.1440-1614.2002.t01-4-01015.x

Kircanski, K., Joormann, J., & Gotlib, I. H. (2012). Cognitive aspects of depression. *Wiley Interdisciplinary Reviews: Cognitive Science*, *3*(3), 301–313. https://doi.org/10.1002/wcs.1177

Kizilbash, A. H., Vanderploeg, R. D., & Curtiss, G. (2002). The effects of depression and anxiety on memory performance. *Archives of Clinical Neuropsychology : The Official Journal of the National Academy of Neuropsychologists*, *17*(1), 57–67. https://doi.org/10.1016/S0887-6177(00)00101-3

Kliegl, R., Wei, P., Dambacher, M., Yan, M., & Zhou, X. (2011). Experimental effects and individual differences in linear mixed models: Estimating the relationship between spatial, object, and attraction effects in visual attention. *Frontiers in Psychology*, *1*(JAN), 238. https://doi.org/10.3389/fpsyg.2010.00238

Kripke, D. F. (1998). Light treatment for nonseasonal depression: Speed, efficacy, and combined treatment. *Journal of Affective Disorders*, *49*(2), 109–117. https://doi.org/10.1016/S0165-0327(98)00005-6

Kuppens, P., Van Mechelen, I., Nezlek, J. B., Dossche, D., & Timmermans, T. (2007). Individual differences in core affect variability and their relationship to personality and psychological adjustment. *Emotion*, *7*(2), 262–274. https://doi.org/10.1037/1528-3542.7.2.262

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*, *82*(13). https://doi.org/10.18637/jss.v082.i13

Larsen, R. (1984). Theory and measurement of affect intensity as an individual difference characteristic. *Dissertation Abstracts International*, *85*(2297B),

University Microfilms No. 84-22112.

Larsen, R. J., & Diener, E. (1987, March 1). Affect intensity as an individual difference characteristic: A review. *Journal of Research in Personality*, Vol. 21, pp. 1–39. https://doi.org/10.1016/0092-6566(87)90023-7

Lee, B. T., Seok, J. H., Lee, B. C., Cho, S. W., Yoon, B. J., Lee, K. U., … Ham, B. J. (2008). Neural correlates of affective processing in response to sad and angry facial stimuli in patients with major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(3), 778–785. https://doi.org/10.1016/j.pnpbp.2007.12.009

Lee, B. T., Seong Whi Cho, Hyung Soo Khang, Lee, B. C., Choi, I. G., In Kyoon Lyoo, & Ham, B. J. (2007). The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *31*(7), 1487–1492. https://doi.org/10.1016/j.pnpbp.2007.06.030

Lembke, A., & Ketter, T. A. (2002). Impaired recognition of facial emotion in mania. *American Journal of Psychiatry*, *159*(2), 302–304. https://doi.org/10.1176/appi.ajp.159.2.302

Lewy, A. J., Kern, H. A., Rosenthal, N. E., & Wehr, T. A. (1982). Bright artificial light treatment of a manic-depressive patient with a seasonal mood cycle. *American Journal of Psychiatry*, *139*(11), 1496–1498. https://doi.org/10.1176/ajp.139.11.1496

Liu, C. H., Ma, X., Li, F., Wang, Y. J., Tie, C. Le, Li, S. F., … Wang, C. Y. (2012). Regional Homogeneity within the Default Mode Network in Bipolar Depression: A Resting-State Functional Magnetic Resonance Imaging Study. *PLoS ONE*, *7*(11), e48181. https://doi.org/10.1371/journal.pone.0048181

Lyall, L. M., Wyse, C. A., Graham, N., Ferguson, A., Lyall, D. M., Cullen, B., … Smith, D. J. (2018). Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91 105 participants from the UK Biobank. *The Lancet Psychiatry*, *5*(6), 507–514. https://doi.org/10.1016/S2215-0366(18)30139-1

Ma, S., Calhoun, V. D., Phlypo, R., & Adali, T. (2014). Dynamic changes of spatial functional network connectivity in healthy individuals and schizophrenia patients using independent vector analysis. *NeuroImage*, *90*, 196–206. https://doi.org/10.1016/j.neuroimage.2013.12.063

Mackert, A., Volz, H. P., Stieglitz, R. D., & Müller-Oerlinghausen, B. (1991). Phototherapy in nonseasonal depression. *Biological Psychiatry*, *30*(3), 257–268. https://doi.org/10.1016/0006-3223(91)90110-8

MacQueen, G. M., Marriott, M., Begin, H., Robb, J., Joffe, R. T., & Young, L. T. (2003). Subsyndromal symptoms assessed in longitudinal, prospective follow-up of a cohort of patients with bipolar disorder. *Bipolar Disorders*, *5*(5), 349–355. https://doi.org/10.1034/j.1399-5618.2003.00048.x

Magnusson, A., & Boivin, D. (2003, March). Seasonal Affective Disorder: An overview. *Chronobiology International*, Vol. 20, pp. 189–207. https://doi.org/10.1081/CBI-120019310

Makeig, S., Debener, S., Onton, J., & Delorme, A. (2004). Mining event-related brain dynamics. *Trends in Cognitive Sciences*, *8*(5), 204–210. https://doi.org/10.1016/j.tics.2004.03.008

Marchand, W. R., Lee, J. N., Johnson, S., Gale, P., & Thatcher, J. (2013). Differences in functional connectivity in major depression versus bipolar II depression. *Journal of Affective Disorders*.

https://doi.org/10.1016/j.jad.2013.01.028

Martínez-Arán, a, Vieta, E., Colom, F., Torrent, C., Sánchez-Moreno, J., Reinares, M., … Salamero, M. (2004). Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disorders*, *6*(3), 224–232. https://doi.org/10.1111/j.1399-5618.2004.00111.x

Martino, D. J., Strejilevich, S. A., Fassi, G., Marengo, E., & Igoa, A. (2011). Theory of mind and facial emotion recognition in euthymic bipolar I and bipolar II disorders. *Psychiatry Research*, *189*(3), 379–384. https://doi.org/10.1016/j.psychres.2011.04.033

Marwaha, S., Parsons, N., & Broome, M. (2013). Mood instability, mental illness and suicidal ideas: Results from a household survey. *Social Psychiatry and Psychiatric Epidemiology*, *48*(9), 1431–1437. https://doi.org/10.1007/s00127-013-0653-7

Marwaha, S., Parsons, N., Flanagan, S., & Broome, M. (2013). The prevalence and clinical associations of mood instability in adults living in England: Results from the Adult Psychiatric Morbidity Survey 2007. *Psychiatry Research*. https://doi.org/10.1016/j.psychres.2012.09.036

Matsuo, K., Nicoletti, M. A., Peluso, M. A. M., Hatch, J. P., Nemoto, K., Watanabe, Y., … Soares, J. C. (2009). Anterior cingulate volumes associated with trait impulsivity in individuals with bipolar disorder. *Bipolar Disorders*, *11*(6), 628–636. https://doi.org/10.1111/j.1399-5618.2009.00732.x

McClung, C. A. (2007). Circadian genes, rhythms and the biology of mood disorders. *Pharmacology and Therapeutics*, Vol. 114, pp. 222–232. https://doi.org/10.1016/j.pharmthera.2007.02.003

McConville, C., & Cooper, C. (1996). Mood variability and the intensity of depressive

states. *Current Psychology*, *14*(4), 329–338. https://doi.org/10.1007/bf02686921

McGowan, N. M., Goodwin, G. M., Bilderbeck, A. C., & Saunders, K. E. A. (2019). Circadian rest-activity patterns in bipolar disorder and borderline personality disorder. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-019-0526-2

McGuffin, P., & Katz, R. (1989). The Genetics of Depression and Manic-Depressive Disorder. *British Journal of Psychiatry*, *155*(03), 294–304. https://doi.org/10.1192/bjp.155.3.294

McKenna, B. S., Drummond, S. P. A., & Eyler, L. T. (2014). Associations between circadian activity rhythms and functional brain abnormalities among euthymic bipolar patients: A preliminary study. *Journal of Affective Disorders*, *164*, 101–106. https://doi.org/10.1016/j.jad.2014.04.034

Mennin, D. S., Heimberg, R. G., Turk, C. L., & Fresco, D. M. (2005). Preliminary evidence for an emotion dysregulation model of generalized anxiety disorder. *Behaviour Research and Therapy*, *43*(10), 1281–1310. https://doi.org/10.1016/j.brat.2004.08.008

Mennin, D. S., Holaway, R. M., Fresco, D. M., Moore, M. T., & Heimberg, R. G. (2007). Delineating Components of Emotion and its Dysregulation in Anxiety and Mood Psychopathology. *Behavior Therapy*, *38*(3), 284–302. https://doi.org/10.1016/j.beth.2006.09.001

Mental disorders. (2017). Retrieved from World Health Organisation (WHO) website: http://www.who.int/mediacentre/factsheets/fs396/en/

Miller, D. J., Vachon, D. D., & Lynam, D. R. (2009). Neuroticism, negative affect, and negative affect instability: Establishing convergent and discriminant validity using ecological momentary assessment. *Personality and Individual Differences*,

47(8), 873–877. https://doi.org/10.1016/j.paid.2009.07.007

Miller, J. D., & Pilkonis, P. A. (2006). Neuroticism and affective instability: The same or different? *American Journal of Psychiatry*, *163*(5), 839–845. https://doi.org/10.1176/ajp.2006.163.5.839

Miller, R. L., Yaesoubi, M., Turner, J. A., Mathalon, D., Preda, A., Pearlson, G., … Calhoun, V. D. (2016). Higher Dimensional Meta-State Analysis Reveals Reduced Resting fMRI Connectivity Dynamism in Schizophrenia Patients. *PloS One*, *11*(3), e0149849. https://doi.org/10.1371/journal.pone.0149849

Minassian, A., Paulus, M. P., & Perry, W. (2004). Increased sensitivity to error during decision-making in bipolar disorder patients with acute mania. *Journal of Affective Disorders*, *82*(2), 203–208. https://doi.org/10.1016/j.jad.2003.11.010

Mogg, K., Bradley, B. P., & Williams, R. (1995). Attentional bias in anxiety and depression: the role of awareness. *The British Journal of Clinical Psychology*, *34 (Pt 1)*, 17–36.

Mohan, A., Roberto, A. J., Mohan, A., Lorenzo, A., Jones, K., Carney, M. J., … Lapidus, K. A. B. (2016). The significance of the Default Mode Network (DMN) in neurological and neuropsychiatric disorders: A review. *Yale Journal of Biology and Medicine*, Vol. 89, pp. 49–57.

Monteleone, P., & Maj, M. (2008, October). The circadian basis of mood disorders: Recent developments and treatment implications. *European Neuropsychopharmacology*, Vol. 18, pp. 701–711. https://doi.org/10.1016/j.euroneuro.2008.06.007

Murphy, F. C., Michael, A., Robbins, T. W., & Sahakian, B. J. (2003). Neuropsychological impairment in patients with major depressive disorder: The effects of feedback on task performance. *Psychological Medicine*, *33*(3), 455–

467. https://doi.org/10.1017/S0033291702007018

Murphy, F. C., Rubinsztein, J. S., Michael, A., Rogers, R. D., Robbins, T. W., Paykel, E. S., & Sahakian, B. J. (2001). *Decision-making cpgnition in mania and depression*. *31*, 679–693.

Murphy, F. C., Sahakian, B. J., Rubinsztein, J. S., Michael, A., Rogers, R. D., Robbins, T. W., & Paykel, E. S. (1999). Emotional bias and inhibitory control processes in mania and depression. *Psychological Medicine*, *29*(6), 1307–1321.

Nesse, R. M., & Stein, D. J. (2012). Towards a genuinely medical model for psychiatric nosology. *BMC Medicine*, *10*(1), 5. https://doi.org/10.1186/1741-7015-10-5

Ng, T. H., Chung, K. F., Ho, F. Y. Y., Yeung, W. F., Yung, K. P., & Lam, T. H. (2015, April 1). Sleep-wake disturbance in interepisode bipolar disorder and high-risk individuals: A systematic review and meta-analysis. *Sleep Medicine Reviews*, Vol. 20, pp. 46–58. https://doi.org/10.1016/j.smrv.2014.06.006

Nguyen, T. T., Kovacevic, S., Dev, S. I., Lu, K., Liu, T. T., & Eyler, L. T. (2017). Dynamic functional connectivity in bipolar disorder is associated with executive function and processing speed: A preliminary study. *Neuropsychology*, *31*(1), 73–83. https://doi.org/10.1037/neu0000317

Nica, E. I., & Links, P. S. (2009). Affective instability in borderline personality disorder: Experience sampling findings. *Current Psychiatry Reports*, Vol. 11, pp. 74–81. https://doi.org/10.1007/s11920-009-0012-2

NICE. (n.d.). *Bipolar disorder The management of bipolar disorder in adults, children and adolescents, in primary and secondary care*. Retrieved from www.bps.org.uk

Noble, S., Scheinost, D., & Constable, R. T. (2019). A decade of test-retest reliability

of functional connectivity: A systematic review and meta-analysis. *NeuroImage*, *203*. https://doi.org/10.1016/j.neuroimage.2019.116157

Norbeck, J. S. (1984). Modification of Life Event Questionnaires for Use with Female Respondents. *Research in Nursing & Health*, *7*(1), 61–71. https://doi.org/10.1002/nur.4770070110

Nurnberger, J. I., Adkins, S., Lahiri, D. K., Mayeda, A., Hu, K., Lewy, A., … Davis-Singh, D. (2000). Melatonin suppression by light in euthymic bipolar and unipolar patients. *Archives of General Psychiatry*, *57*(6), 572–579. https://doi.org/10.1001/archpsyc.57.6.572

Oliver, M. N. I., & Simons, J. S. (2004). The affective lability scales: Development of a short-form measure. *Personality and Individual Differences*, *37*(6), 1279–1288. https://doi.org/10.1016/j.paid.2003.12.013

Öngür, D., Lundy, M., Greenhouse, I., Shinn, A. K., Menon, V., Cohen, B. M., & Renshaw, P. F. (2010). Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Research - Neuroimaging*, *183*(1), 59–68. https://doi.org/10.1016/j.pscychresns.2010.04.008

Onton, J., & Makeig, S. (2006). Chapter 7 Information-based modeling of event-related brain dynamics. *Progress in Brain Research*, Vol. 159, pp. 99–120. https://doi.org/10.1016/S0079-6123(06)59007-7

Panchal, P., Kaltenboeck, A., & Harmer, C. J. (2019). Cognitive emotional processing across mood disorders. *CNS Spectrums*, *24*(1), 54–63. https://doi.org/10.1017/S109285291800130X

Parker, G., Austin, M. P., Mitchell, P., Wilhelm, K., Boyce, P., & Eyers, K. (1995). Sub-Typing Depression, I. Is Psychomotor Disturbance Necessary and Sufficient to the Definition of Melancholia? *Psychological Medicine*, *25*(4), 815–

823. https://doi.org/10.1017/S0033291700035066

Patel, R., Lloyd, T., Jackson, R., Ball, M., Shetty, H., Broadbent, M., … Taylor, M. (2015). Mood instability is a common feature of mental health disorders and is associated with poor clinical outcomes. *BMJ Open*, *5*(5), e007504. https://doi.org/10.1136/bmjopen-2014-007504

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*(6), 768–774. https://doi.org/10.1002/1097-4679(199511)51:6<768::AID-JCLP2270510607>3.0.CO;2-1

Peeters, F., Berkhof, J., Delespaul, P., Rottenberg, J., & Nicolson, N. A. (2006). Diurnal mood variation in major depressive disorder. *Emotion*, *6*(3), 383–391. https://doi.org/10.1037/1528-3542.6.3.383

Perlman, S. B., Fournier, J. C., Bebko, G., Bertocci, M. A., Hinze, A. K., Bonar, L., … Phillips, M. L. (2013). Emotional face processing in pediatric bipolar disorder: Evidence for functional impairments in the fusiform gyrus. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*(12), 1314-1325.e3. https://doi.org/10.1016/j.jaac.2013.09.004

Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: from a “low road” to “many roads” of evaluating biological significance. *Nature Reviews. Neuroscience*, *11*(11), 773–783. https://doi.org/10.1038/nrn2920

Pinho, M., Sehmbi, M., Cudney, L. E., Kauer-Sant’anna, M., Magalhães, P. V., Reinares, M., … Rosa, A. R. (2016). The association between biological rhythms, depression, and functioning in bipolar disorder: A large multi-center study. *Acta Psychiatrica Scandinavica*, *133*(2), 102–108. https://doi.org/10.1111/acps.12442

Pizzagalli, D. A., Goetz, E., Ostacher, M., Iosifescu, D. V., & Perlis, R. H. (2008). Euthymic Patients with Bipolar Disorder Show Decreased Reward Learning in a Probabilistic Reward Task. *Biological Psychiatry*, *64*(2), 162–168. https://doi.org/10.1016/j.biopsych.2007.12.001

Pizzagalli, D. A., Iosifescu, D., Hallett, L. A., Ratner, K. G., & Fava, M. (2008). Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. *Journal of Psychiatric Research*, *43*(1), 76–87. https://doi.org/10.1016/j.jpsychires.2008.03.001

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2013, August 1). Steps toward optimizing motion artifact removal in functional connectivity MRI; a reply to Carp. *NeuroImage*, Vol. 76, pp. 439–441. https://doi.org/10.1016/j.neuroimage.2012.03.017

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048

Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology*, *35*(1), 192–216. https://doi.org/10.1038/npp.2009.104

Price, J. L., & Drevets, W. C. (2012). Neural circuits underlying the pathophysiology of mood disorders. *Trends in Cognitive Sciences*, *16*(1), 61–71.

https://doi.org/10.1016/j.tics.2011.12.011

R Core Team. (2013). *R: A language and environment for statistical computing*. Retrieved from http://www.r-project.org

Rashid, B., Damaraju, E., Pearlson, G. D., & Calhoun, V. D. (2014). Dynamic connectivity states estimated from resting fMRI Identify differences among Schizophrenia, bipolar disorder, and healthy control subjects. *Frontiers in Human Neuroscience*, *8*(November). https://doi.org/10.3389/fnhum.2014.00897

Regier, D. A., Rae, D. S., Narrow, W. E., Kaelber, C. T., & Schatzberg, A. F. (1998). Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. *British Journal of Psychiatry*, *173*(JULY SUPPL. 34), 24–28. https://doi.org/10.1192/s0007125000293483

Reppert, S. M., & Weaver, D. R. (2001). Molecular Analysis of Mammalian Circadian Rhythms. *Annual Review of Physiology*, *63*(1), 647–676. https://doi.org/10.1146/annurev.physiol.63.1.647

Roberson-Nay, R., McClure, E. B., Monk, C. S., Nelson, E. E., Guyer, A. E., Fromm, S. J., … Pine, D. S. (2006). Increased amygdala activity during successful memory encoding in adolescent major depressive disorder: An FMRI study. *Biological Psychiatry*, *60*(9), 966–973. https://doi.org/10.1016/j.biopsych.2006.02.018

Robillard, R., Hermens, D. F., Naismith, S. L., White, D., Rogers, N. L., Ip, T. K. C., … Hickie, I. B. (2014). Ambulatory sleep-wake patterns and variability in young people with emerging mental disorders. *Journal of Psychiatry & Neuroscience : JPN*, *39*(5), 130247. https://doi.org/10.1503/jpn.130247

Robillard, R., Naismith, S. L., Rogers, N. L., Ip, T. K. C., Hermens, D. F., Scott, E. M., & Hickie, I. B. (2013). Delayed sleep phase in young people with unipolar or

bipolar affective disorders. *Journal of Affective Disorders*, *145*(2), 260–263. https://doi.org/10.1016/j.jad.2012.06.006

Rock, P., Goodwin, G., Harmer, C., & Wulff, K. (2014). Daily rest-activity patterns in the bipolar phenotype: A controlled actigraphy study. *Chronobiology International*, *31*(2), 290–296. https://doi.org/10.3109/07420528.2013.843542

Roiser, J. P., Cannon, D. M., Gandhi, S. K., Taylor Tavares, J., Erickson, K., Wood, S., … Drevets, W. C. (2009). Hot and cold cognition in unmedicated depressed subjects with bipolar disorder. *Bipolar Disorders*, *11*(2), 178–189. https://doi.org/10.1111/j.1399-5618.2009.00669.x

Roiser, J., & Sahakian, B. J. (2016). Information Processing in Mood Disorders. In R. J. DeRubeis & D. R. Strunk (Eds.), *The Oxford Handbook of Mood Disorders*. https://doi.org/10.1093/oxfordhb/9780199973965.013.16

Rosenthal, N. E., Sack, D. A., Gillin, J. C., Lewy, A. J., Goodwin, F. K., Davenport, Y., … Wehr, T. A. (1984). Seasonal Affective Disorder: A Description of the Syndrome and Preliminary Findings With Light Therapy. *Archives of General Psychiatry*, *41*(1), 72–80. https://doi.org/10.1001/archpsyc.1984.01790120076010

Rottenberg, J., Gross, J. J., & Gotlib, I. H. (2005). Emotion context insensitivity in major depressive disorder. *Journal of Abnormal Psychology*, *114*(4), 627–639. https://doi.org/10.1037/0021-843X.114.4.627

Rubinsztein, J. S., Michael, a, Paykel, E. S., & Sahakian, B. J. (2000). Cognitive impairment in remission in bipolar affective disorder. *Psychol Med*, *30*(5), 1025–1036. https://doi.org/10.1017/S0033291799002664

Rush, A. J., Giles, D. E., & Schlesser, M. A. (1996). The inventory of depressive symptomatology (IDS): Preliminary findings. *Psychopharmacology Bulletin*,

22(3), 985–990.

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., … Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive. *Depression*, *54*(5), 573–583. https://doi.org/10.1016/S0006-3223(03)01866-8

Sachs, G. S. (1996). Bipolar Mood Disorder: Practical Strategies for Acute and Maintenance Phase Treatment. *Journal of Clinical Psychopharmacology*, *16*(2 SUPPL. 1). https://doi.org/10.1097/00004714-199604001-00005

Sakoğlu, Ü., Pearlson, G. D., Kiehl, K. A., Wang, Y. M., Michael, A. M., & Calhoun, V. D. (2010). A method for evaluating dynamic functional network connectivity and task-modulation: Application to schizophrenia. *Magnetic Resonance Materials in Physics, Biology and Medicine*, *23*(5–6), 351–366. https://doi.org/10.1007/s10334-010-0197-8

Sapolsky, R. M. (2001, October 23). Depression, antidepressants, and the shrinking hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 98, pp. 12320–12322. https://doi.org/10.1073/pnas.231475998

Sarason, I. G., Johnson, J. H., & Siegel, J. M. (1978). Assessing the impact of life changes: Development of the Life Experiences Survey. *Journal of Consulting and Clinical Psychology*, *46*(5), 932–946. https://doi.org/10.1037/0022-006X.46.5.932

Saunders, K. E.A., Bilderbeck, A. C., Panchal, P., Atkinson, L. Z., Geddes, J. R., & Goodwin, G. M. (2017). Experiences of remote mood and activity monitoring in bipolar disorder: A qualitative study. *European Psychiatry*, *41*, 115–121. https://doi.org/10.1016/j.eurpsy.2016.11.005

Saunders, Kate E. A., Cipriani, A., Rendell, J., Attenburrow, M.-J., Nelissen, N.,

Bilderbeck, A. C., … Lyons, T. (2016). Oxford Lithium Trial (OxLith) of the early affective, cognitive, neural and biochemical effects of lithium carbonate in bipolar disorder: study protocol for a randomised controlled trial. *Trials*, *17*(1), 116. https://doi.org/10.1186/s13063-016-1230-7

Saunders, Kate E.A., Cipriani, A., Rendell, J., Attenburrow, M. J., Nelissen, N., Bilderbeck, A. C., … Geddes, J. R. (2016). Oxford Lithium Trial (OxLith) of the early affective, cognitive, neural and biochemical effects of lithium carbonate in bipolar disorder: Study protocol for a randomised controlled trial. *Trials*, *17*(1), 116. https://doi.org/10.1186/s13063-016-1230-7

Scammell, T. E., Arrigoni, E., & Lipton, J. O. (2017, February 22). Neural Circuitry of Wakefulness and Sleep. *Neuron*, Vol. 93, pp. 747–765. https://doi.org/10.1016/j.neuron.2017.01.014

Schmaal, L., Veltman, D. J., Van Erp, T. G. M., Smann, P. G., Frodl, T., Jahanshad, N., … Hibar, D. P. (2016). Subcortical brain alterations in major depressive disorder: Findings from the ENIGMA Major Depressive Disorder working group. *Molecular Psychiatry*, *21*(6), 806–812. https://doi.org/10.1038/mp.2015.69

School, H. M. (2007). *National Comorbidity Survey (NCS)*. Retrieved from https://www.hcp.med.harvard.edu/ncs/index.php

Scott, J., & Colom, F. (2008). Gaps and Limitations of Psychological Interventions for Bipolar Disorders. *Psychotherapy and Psychosomatics*, *77*(1), 4–11. https://doi.org/10.1159/000110054

Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. *Frontiers in Public Health*, *5*(September), 1–17. https://doi.org/10.3389/fpubh.2017.00258

Sheline, Y. I. (2011, August 15). Depression and the hippocampus: Cause or effect?

Biological Psychiatry, Vol. 70, pp. 308–309. https://doi.org/10.1016/j.biopsych.2011.06.006

Shen, K., Hutchison, R. M., Bezgin, G., Gati, J. S., Menon, R. S., Everling, S., & McIntosh, A. R. (2013). Resting-state functional connectivity dynamics are influenced by network structure. *Canadian Association for Neuroscience AnnualMeeting.*

Shirayama, M., Shirayama, Y., Iida, H., Kato, M., Kajimura, N., Watanabe, T., … Takahashi, K. (2003). The psychological aspects of patients with delayed sleep phase syndrome (DSPS). *Sleep Medicine*, *4*(5), 427–433. https://doi.org/10.1016/S1389-9457(03)00101-1

Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2012). Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cerebral Cortex*, *22*(1), 158–165. https://doi.org/10.1093/cercor/bhr099

Simon, J., Budge, K., Price, J., Goodwin, G. M., & Geddes, J. R. (2017). Remote mood monitoring for adults with bipolar disorder: An explorative study of compliance and impact on mental health service use and costs. *European Psychiatry*. https://doi.org/10.1016/j.eurpsy.2017.06.007

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062

Smith, S. M., Fox, P. T. M., Miller, K. L., Glahn, D. C., Fox, P. T. M., Mackay, C. E., … Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(31), 13040–13045. https://doi.org/10.1073/pnas.0905267106

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J.,

Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(SUPPL. 1). https://doi.org/10.1016/j.neuroimage.2004.07.051

Sole, B., Bonnin, C. M., Torrent, C., Martinez-Aran, A., Popovic, D., Tabarés-Seisdedos, R., & Vieta, E. (2012). Neurocognitive Impairment Across the Bipolar Spectrum. *CNS Neuroscience and Therapeutics*, *18*(3), 194–200. https://doi.org/10.1111/j.1755-5949.2011.00262.x

Solhan, M. B., Trull, T. J., Jahng, S., & Wood, P. K. (2009). Clinical Assessment of Affective Instability: Compating EMA indices, questionnaire reports, and retrospective recall. *Psychol Assessment*, *21*(3), 425–436. https://doi.org/10.1037/a0016869.Clinical

Sormaz, M., Murphy, C., Wang, H. T., Hymers, M., Karapanagiotidis, T., Poerio, G., … Smallwood, J. (2018). Default mode network can support the level of detail in experience during active task states. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(37), 9318–9323. https://doi.org/10.1073/pnas.1721259115

Souetre, E., Salvati, E., Wehr, T. A., Sack, D. A., Krebs, B., & Darcourt, G. (1988). Twenty-four-hour profiles of body temperature and plasma TSH in bipolar patients during depression and during remission and in normal control subjects. *American Journal of Psychiatry*, *145*(9), 1133–1137. https://doi.org/10.1176/ajp.145.9.1133

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Lo, B. (2006). A Brief Measure for Assessing Generalized Anxiety Disorder. *JAMA Internal Medicine*, *166*(10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092.ABSTRACT

Steele, J. D., Kumar, P., & Ebmeier, K. P. (2007). Blunted response to feedback

information in depressive illness. *Brain*, *130*(9), 2367–2374. https://doi.org/10.1093/brain/awm150

Strakowski, S M, Delbello, M. P., & Adler, C. M. (2005). *The functional neuroanatomy of bipolar disorder : a review of neuroimaging findings*. (August 2003), 105–116. https://doi.org/10.1038/sj.mp.4001585

Strakowski, Stephen M, Adler, C. M., & DelBello, M. P. (2002). Volumetric MRI studies of mood disorders: do they distinguish unipolar and bipolar disorder? *Bipolar Disorders*, *4*(2), 80–88.

Stringaris, A., Cohen, P., Pine, D. S., & Leibenluft, E. (2009). Adult outcomes of youth irritability: A 20-year prospective community-based study. *American Journal of Psychiatry*, *166*(9), 1048–1054. https://doi.org/10.1176/appi.ajp.2009.08121849

Syan, S. K., Smith, M., Frey, B. N., Remtulla, R., Kapczinski, F., Hall, G. B. C., & Minuzzi, L. (2018). Resting-state functional connectivity in individuals with bipolar disorder during clinical remission: A systematic review. *Journal of Psychiatry and Neuroscience*, *43*(5), 298–316. https://doi.org/10.1503/jpn.170175

Sylvia, L. G., Dupuy, J. M., Ostacher, M. J., Cowperthwait, C. M., Hay, A. C., Sachs, G. S., … Perlis, R. H. (2012). Sleep disturbance in euthymic bipolar patients. *Journal of Psychopharmacology*, *26*(8), 1108–1112. https://doi.org/10.1177/0269881111421973

Taquet, M. (2020). The connectivity fingerprint of the posterior insula is specifically associated with the digital phenotype of mood instability. *In Prep*.

The MathWorks Inc. (2010). *MATLAB*. Natick, Massachusetts.

Thoma, P., Norra, C., Juckel, G., Suchan, B., & Bellebaum, C. (2015). Performance

monitoring and empathy during active and observational learning in patients with major depression. *Biological Psychology*, *109*, 222–231. https://doi.org/10.1016/j.biopsycho.2015.06.002

Thompson, E. R. (2007). Development and Validation of an Internationally Reliable Short-Form of the Positive and Negative Affect Schedule (PANAS). *Journal of Cross-Cultural Psychology*, *38*(2), 227–242. https://doi.org/10.1177/0022022106297301

Thompson, P. M., Stein, J. L., Medland, S. E., Hibar, D. P., Vasquez, A. A., Renteria, M. E., … Drevets, W. (2014). The ENIGMA Consortium: Large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging and Behavior*, *8*(2), 153–182. https://doi.org/10.1007/s11682-013-9269-5

Thompson, R. J., Berenbaum, H., & Bredemeier, K. (2011). Cross-sectional and longitudinal relations between affective instability and depression. *Journal of Affective Disorders*, *130*(1–2), 53–59. https://doi.org/10.1016/j.jad.2010.09.021

Thorberg, F. A., & Lyvers, M. (2006). Negative Mood Regulation (NMR) expectancies, mood, and affect intensity among clients in substance disorder treatment facilities. *Addictive Behaviors*, *31*(5), 811–820. https://doi.org/10.1016/j.addbeh.2005.06.008

Treadway, M. T., & Zald, D. H. (2011, January 1). Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neuroscience and Biobehavioral Reviews*, Vol. 35, pp. 537–555. https://doi.org/10.1016/j.neubiorev.2010.06.006

True Colours Team Department of Psychiatry University of Oxford. (n.d.). *True Colours - self-management system*. Retrieved from https://www.truecolours.nhs.uk/www/

Trull, T. J., Solhan, M. B., Tragesser, S. L., Jahng, S., Wood, P. K., Piasecki, T. M., & Watson, D. (2008). Affective Instability: Measuring a Core Feature of Borderline Personality Disorder With Ecological Momentary Assessment. *Journal of Abnormal Psychology*, *117*(3), 647–661. https://doi.org/10.1037/a0012532

Uher, R., & Rutter, M. (2012). Basing psychiatric classification on scientific foundation: problems and prospects. *International Review of Psychiatry (Abingdon, England)*, *24*(6), 591–605. https://doi.org/10.3109/09540261.2012.721346

Van Den Heuvel, M. P., & Pol, H. E. H. (2011, January 1). Exploring the brain network: A review on resting-state fMRI functional connectivity. *Psiquiatria Biologica*, Vol. 18, pp. 28–41. https://doi.org/10.1016/j.psiq.2011.05.001

Van Hees, V. T., Fang, Z., Langford, J., Assah, F., Mohammad, A., Da Silva, I. C. M., … Brage, S. (2014). Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: An evaluation on four continents. *Journal of Applied Physiology*, *117*(7), 738–744. https://doi.org/10.1152/japplphysiol.00421.2014

van Hees, V. T., Gorzelniak, L., Dean León, E. C., Eder, M., Pias, M., Taherian, S., … Brage, S. (2013). Separating Movement and Gravity Components in an Acceleration Signal and Implications for the Assessment of Human Daily Physical Activity. *PLoS ONE*, *8*(4), e61691. https://doi.org/10.1371/journal.pone.0061691

van Praag, H. M. (1999). The impact of classification on psychopharmacology and biological psychiatry. *Dialogues in Clinical Neuroscience*, *1*(3), 141–151. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22034250

Van Someren, E. J. W., Swaab, D. F., Colenda, C. C., Cohen, W., McCall, W. V., & Rosenquist, P. B. (1999). Bright light therapy: Improved sensitivity to its effects on rest- activity rhythms in Alzheimer patients by application of nonparametric methods. *Chronobiology International*, *16*(4), 505–518. https://doi.org/10.3109/07420529908998724

Vargas, C., López-Jaramillo, C., & Vieta, E. (2013, September 25). A systematic literature review of resting state network-functional MRI in bipolar disorder. *Journal of Affective Disorders*, Vol. 150, pp. 727–735. https://doi.org/10.1016/j.jad.2013.05.083

Vaskinn, A., Sundet, K., Friis, S., Simonsen, C., Birkenæs, A. B., Engh, J. A., … Andreassen, O. A. (2007). The effect of gender on emotion perception in schizophrenia and bipolar disorder. *Acta Psychiatrica Scandinavica*, *116*(4), 263–270. https://doi.org/10.1111/j.1600-0447.2007.00991.x

Venn, H. R., Gray, J. M., Montagne, B., Murray, L. K., Michael Burt, D., Frigerio, E., … Young, A. H. (2004). Perception of facial expressions of emotion in bipolar disorder. *Bipolar Disord*, *6*(4), 286–293. https://doi.org/10.1111/j.1399-5618.2004.00121.x

von Neumann, J., Kent, R. H., Bellinson, H. R., & Hart, B. I. (1941). The Mean Square Successive Difference. *The Annals of Mathematical Statistics*, *12*(2), 153–162. https://doi.org/10.1214/aoms/1177731746

Wagner, V., Muller, J. L., Sommer, M., Klein, H. E., & Hajak, G. (2004). [Changes in the emotional processing in depressive patients: a study with functional magnetoresonance tomography under the employment of pictures with affective contents]. *Psychiatrische Praxis*, *31 Suppl 1*, S70-2. https://doi.org/10.1055/s-2004-828410

Wang, L., Hermens, D. F., Hickie, I. B., & Lagopoulos, J. (2012, December 15). A systematic review of resting-state functional-MRI studies in major depression. *Journal of Affective Disorders*, Vol. 142, pp. 6–12. https://doi.org/10.1016/j.jad.2012.04.013

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology*, *54*(6), 1063–1070. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3397865

Williamson, P. C., & Allman, J. M. (2012, June 21). A framework for interpreting functional networks in schizophrenia. *Frontiers in Human Neuroscience*, Vol. 6, p. 184. https://doi.org/10.3389/fnhum.2012.00184

Wolfe, J., Granholm, E., Butters, N., Saunders, E., & Janowsky, D. (1987). Verbal memory deficits associated with major affective disorders: a comparison of unipolar and bipolar patients. *Journal of Affective Disorders*, *13*(1), 83–92. https://doi.org/10.1016/0165-0327(87)90077-2

Woolrich, M. (2008). Robust group analysis using outlier inference. *NeuroImage*, *41*(2), 286–301. https://doi.org/10.1016/j.neuroimage.2008.02.042

Woolrich, M. W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., … Smith, S. M. (2009). Bayesian analysis of neuroimaging data in FSL. *NeuroImage*, *45*(1 Suppl). https://doi.org/10.1016/j.neuroimage.2008.10.055

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. *NeuroImage*, *14*(6), 1370–1386. https://doi.org/10.1006/nimg.2001.0931

Wu, J. C., & Bunney, W. E. (1990, January). The biological basis of an antidepressant response to sleep deprivation and relapse: Review and

hypothesis. *American Journal of Psychiatry*, Vol. 147, pp. 14–21. https://doi.org/10.1176/ajp.147.1.14

Yan, C., Liu, D., He, Y., Zou, Q., Zhu, C., Zuo, X., … Zang, Y. (2009). Spontaneous brain activity in the default mode network is sensitive to different resting-state conditions with limited cognitive load. *PLoS ONE*, *4*(5). https://doi.org/10.1371/journal.pone.0005743

Yatham, L. N., Kennedy, S. H., O'donovan, C., Parikh, S. V., Macqueen, G., Mclntyre, R. S., … Gorman, C. P. (2006). Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: Update 2007. *Bipolar Disorders*, *8*(6), 721–739. https://doi.org/10.1111/j.1399-5618.2006.00432.x

Yong, H. H. (2006). Can attitudes of stoicism and cautiousness explain observed age-related variation in levels of self-rated pain, mood disturbance and functional interference in chronic pain patients? *European Journal of Pain*, *10*(5), 399. https://doi.org/10.1016/j.ejpain.2005.05.004

Yu, Q., A. Allen, E., Sui, J., R. Arbabshirani, M., Pearlson, G., & D. Calhoun, V. (2013). Brain Connectivity Networks in Schizophrenia Underlying Resting State Functional Magnetic Resonance Imaging. *Current Topics in Medicinal Chemistry*, *12*(21), 2415–2425. https://doi.org/10.2174/1568026611212210012

Zanarini, M. C., Vujanovic, A. A., Parachini, E. A., Boulanger, J. L., Frankenburg, F. R., & Hennen, J. (2003). A screening measure for BPD: the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). *Journal of Personality Disorders*, *17*(6), 568–573. Retrieved from http://search.proquest.com/docview/71511305?accountid=13042

Zuo, X. N., & Xing, X. X. (2014, September 1). Test-retest reliabilities of resting-state

FMRI measurements in human brain functional connectomics: A systems neuroscience perspective. *Neuroscience and Biobehavioral Reviews*, Vol. 45, pp. 100–118. https://doi.org/10.1016/j.neubiorev.2014.05.009

Appendix

2.1 MDQ Questionnaire

STABLE RESOURCE TOOLKIT

Mood Disorder Questionnaire

Patient Name _____ Date of Visit _____

Please answer each question to the best of your ability

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

This instrument is designed for screening purposes only and not to be used as a diagnostic tool.
Permission for use granted by RMA Hirschfeld, MD

Figure 55: Mood Disorder Questionnaire.

2.2 COMET Study Flow Chart

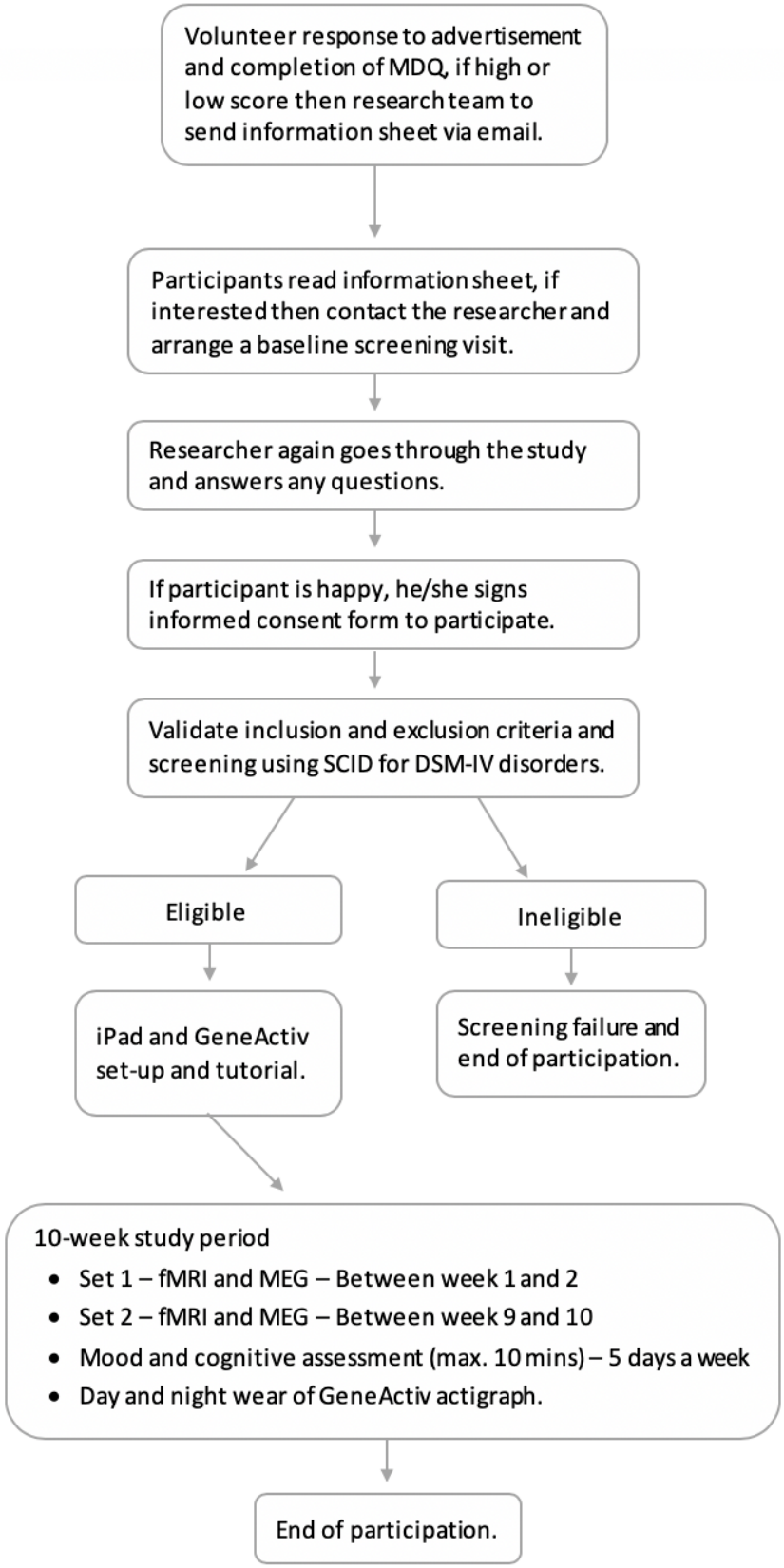


Figure 56: COMET study flow chart.

2.3 Screening Questionnaires

2.3.1 AIM

DIRECTIONS: The following questions refer to emotional reactions to typical life-events. Please indicate how YOU react to these events by placing a number from the following scale in the blank space preceding each item. Please base your answers on how YOU react, not on how you think others react or how you think a person should react.

NEVER	ALMOST NEVER	OCCASIONALLY	USUALLY	ALWAYS	ALMOST ALWAYS
1	2	3	4	5	6

1. _____ When I accomplish something difficult I feel delighted or elated.
2. _____ When I feel happy it is a strong type of exuberance.
3. _____ I enjoy being with other people very much.
4. _____ I feel pretty bad when I tell a lie.
5. _____ When I solve a small personal problem, I feel euphoric.
6. _____ My emotions tend to be more intense than those of most people.
7. _____ My happy moods are so strong that I feel like I'm in heaven.
8. _____ I get overly enthusiastic.
9. _____ If I complete a task I thought was impossible, I am ecstatic.
10. _____ My heart races at the anticipation of some exciting event.
11. _____ Sad movies deeply touch me.
12. _____ When I'm happy it's a feeling of being untroubled and content rather than being zestful and aroused.
13. _____ When I talk in front of a group for the first time my voice gets shaky and my heart races.
14. _____ When something good happens, I'm usually much more jubilant than others.
15. _____ My friends might say I'm emotional.
16. _____ The memories I like the most are of those times when I felt content and peaceful rather than zestful and enthusiastic.
17. _____ The sight of someone who is hurt badly affects me strongly.
18. _____ When I'm feeling well it's easy for me to go from being in a good mood to being really joyful.
19. _____ "Calm and cool" could easily describe me.
20. _____ When I'm happy I feel like I'm bursting with joy.
21. _____ Seeing a picture of some violent car accident in a newspaper makes me feel sick to my stomach.

NEVER	ALMOST NEVER	OCCASIONALLY	USUALLY	ALMOST ALWAYS	ALWAYS
1	2	3	4	5	6

22. _____ When I'm happy I feel very energetic.

23. _____ When I receive a reward I become overjoyed.

24. _____ When I succeed at something, my reaction is calm and contentment.

25. _____ When I do something wrong I have strong feelings of shame and guilt.

26. _____ I can remain calm even on the most trying days.

27. _____ When things are going good I feel 'on top of the world'.

28. _____ When I get angry it's easy for me to still be rational and not overreact.

29. _____ When I know I have done something very well, I feel relaxed and content rather than excited and elated.

30. _____ When I do feel anxiety it is normally very strong.

31. _____ My negative moods are mild in intensity.

32. _____ When I am excited over something I want to share my feelings with everyone.

33. _____ When I feel happiness, it is a quiet type of contentment.

34. _____ My friends would probably say I'm a tense or 'high-strung' person.

35. _____ When I'm happy I bubble over with energy.

36. _____ When I feel guilty, this emotion is quite strong.

37. _____ I would characterize my happy moods as closer to contentment than joy.

38. _____ When someone compliments me, I get so happy I could 'burst'.

39. _____ When I am nervous I get shaky all over.

40. _____ When I am happy the feeling is more like contentment and inner calm than one of exhilaration and excitement.

Figure 57: Affect Intensity Measure.

2.3.2 ALS-SF

1. At times I feel just as relaxed as everyone else and then within minutes I become so nervous that I feel light-headed and dizzy.
2. There are times when I have very little energy and then just afterwards I have about the same energy level as most people.
3. One minute I can be feeling OK and then the next minute I'm tense, jittery, and nervous.
4. I frequently switch from being able to control my temper very well to not being able to control it very well at all.
5. Many times I feel nervous and tense and then I suddenly feel very sad and down.
6. Sometimes I go from feeling extremely anxious about something to feeling very down about it.
7. I shift back and forth from feeling perfectly calm to feeling uptight and nervous.
8. There are times when I feel perfectly calm one minute and then the next minute the least little thing makes me furious.
9. Frequently, I will be feeling OK but then I suddenly get so mad that I could hit something.
10. Sometimes I can think clearly and concentrate well one minute and then the next minute I have a great deal of difficulty concentrating and thinking clearly.
11. There are times when I am so mad that I can barely stop yelling and other times shortly afterwards when I wouldn't think of yelling at all.
12. I switch back and forth between being extremely energetic and having so little energy that it's a huge effort just to get where I am going.
13. There are times when I feel absolutely wonderful about myself but soon afterwards I often feel that I am just about the same as everyone else.
14. There are times when I'm so mad that my heart starts pounding and/or I start shaking and then shortly afterwards I feel quite relaxed.
15. I shift back and forth between being very unproductive and being just as productive as everyone else.
16. Sometimes I feel extremely energetic one minute and then the next minute I might have so little energy that I can barely do a thing.
17. There are times when I have more energy than usual and more than most people and then soon afterwards I have about the same energy level as everyone else.
18. At times I feel that I'm doing everything at a very slow pace but then soon afterwards I feel that I'm no more slowed down than anyone else.

Figure 58: Affective Lability Scale – Short Form.

2.3.3 BIS-II

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

① Rarely/Never ② Occasionally ③ Often ④ Almost Always/Always

1	I plan tasks carefully.	①	②	③	④
2	I do things without thinking.	①	②	③	④
3	I make-up my mind quickly.	①	②	③	④
4	I am happy-go-lucky.	①	②	③	④
5	I don't "pay attention."	①	②	③	④
6	I have "racing" thoughts.	①	②	③	④
7	I plan trips well ahead of time.	①	②	③	④
8	I am self controlled.	①	②	③	④
9	I concentrate easily.	①	②	③	④
10	I save regularly.	①	②	③	④
11	I "squirm" at plays or lectures.	①	②	③	④
12	I am a careful thinker.	①	②	③	④
13	I plan for job security.	①	②	③	④
14	I say things without thinking.	①	②	③	④
15	I like to think about complex problems.	①	②	③	④
16	I change jobs.	①	②	③	④
17	I act "on impulse."	①	②	③	④
18	I get easily bored when solving thought problems.	①	②	③	④
19	I act on the spur of the moment.	①	②	③	④
20	I am a steady thinker.	①	②	③	④
21	I change residences.	①	②	③	④
22	I buy things on impulse.	①	②	③	④
23	I can only think about one thing at a time.	①	②	③	④
24	I change hobbies.	①	②	③	④
25	I spend or charge more than I earn.	①	②	③	④
26	I often have extraneous thoughts when thinking.	①	②	③	④
27	I am more interested in the present than the future.	①	②	③	④
28	I am restless at the theater or lectures.	①	②	③	④
29	I like puzzles.	①	②	③	④
30	I am future oriented.	①	②	③	④

Figure 59: Barratt Impulsiveness Scale.

2.3.4 SCI-R

Sleep Condition Indicator

Instructions:

Name _____, Student ID _____

1. Read the items carefully.
2. Circle the most accurate of the five responses given for each item.
3. After completing all nine items, sum up your total score and enter it here. Total Score _____.

	Score	Score	Score	Score	Score
Item	4	3	2	1	0
Thinking about a typical night in the last month . . .					
1. . . . how long does it take you to fall asleep?	0-15 min	16-30 min	31-45 min	46-60 min	>60 min
2. . . . if you then wake up during the night, how long are you awake for in total? *(add up all the wakenings)*	0-15 min	16-30 min	31-45 min	46-60 min	>60 min
3. . . . if your final wake up time occurs before you intend to wake up, how much earlier is this?	I don't wake up too early/Up to 15 min early	16-30 min early	31-45 min early	46-60 min early	>60 min early
4. . . . how many nights a week do you have a problem with your sleep?	0-1	2	3	4	5-7
5. . . . how would you rate your sleep quality?	Very good	Good	Average	Poor	Very poor
Thinking about the past month, to what extent has poor sleep . . .					
6. . . . affected your mood, energy or relationships?	Not at all	A little	Somewhat	Much	Very much
7. . . . affected your concentration, productivity, or ability to stay awake?	Not at all	A little	Somewhat	Much	Very much
8. . . . troubled you in general?	Not at all	A little	Somewhat	Much	Very much
Finally . . .					
9. . . . how long have you had a problem with your sleep?	I don't have a problem/ < 1 month	1-2 months	3-6 months	7-12 months	>1 year

Figure 60: Sleep Condition Indicator – Revised.

2.3.5 McLean Screen for BPD

McLean Screening Instrument for Borderline Personality Disorder

1. Have any of your closest relationships been troubled by a lot of arguments or repeated breakups?	1 = yes 0 = no
2. Have you deliberately hurt yourself physically (e.g., (punched yourself, cut yourself, burned yourself)? How about made a suicide attempt?	1 = yes 0 = no
3. Have you had at least two other problems with impulsivity (e.g., eating binges and spending sprees, drinking too much and verbal outbursts)?	1 = yes 0 = no
4. Have you been extremely moody?	1 = yes 0 = no
5. Have you felt very angry a lot of the time? How about often acted in an angry or sarcastic manner?	1 = yes 0 = no
6. Have you often been distrustful of other people?	1 = yes 0 = no
7. Have you frequently felt unreal or as if things around you were unreal?	1 = yes 0 = no
8. Have you chronically felt empty?	1 = yes 0 = no
9. Have you often felt that you had no idea of who you are or that you have no identity?	1 = yes 0 = no
10. Have you made desperate efforts to avoid feeling abandoned or being abandoned (e.g., repeatedly called someone to reassure yourself that he or she still cared, begged them not to leave you, clung to them physically)?	1 = yes 0 = no

Figure 61: McLean Screening Instrument for Borderline Personality Disorder (BPD).

2.4 I-PANAS-SF

Figure 62: Screenshot of the I-PANAS-SF scale used on the COMET iPad testing platform.

2.5 Happiness Scale

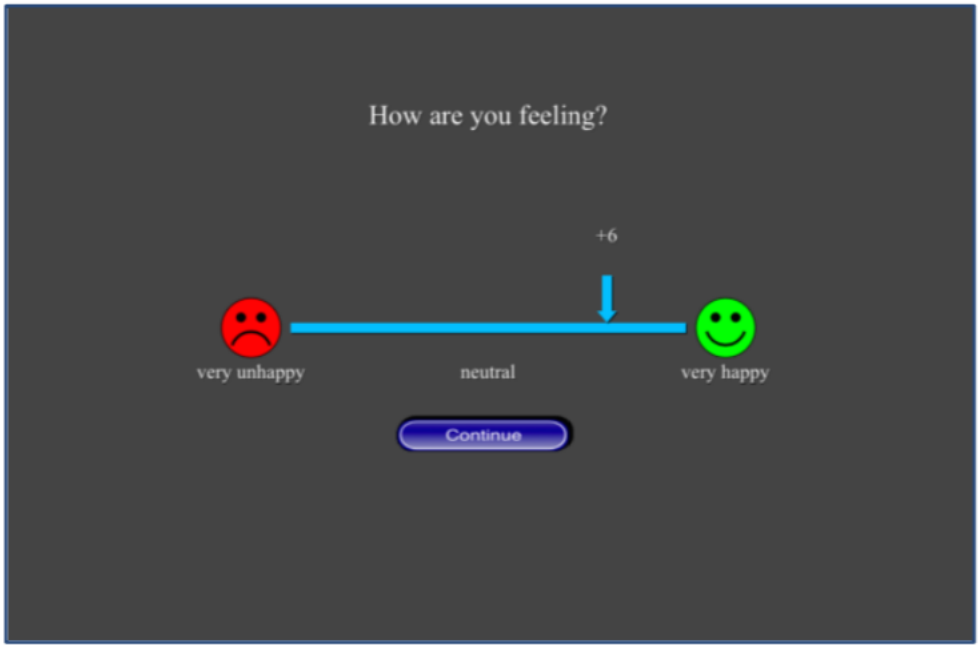
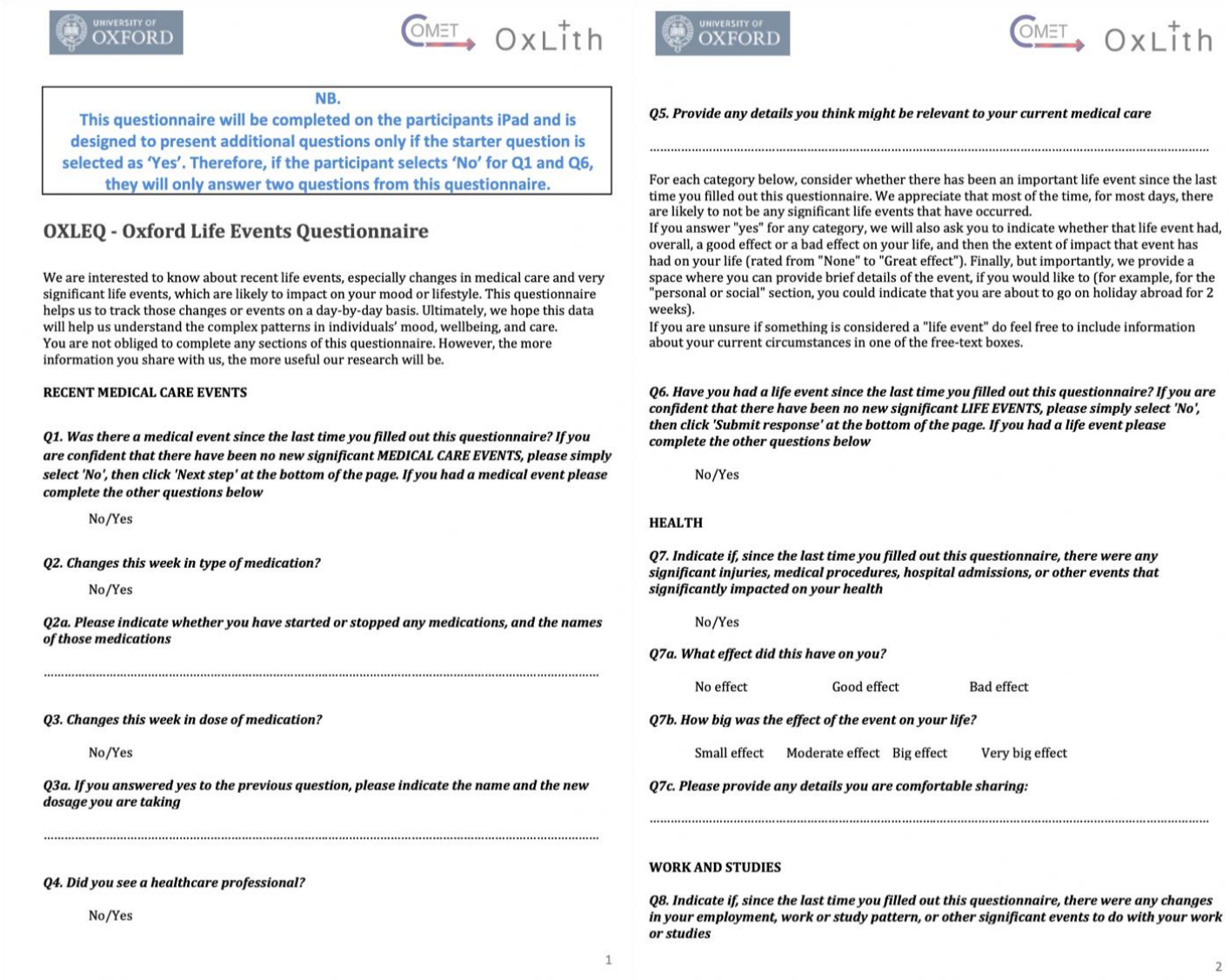


Figure 63: Screenshot of the happiness scale.

2.6 OxLeq



NB.
This questionnaire will be completed on the participants iPad and is designed to present additional questions only if the starter question is selected as 'Yes'. Therefore, if the participant selects 'No' for Q1 and Q6, they will only answer two questions from this questionnaire.

OXLEQ - Oxford Life Events Questionnaire

We are interested to know about recent life events, especially changes in medical care and very significant life events, which are likely to impact on your mood or lifestyle. This questionnaire helps us to track those changes or events on a day-by-day basis. Ultimately, we hope this data will help us understand the complex patterns in individuals' mood, wellbeing, and care.
You are not obliged to complete any sections of this questionnaire. However, the more information you share with us, the more useful our research will be.

RECENT MEDICAL CARE EVENTS

Q1. Was there a medical event since the last time you filled out this questionnaire? If you are confident that there have been no new significant MEDICAL CARE EVENTS, please simply select 'No', then click 'Next step' at the bottom of the page. If you had a medical event please complete the other questions below

No/Yes

Q2. Changes this week in type of medication?

No/Yes

Q2a. Please indicate whether you have started or stopped any medications, and the names of those medications

.....

Q3. Changes this week in dose of medication?

No/Yes

Q3a. If you answered yes to the previous question, please indicate the name and the new dosage you are taking

.....

Q4. Did you see a healthcare professional?

No/Yes

1

Q5. Provide any details you think might be relevant to your current medical care

.....

For each category below, consider whether there has been an important life event since the last time you filled out this questionnaire. We appreciate that most of the time, for most days, there are likely to not be any significant life events that have occurred.
If you answer "yes" for any category, we will also ask you to indicate whether that life event had, overall, a good effect or a bad effect on your life, and then the extent of impact that event has had on your life (rated from "None" to "Great effect"). Finally, but importantly, we provide a space where you can provide brief details of the event, if you would like to (for example, for the "personal or social" section, you could indicate that you are about to go on holiday abroad for 2 weeks).
If you are unsure if something is considered a "life event" do feel free to include information about your current circumstances in one of the free-text boxes.

Q6. Have you had a life event since the last time you filled out this questionnaire? If you are confident that there have been no new significant LIFE EVENTS, please simply select 'No', then click 'Submit response' at the bottom of the page. If you had a life event please complete the other questions below

No/Yes

HEALTH

Q7. Indicate if, since the last time you filled out this questionnaire, there were any significant injuries, medical procedures, hospital admissions, or other events that significantly impacted on your health

No/Yes

Q7a. What effect did this have on you?

No effect Good effect Bad effect

Q7b. How big was the effect of the event on your life?

Small effect Moderate effect Big effect Very big effect

Q7c. Please provide any details you are comfortable sharing:

.....

WORK AND STUDIES

Q8. Indicate if, since the last time you filled out this questionnaire, there were any changes in your employment, work or study pattern, or other significant events to do with your work or studies

2

No/Yes

Q8a. What effect did this have on you?

No effect Good effect Bad effect

Q8b. How big was the effect of the event on your life?

Small effect Moderate effect Big effect Very big effect

Q8c. Please provide any details you are comfortable sharing:

.....

RESIDENCE, AND HOUSING

Q9. Indicate if, since the last time you filled out this questionnaire, you have had a change in residence, or had other significant improvements or difficulties associated with your housing.

No/Yes

Q9a. What effect did this have on you?

No effect Good effect Bad effect

Q9b. How big was the effect of the event on your life?

Small effect Moderate effect Big effect Very big effect

Q9c. Please provide any details you are comfortable sharing:

.....

LOVE AND MARRIAGE

Q10. Indicate if, since the last time you filled out this questionnaire, you have experienced significant relationship events – such as starting a new relationship, becoming engaged, separating from a partner, changing co-habitation arrangements, pregnancy, or other events involving a romantic partner

No/Yes

Q10a. What effect did this have on you?

No effect Good effect Bad effect

Q10b. How big was the effect of the event on your life?

3

Small effect Moderate effect Big effect Very big effect

Q10c. Please provide any details you are comfortable sharing:

.....

FAMILY AND CLOSE FRIENDS

Q11. Indicate if, since the last time you filled out this questionnaire, you have experienced any significant changes related to family or close friends. Examples: as a family member moving out, change in childcare arrangements, or illness of a family member or close friend

No/Yes

Q11a. What effect did this have on you?

No effect Good effect Bad effect

Q11b. How big was the effect of the event on your life?

Small effect Moderate effect Big effect Very big effect

Q11c. Please provide any details you are comfortable sharing:

.....

OTHER PERSONAL EVENTS

Q12. Indicate if, since the last time you filled out this questionnaire, you have experienced any other significant changes, such as a major achievement, decision, change in lifestyle pattern, change in religious or political beliefs, new hobbies, or going on holiday.

No/Yes

Q12a. What effect did this have on you?

No effect Good effect Bad effect

Q12b. How big was the effect of the event on your life?

Small effect Moderate effect Big effect Very big effect

Q12c. Please provide any details you are comfortable sharing:

.....

FINANCIAL

Q13. Indicate if, *since the last time you filled out this questionnaire*, you have experienced any significant financial event or change. For example, significantly increased or

4

decreased income; making a substantial purchase (e.g. a car); taking out a mortgage; experiencing a foreclosure on a mortgage or loan.

No/Yes

Q13a. What effect did this have on you?

No effect Good effect Bad effect

Q13b. How big was the effect of the event on your life?

Small effect Moderate effect Big effect Very big effect

Q13c. Please provide any details you are comfortable sharing:

.....

Q14. The sections above are unlikely to cover all the life events that individuals experience. If you would like to, feel free to add any additional details in the space below

.....

5

Figure 64: The Oxford Life Events Questionnaire (OxLeq).

2.7 True Colours Questionnaires

2.7.1 QIDS

The Quick Inventory of Depressive Symptomatology (QIDS)

The Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SR16)

Name or ID: _____ Date: _____

CHECK THE ONE RESPONSE TO EACH ITEM THAT BEST DESCRIBES YOU FOR THE PAST SEVEN DAYS.

During the past seven days...

1. Falling Asleep:

☐ 0 I never take longer than 30 minutes to fall asleep.

☐ 1 I take at least 30 minutes to fall asleep, less than half the time.

☐ 2 I take at least 30 minutes to fall asleep, more than half the time.

☐ 3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night

☐ 0 I do not wake up at night.

☐ 1 I have a restless, light sleep with a few brief awakenings each night.

☐ 2 I wake up at least once a night, but I go back to sleep easily.

☐ 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:

☐ 0 Most of the time, I awaken no more than 30 minutes before I need to get up.

☐ 1 More than half the time, I awaken more than 30 minutes before I need to get up.

☐ 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.

☐ 3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:

☐ 0 I sleep no longer than 7-8 hours/night, without napping during the day.

☐ 1 I sleep no longer than 10 hours in a 24-hour period including naps.

☐ 2 I sleep no longer than 12 hours in a 24-hour period including naps.

☐ 3 I sleep longer than 12 hours in a 24-hour period including naps.

During the past seven days...

5. Feeling Sad:

☐ 0 I do not feel sad.

☐ 1 I feel sad less than half the time.

☐ 2 I feel sad more than half the time.

☐ 3 I feel sad nearly all of the time.

Please complete either 6 or 7 (not both)

6. Decreased Appetite:

☐ 0 There is no change in my usual appetite.

☐ 1 I eat somewhat less often or lesser amounts of food than usual.

☐ 2 I eat much less than usual and only with personal effort.

☐ 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

- OR -

7. Increased Appetite:

☐ 0 There is no change from my usual appetite.

☐ 1 I feel a need to eat more frequently than usual.

☐ 2 I regularly eat more often and/or greater amounts of food than usual.

☐ 3 I feel driven to overeat both at mealtime and between meals.

Please complete either 8 or 9 (not both)

8. Decreased Weight (Within the Last Two Weeks):

☐ 0 I have not had a change in my weight.

☐ 1 I feel as if I have had a slight weight loss.

☐ 2 I have lost 2 pounds or more.

☐ 3 I have lost 5 pounds or more.

- OR -

9. Increased Weight (Within the Last Two Weeks):

☐ 0 I have not had a change in my weight.

☐ 1 I feel as if I have had a slight weight gain.

☐ 2 I have gained 2 pounds or more.

☐ 3 I have gained 5 pounds or more.

Pg. 1 of 2

During the past seven days...

10. Concentration / Decision Making:

☐ 0 There is no change in my usual capacity to concentrate or make decisions.

☐ 1 I occasionally feel indecisive or find that my attention wanders.

☐ 2 Most of the time, I struggle to focus my attention or to make decisions.

☐ 3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:

☐ 0 I see myself as equally worthwhile and deserving as other people.

☐ 1 I am more self-blaming than usual.

☐ 2 I largely believe that I cause problems for others.

☐ 3 I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:

☐ 0 I do not think of suicide or death.

☐ 1 I feel that life is empty or wonder if it's worth living.

☐ 2 I think of suicide or death several times a week for several minutes.

☐ 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest

☐ 0 There is no change from usual in how interested I am in other people or activities.

☐ 1 I notice that I am less interested in people or activities.

☐ 2 I find I have interest in only one or two of my formerly pursued activities.

☐ 3 I have virtually no interest in formerly pursued activities.

During the past seven days...

14. Energy Level:

☐ 0 There is no change in my usual level of energy.

☐ 1 I get tired more easily than usual.

☐ 2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking, or going to work).

☐ 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling Slowed Down:

☐ 0 I think, speak, and move at my usual rate of speed.

☐ 1 I find that my thinking is slowed down or my voice sounds dull or flat.

☐ 2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.

☐ 3 I am often unable to respond to questions without extreme effort.

16. Feeling Restless:

☐ 0 I do not feel restless.

☐ 1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.

☐ 2 I have impulses to move about and am quite restless.

☐ 3 At times, I am unable to stay seated and need to pace around.

Pg. 2 of 2

Figure 65: The Quick Inventory of Depressive Symptomatology (QIDS).

2.7.2 ASRM

Altman Self-Rating Mania Scale (ASRM)

Name _____ Date _____

Instructions:

1. There are 5 statements groups on this questionnaire: read each group of statements carefully.
2. Choose the one statement in each group that best describes the way you have been feeling for the past week.
3. Check the box next to the number/statement selected.
4. Please note: The word "occasionally" when used here means once or twice; "often" means several times or more and "frequently" means most of the time.

Question 1

☐ 0 I do not feel happier or more cheerful than usual.
☐ 1 I occasionally feel happier or more cheerful than usual.
☐ 2 I often feel happier or more cheerful than usual.
☐ 3 I feel happier or more cheerful than usual most of the time.
☐ 4 I feel happier or more cheerful than usual all of the time.

Question 2

☐ 0 I do not feel more self-confident than usual.
☐ 1 I occasionally feel more self-confident than usual.
☐ 2 I often feel more self-confident than usual.
☐ 3 I feel more self-confident than usual.
☐ 4 I feel extremely self-confident all of the time.

Question 3

☐ 0 I do not need less sleep than usual.
☐ 1 I occasionally need less sleep than usual.
☐ 2 I often need less sleep than usual.
☐ 3 I frequently need less sleep than usual.
☐ 4 I can go all day and night without any sleep and still not feel tired.

Question 4

☐ 0 I do not talk more than usual
☐ 1 I occasionally talk more than usual.
☐ 2 I often talk more than usual.
☐ 3 I frequently talk more than usual.
☐ 4 I talk constantly and cannot be interrupted

Question 5

☐ 0 I have not been more active (either socially, sexually, at work, home or school) than usual.
☐ 1 I have occasionally been more active than usual.
☐ 2 I have often been more active than usual
☐ 3 I have frequently been more active than usual.
☐ 4 I am constantly active or on the go all the time.

Permission for use granted by EG Altman, MD

Figure 66: Altman Self-Rating Mania Scale (ASRM).

2.7.3 EQ-5D

EQ-5D Health Questionnaire

Client ID ☐ New User ☐ Existing User ☐

Date ☐

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care
I have no problems with self-care ☐
I have some problems with washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities*)
I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain / Discomfort
I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety / Depression
I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

Figure 67: EQ-5D Health Questionnaire.

2.7.4 GAD-7

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

Figure 68: Generalised Anxiety Disorder questionnaire (GAD-7).

2.8 iPad Cognitive Tasks

2.8.1 "Wheel of Fortune"

In this gambling decision-making task, participants were asked to pick the best out of 2 fair gambling options, with the aim of winning as many bonus points as possible. Probability was indicated by size of the segment (green for a win, red for a loss) and magnitude, or potential outcome, was shown as the number of points (positive or negative) indicated within the segments. At each trial, participants selected one of the two wheels to "gamble" on. The wheel was then randomly spun. Depending on the placement of the counter, participants were then able to see if they had won or lost points (i.e., stopping on the green or red segment) and the magnitude won or lost. A cumulative count of their points for each session was displayed at the top of the screen throughout the task. Participants completed 20 trials at each testing session.

2.8.2 "Fractals"

In this task, participants learned about reward and probabilities across time. At every testing session, participants were shown the same 5 stimuli, or fractals, with each fractal having its own unique reward magnitude and probability assigned to it. These variables were consistent across trials for each participant in order to facilitate learning across the 10-week study period. Participants were asked to pick the most rewarding fractal, in order to gain as many bonus points as possible. They were presented with a combination of the 5 fractals in order to make pairwise choices (i.e., 10 trials), followed by 5 trials of free choice where all 5 fractals appeared. When selecting a fractal during the pairwise choice stage, participants were given feedback on both fractals (selected and non-selected), again to facilitate learning.

2.8.3 "Guess the Gap"

The aim of this task was for participants to learn about integrating information about personal performance and responding to feedback. They were presented with a flashing circle followed by another and were asked to track the difference in time between flashes internally (T1), without using any external sources. Based on this time, participants were then required to predict when the next flash should occur (T2) by clicking within the circle. They received a score between 0 and 30 based on the accuracy of this prediction, across 20 trials per session.

Importantly, participants were asked to predict how well they thought they would perform (or score in terms of accuracy) before completing this task, and also rate how well they thought they performed (again, in terms of their accuracy score) after the task. Depending on how close their predicted score was to their actual score, and their latter rating to their actual score, participants could gain up to 20 bonus points (+15 for prediction, +5 for rating).

2.8.4 "Whack-a-T"

In this task, a basic contextual cueing paradigm (Chun & Jiang, 1998) was used to explore how participants learned regularities in the environment, without a reward-based context. In a series of 50 trials, participants were required to identify the one "T" amongst distracting "L" s. The "T" could be presented in any orientation. Importantly, a number of arrays were repeated within a day, or session, and also across days. Participants gained bonus points based on how accurate they were across all 50 trials.

3.1 Shapiro-Wilk tests of normality results for daily I-PANAS-SF data

		High MDQ		Low MDQ	
		W	*Sig.*	*W*	*Sig.*
Positive Affect I-PANAS-SF	*Average*	0.98	.810	0.96	.200
	SD	**0.92**	**.008****	**0.93**	**.031***
	tRMSSD	**0.94**	**.040***	**0.87**	**.001*****
Negative Affect I-PANAS-SF	*Average*	**0.91**	**.006****	**0.72**	**.000*****
	SD	0.98	.658	**0.92**	**.012****
	tRMSSD	0.97	.463	**0.86**	**.000*****

Table 45: Shapiro-Wilk tests of normality for overall daily I-PANAS-SF scores.

* $p < .05$, ** $p < .01$, *** $p < .001$

3.2 Shapiro-Wilk tests of normality results for weekly True Colours data

	High MDQ		Low MDQ	
	W	*Sig.*	*W*	*Sig.*
ASRM	**0.93**	**.020***	0.99	.877
QIDS	0.97	.353	0.99	.880
GAD-7	0.98	.780	0.98	.548

Table 46: Shapiro-Wilk tests of normality for overall weekly True Colours scores.

* $p < .05$, ** $p < .01$, *** $p < .001$

4.1 Shapiro-Wilk tests of normality results for overall rest-activity data

		High MDQ		Low MDQ	
		W	*Sig.*	*W*	*Sig.*
L_5	**Onset**	**0.84**	**.000*** **	**0.67**	**.000*** **
	Activity	**0.91**	**.012** **	**0.81**	**.000*** **
M_{10}	**Onset**	0.97	.410	0.97	.569
	Activity	**0.89**	**.003** **	0.97	.425
RA		0.95	.129	0.93	.049
IS		0.96	.330	**0.92**	**.024***
IV		0.98	.739	0.95	.137

Table 47: Shapiro-Wilk tests of normality for overall rest-activity data.

*$p < .05$, ** $p < .01$, *** $p < .001$

4.2 Rest-activity patterns and mood across time (LMMs)

4.2.1 LMM 1: L_5 activity

			L_5 activity	
			Estimate	*t*
			Average	
Mood	Average	Time	0.16	1.14
		Group	0.30	1.42
		Positive affect	-0.02	-0.27
		Time x group	-0.03	-0.34
		Time	0.15	1.10
		Group	0.31	1.45
		Negative affect	0.02	0.28
		Time x group	-0.03	-0.30
	SD	Time	0.14	1.03
		Group	0.29	1.36
		Positive affect	-0.03	-0.58
		Time x group	-0.02	-0.26
		Time	0.13	0.99
		Group	0.25	1.18
		Negative affect	-0.07	-1.31
		Time x group	-0.02	-0.21
			SD	
	Average	Time	0.14	0.89
		Group	0.02	0.11
		Positive affect	0.02	0.27
		Time x group	-0.08	-0.79
		Time	0.13	0.81
		Group	0.08	0.50
		Negative affect	0.08	1.18
		Time x group	-0.07	-0.72
	SD	Time	0.15	0.92
		Group	0.02	0.14
		Positive affect	0.01	0.24
		Time x group	-0.08	-0.82
		Time	0.16	0.99
		Group	0.05	0.34
		Negative affect	0.05	0.90
		Time x group	-0.09	-0.87

Table 48: Results of the linear mixed-effects model (LMM) for L5 activity with group by time interactions, including estimated regression coefficients together with the t-statistic.

4.2.2 LMM 1: M_{10} onset

		M_{10} onset		
			Estimate	*t*
		Average		
Mood	Average	Time	-0.09	-0.35
		Group	-0.05	-0.12
		Positive affect	-0.38	-2.71**
		Time x group	0.11	0.64
	SD	Time	-0.09	-0.33
		Group	-0.09	-0.21
		Negative affect	-0.08	-0.61
		Time x group	0.12	0.70
		Time	-0.082	-0.31
		Group	-0.00	-0.01
		Positive affect	0.05	0.49
		Time x group	0.12	0.70
		Time	-0.12	-0.45
		Group	-0.07	-0.17
		Negative affect	-0.07	-0.61
		Time x group	0.14	0.81
		SD		
	Average	Time	0.21	1.22
		Group	0.05	0.32
		Positive affect	-0.05	-0.78
		Time x group	-0.14	-1.20
	SD	Time	0.21	1.22
		Group	0.04	0.25
		Negative affect	-0.02	-0.23
		Time x group	-0.13	-1.17
		Time	0.19	1.08
		Group	0.03	0.21
		Positive affect	-0.05	-0.80
		Time x group	-0.12	-1.08
		Time	0.23	1.29
		Group	0.09	0.57
		Negative affect	0.06	0.88
		Time x group	-0.14	-1.23

Table 49: Results of the linear mixed-effects model (LMM) for M10 onset with group by time interactions, including estimated regression coefficients together with the t-statistic.

4.2.3 LMM 1: RA

		RA		
			Estimate	*t*
		Average		
Mood	Average	Time	-1.45e-03	-0.28
		Group	1.10e-02	1.21
		Positive affect	2.17e-03	0.74
		Time x group	-5.86e-04	-0.18
	SD	Time	-1.49e-03	-0.29
		Group	1.12e-02	1.21
		Negative affect	5.04e-04	0.19
		Time x group	-6.41e-04	-0.19
	Average	Time	-3.47e-04	-0.07
		Group	1.19e-02	1.30
		Positive affect	2.69e-03	1.28
		Time x group	-1.16e-03	-0.34
	SD	Time	-4.77e-04	-0.09
		Group	1.31e-02	1.43
		Negative affect	3.49e-03	1.58
		Time x group	-1.13e-03	-0.34
		SD		
	Average	Time	-3.15e-04	-0.07
		Group	-5.11e-03	-1.21
		Positive affect	-5.56e-04	-0.30
		Time x group	3.57e-04	0.13
	SD	Time	-4.40e-04	0.92
		Group	-4.66e-03	0.30
		Negative affect	5.21e-04	0.78
		Time x group	4.53e-04	0.87
	SD	Time	-3.12e-04	-0.07
		Group	-5.04e-03	-1.18
		Positive affect	8.53e-05	0.05
		Time x group	3.83e-04	0.14
	SD	Time	-3.86e-04	-0.09
		Group	-5.17e-03	-1.19
		Negative affect	-1.51e-04	-0.09
		Time x group	4.17e-04	0.15

Table 50: Results of the linear mixed-effects model (LMM) for RA with group by time interactions, including estimated regression coefficients together with the t-statistic.

4.2.4 LMM 2: M_{10} Onset

		M_{10} onset		
			Estimate	*t*
		Average		
Mood	Average	Time	0.06	0.76
		Group	-0.05	-0.13
		Positive affect	-0.07	-0.17
		Positive affect x group	-0.21	-0.75
		Time	0.08	0.94
		Group	-0.21	-0.51
		Negative affect	0.53	1.31
		Negative affect x group	-0.51	-1.61
	SD	Time	0.09	1.04
		Group	0.01	0.01
		Positive affect	-0.24	-0.76
		Positive affect x group	0.22	1.01
		Time	0.09	1.05
		Group	-0.10	-0.25
		Negative affect	0.37	1.14
		Negative affect x group	-0.33	-1.41
		SD		
	Average	Time	0.01	0.24
		Group	0.05	0.34
		Positive affect	0.12	0.54
		Positive affect x group	-0.11	-0.80
		Time	0.02	0.35
		Group	0.07	0.39
		Negative affect	-0.10	-0.46
		Negative affect x group	0.08	0.44
	SD	Time	0.01	0.15
		Group	0.03	0.23
		Positive affect	-0.13	-0.70
		Positive affect x group	0.05	0.42
		Time	0.02	0.32
		Group	0.11	0.68
		Negative affect	-0.19	-0.96
		Negative affect x group	0.18	1.28

Table 51: Results of the linear mixed-effects model (LMM) for M10 onset with group by mood interactions, including estimated regression coefficients together with the t-statistic.

5.1 Resting-state fMRI protocol

5.1.1 Scan 1

SIEMENS MAGNETOM TrioTim syngo MR B17

\\USER\neuro\N14\N14_21_COMET\Resting_TR2ms

TA: 6:04 PAT: Off Voxel size: 3.0×3.0×3.5 mm Rel. SNR: 1.00 SIEMENS: ep2d_bold

Properties	
Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	On
Start measurements	single

Routine	
Slice group 1	
Slices	34
Dist. factor	0 %
Position	R0.7 A12.0 F12.8
Orientation	T > C-30.0
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	192 mm
FoV phase	100.0 %
Slice thickness	3.5 mm
TR	2000 ms
TE	28 ms
Averages	1
Concatenations	1
Filter	None
Coil elements	HEA;HEP

Contrast	
MTC	Off
Flip angle	89 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	180
Delay in TR	0 ms
Multiple series	Off

Resolution	
Base resolution	64
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Matrix Coil Mode	Auto (CP)
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	On
Elliptical filter	Off
Hamming	Off

Geometry	
Multi-slice mode	Interleaved
Series	Descending
Special sat.	None

System

Body	Off
HEP	On
HEA	On
SP4	Off
SP2	Off
SP8	Off
SP6	Off
SP3	Off
SP1	Off
SP7	Off
SP5	Off
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	R0.7 A12.0 F12.8
Orientation	T > C-30.0
Rotation	0.00 deg
R >> L	192 mm
A >> P	192 mm
F >> H	119 mm

Physio	
1st Signal/Mode	None

BOLD	
GLM Statistics	Off
Dynamic t-maps	Off
Starting ignore meas	0
Ignore after transition	0
Model transition states	Off
Temp. highpass filter	Off
Threshold	4.00
Paradigm size	3
Meas[1]	Baseline
Meas[2]	Baseline
Meas[3]	Active
Motion correction	Off
Spatial filter	Off

Sequence	
Introduction	Off
Bandwidth	2368 Hz/Px
Free echo spacing	On
Echo spacing	0.49 ms
EPI factor	64
RF pulse type	Normal
Gradient mode	Fast*

3/+

Figure 69: Resting-state fMRI protocol at scan session 1.

5.1.2 Scan 2

SIEMENS MAGNETOM TrioTim syngo MR B17

\\USER\neuro\N14\N14_21_COMET\Resting_TR2ms

TA: 6:04 PAT: Off Voxel size: 3.0×3.0×3.5 mm Rel. SNR: 1.00 SIEMENS: ep2d_bold

Properties	
Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	On
Start measurements	single

Routine	
Slice group 1	
Slices	34
Dist. factor	0 %
Position	R0.7 A12.0 F12.8
Orientation	T > C-30.0
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	192 mm
FoV phase	100.0 %
Slice thickness	3.5 mm
TR	2000 ms
TE	28 ms
Averages	1
Concatenations	1
Filter	None
Coil elements	HEA;HEP

Contrast	
MTC	Off
Flip angle	89 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	180
Delay in TR	0 ms
Multiple series	Off

Resolution	
Base resolution	64
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	None
Matrix Coil Mode	Auto (CP)
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	On
Elliptical filter	Off
Hamming	Off

Geometry	
Multi-slice mode	Interleaved
Series	Descending
Special sat.	None

System	
Body	Off
HEP	On
HEA	On
SP4	Off
SP2	Off
SP8	Off
SP6	Off
SP3	Off
SP1	Off
SP7	Off
SP5	Off
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Adaptive Combine
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	R0.7 A12.0 F12.8
Orientation	T > C-30.0
Rotation	0.00 deg
R >> L	192 mm
A >> P	192 mm
F >> H	119 mm

Physio	
1st Signal/Mode	None

BOLD	
GLM Statistics	Off
Dynamic t-maps	Off
Starting ignore meas	0
Ignore after transition	0
Model transition states	Off
Temp. highpass filter	Off
Threshold	4.00
Paradigm size	3
Meas[1]	Baseline
Meas[2]	Baseline
Meas[3]	Active
Motion correction	Off
Spatial filter	Off

Sequence	
Introduction	Off
Bandwidth	2368 Hz/Px
Free echo spacing	On
Echo spacing	0.49 ms
EPI factor	64
RF pulse type	Normal
Gradient mode	Fast*

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Figure 70: Resting-state fMRI protocol at scan session 2.

5.2 Identification of RSNs (FSL ICA)

Component	Label by visual inspection	Label by visual inspection (Smith et al., 2009)	Correlation with FIND Lab's 90 ROI atlas (Shirer et al., 2012)	Label as by FIND Lab's 90 ROI atlas (Shirer et al., 2012)
1	DMN	DMN	.60	DMN
2	Visual	Visual	.36	Primary Visual Cortex
3	Left fronto-parietal	Left fronto-parietal	.50	LECN
4	Auditory/motor	Auditory	.28	Auditory
5	Right fronto-parietal	Right fronto-parietal	.49	RECN
6	DMN/executive control	DMN/executive control	.47	Salience
7	DAN	DMN/sensorimotor	.39	Visuospatial
8	DMN	DMN	.52	Precuneus
9	Salience	Auditory	.40	Language
10			.29	Sensorimotor
11	Executive control	Executive control	.25	Visuospatial
12	Visual	Visual	.48	Higher Visual Network
13			.22	Salience
14	DMN	DMN	.42	DMN
15	Cerebellum	Cerebellum	.20	RECN
16			.34	Basal Ganglia
17			.23	Sensorimotor
18	DMN	DMN/executive control	.10	Salience
19	Cerebellum	Cerebellum	.13	Sensorimotor
20	Amygdala			

Table 52: Resting state networks (RSNs) identified via visual inspection (by me, Dr. Liliana Capitao, and Dr. Cassandra Gould van Praag) and Pearson spatial cross-correlation comparison. DMN = Default Mode Network. LECN = Left Executive Control Network. RECN = Right Executive Control Network. DAN = Dorsal Attention Network.

6.1 Identification of RSNs (GIFT ICA)

Component	Correlation with FIND Lab's 90 ROI atlas (Shirer et al., 2012)	Label as by FIND Lab's 90 ROI atlas (Shirer et al., 2012)
1	.46	Higher Visual Network
2	.37	Basal Ganglia
3	.16	Sensorimotor
4	.54	Precuneus
5	.38	Sensorimotor
6	.18	Basal Ganglia
7	.36	Auditory
8		
9	.41	Primary Visual Cortex
10		
11	.26	Sensorimotor
12	.34	Language
13	.13	Sensorimotor
14	.17	Visuospatial
15	.41	Salience
16	.52	DMN
17	.37	RECN
18	.14	DMN
19	.28	Visuospatial
20	.36	DMN
21	.30	LECN
22	.26	Visuospatial
23		
24	.20	DMN
25		

Table 53: Resting state networks (RSNs) identified via Pearson spatial cross-correlation comparison. DMN = Default Mode Network. LECN = Left Executive Control Network. RECN = Right Executive Control Network.