Sleep and Cognitive Function in Bipolar Disorder

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Abstract

Background

People with bipolar disorder (BD) suffer from cognitive dysfunction during all phases of the disorder including euthymia but its origin is unknown. Experimental sleep studies and evidence from people with clinical sleep disorders has demonstrated an association between sleep disruption and cognitive dysfunction. Clinically significant sleep disturbances are common across the course of BD including euthymia but little is known about their association with cognitive function.

Methods

BD patients (n=46) in any mood state and healthy controls (n=42) without known sleep abnormalities were tested cognitively and had comprehensive sleep/circadian rhythm assessment, mood, function and quality of life (QoL) assessed over a 21 day period with actigraphy, respiratory sleep studies and rating scales. Abnormal sleep phenotypes were identified from objective sleep variables including long/short sleepers and those with sleep patterns indicative of a circadian rhythm disorder (CRD). The relationship between sleep, mood, QoL and cognition was explored.

Results

Objectively assessed sleep abnormalities including long sleep, CRD and obstructive sleep apnoea were common in BD patients. BD patients with objectively defined sleep abnormalities had worse psychosocial function and QoL than BD normal sleepers, independent of mood. Only BD abnormal sleepers

performed significantly worse than controls on cognitive tasks of attention, executive control, processing speed and aspects of verbal learning and had increased intra-individual variability in attentional response times. BD normal sleepers did not differ cognitively from controls. The majority of these effects were independent of mood.

Conclusions

Sleep abnormalities are common in BD patients and are associated with impairments in attention, executive control, processing speed and verbal learning. Sleep disturbances are an important therapeutic target in BD and improvement in sleep may lead to improved psychosocial and cognitive function.

Dedicated to my wife Fiona and children Jamie and Kate.

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List of abbreviations.

AASM – American Academy of Sleep Medicine

AHI – Apnoea/hypopnoea index

ASRMS – Altman Self Rating Mania Scale

aMT6S – 6-sulpha-toxymelatonin

ANCOVA – Analysis of covariance

ANT – Attention Network Test

ARAS – Ascending reticular activating system

ASPD – Advanced sleep phase disorder

BD – Bipolar disorder

BDI – Beck Depression Inventory

CANTAB – Cambridge neuropsychological test automated battery

CBTi – Cognitive behavioural therapy for insomnia

CPAP – Continuous positive airways pressure

CPT – Continuous performance test

CRD – circadian rhythm disturbance

CRSD – Circadian rhythm sleep disorder

CSM – Composite Scale of Morningness

DLMO – Dim light melatonin onset

DSISD – Duke Structured Interview for Sleep Disorders

DSM-IV- Diagnostic and Statistical Manual Fourth Edition

DSPD – Delayed sleep phase disorder

DSST – Digit Symbol Substitution Test

EEG – Electroencephalogram

EMG – Electromyography

EOG – Electro-oculography

ESS – Epworth Sleepiness Scale

fMRI – Functional magnetic resonance imaging

GAF – Global Assessment of Functioning

GWAS – Genome Wide Association Study

$HAMD^{17}$ – Seventeen item Hamilton Depression Rating Scale

ICC – Intra-class correlation coefficient

ICSD– International Classification of Sleep Disorders

IDS – Inventory of Depressive Symptomatology

IS – Inter-daily stability

IV – Intra-daily variability

LIFE-RIFT – Life Range of Impaired Functioning Tool

MADRS – Montgomery Asberg Depression Rating Scale

MDD – Major Depressive Disorder

MEQ – Morningness Eveningness Questionnaire

Milli-g – Milli gravitational units

MINI – Mini International Neuropsychiatric Interview

ms – (milli seconds)

MSLT- Multiple sleep latency test

MVPA – Moderate and vigorous physical activity

NREM – Non-rapid eye movement

NSWM – Newcastle Spatial Working Memory Test

nWAK – Number of awakenings

ODI – Oxygen desaturation index

OSA – Obstructive sleep apnoea

PLMS – Periodic Limb Movement in Sleep

PSG – Polysomnography

PSQI – Pittsburgh Sleep Quality Index

PTSD – Post traumatic stress disorder

PVT – Psychomotor Vigilance Test

RA – Relative amplitude

REM – Rapid eye movement

RT – Reaction time

SCN – Suprachiasmatic nucleus

SD – Sleep deprivation

SDB – Sleep disordered breathing

SE – Sleep efficiency

SIBD – Sustained inactivity behaviour daytime

SNP – Single nucleotide polymorphism

SOL – Sleep onset latency

SR – Sleep restriction

STAI – State-Trait Anxiety Inventory

STEP-BD – Systematic Treatment Enhancement Programme for BD

SWS – Slow wave sleep

TIB - Time in bed

TMT – Trial-Making Test

TST – Total sleep time

TWT – Total wake time

VLPO – Ventrolateral preoptic nucleus

WASO – Wake after sleep onset

WCST – Wisconsin Card Sorting Test

WMI – White matter integrity

YMRS – Young Mania Rating Scale

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1. Chapter One. Introduction

1.1 Why is it important to study cognitive function in Bipolar disorder?

Mental illness including mood, anxiety and psychotic disorders are the single largest cause of disability in the UK (World Health Organisation, 2008). In bipolar disorder (BD) although much of this disability is associated with core psychiatric symptoms such as mood disturbances during acute episodes of illness many sufferers continue to experience symptoms and disability such as sleep disturbances (Harvey et al., 2005), poor psychosocial function (Huxley and Baldessarini, 2007), reduced quality of life (Michalak et al., 2005) and cognitive impairments (Robinson et al., 2006) even in the absence of acute mood episodes in so called euthymic periods. Cognitive impairments are important symptoms of BD as they are associated with functional impairments and work disability (Sanchez-Moreno et al., 2009; Wingo et al., 2009) therefore making a significant contribution to the burden of these conditions. Currently the origin of these cognitive deficits is not well understood but the fact that they occur in the absence of core psychiatric symptoms and in unaffected first degree relatives of people with BD (Arts et al., 2008), suggests their underlying neurobiology is probably different to that of core psychiatric symptoms. This is also suggested by the fact that current pharmacological treatments for BD which are effective in alleviating core psychiatric symptoms have demonstrated minimal or no direct benefits on cognitive impairments and may in some cases make them worse (Harvey and Keefe, 2001; Dias et al., 2012). Improving our understanding of the nature and origin of cognitive impairment in BD is therefore an important goal as this will help in the development of more effective treatments to improve

cognitive performance and thereby improve function and quality of life in people who suffer with these conditions.

One mechanism that until recently has received little attention as a possible cause of cognitive impairment in psychiatric disorders is sleep disturbance. This is an attractive research area for a number of reasons. Sleep has a fundamental role in learning and cognition and objective studies have demonstrated that sleep deprivation (SD) (Lim and Dinges, 2010), sleep restriction (SR) (Banks and Dinges, 2007) and clinical sleep disorders such as insomnia (Fortier-Brochu et al., 2012) and obstructive sleep apnoea (OSA) (Beebe et al., 2003) are associated with a broad array of cognitive impairments. SD has been demonstrated to influence the function of cerebral circuits (Dang-Vu et al., 2007) so there is a plausible mechanism by which sleep loss may influence cognitive function. Finally, people with BD suffer from disturbed sleep and circadian rhythm including during periods of euthymia (Harvey, 2008). The pattern of cognitive impairment in BD also overlaps that seen following SD and SR and this suggests that cognitive impairment arising from chronic sleep disturbance may contribute to the variance and severity of cognitive deficits in BD. This thesis aims to examine the association of sleep and circadian rhythm abnormalities to cognitive impairments found in people with BD.

1.1.1 Sleep and its regulation.

1.1.2 Overview of sleep

Sleep is characterised by both behavioural and physiological measures. Behaviourally during sleep people are normally recumbent with closed eyes, immobile, unresponsive to stimuli and reversibly unconscious (Chokroverty,

2010). Physiologically sleep is defined by electrical activity in the brain, measured by electroencephalogram (EEG), electrical activity from the eyes, measured by electro-oculography (EOG) and electrical activity from the muscles, measured by electromyography (EMG) which is collectively termed polysomnography (Silber et al., 2007; Patil, 2010). The EEG defines two types of sleep, rapid eye movement (REM) sleep and non-rapid eye movement (NREM)

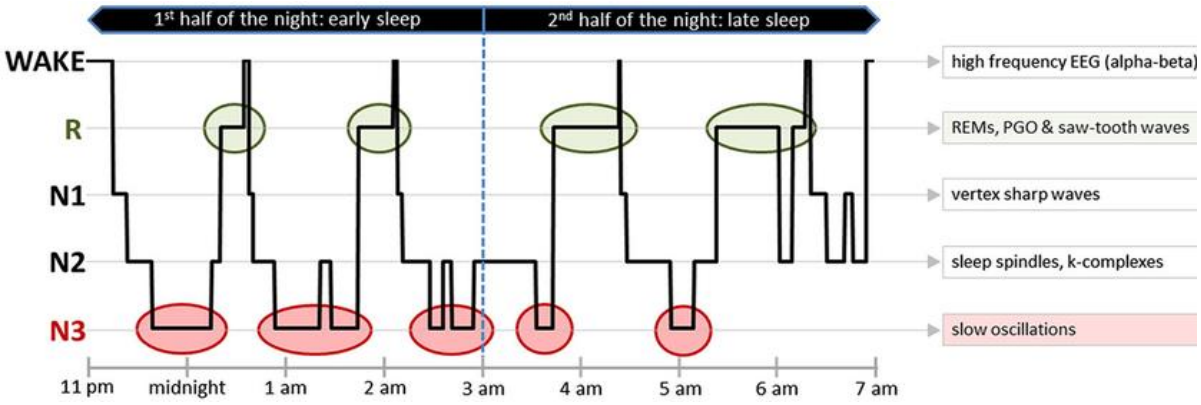


Figure 1.1 Sleep hypnogram showing different sleep stages over 8 hours of nocturnal sleep in a healthy human (from Blume et al., 2015).

sleep which alternate in a cyclical manner throughout the night (Figure 1.1). NREM sleep predominates in the first third of the sleep period and has been subdivided into three stages N1 (drowsiness), N2 (light sleep) and N3 (deep sleep) on the basis of EEG criteria which demonstrate a slowing of the EEG from high frequency low voltage waves to low frequency higher voltage waves as sleep develops (Silber et al., 2007). N3 sleep is also termed slow wave sleep (SWS) and the amount of SWS has been found to increase following sleep deprivation and decrease after reduced waking time (Daan et al., 1984). REM sleep accounts for approximately 20-25% of sleep time and dominates in the final third of the sleep period. It is characterised by high frequency low voltage waves accompanied by rapid eye movements and a lack of muscular activity identified by the chin EMG

(Chokroverty, 2010). In humans the requirement for sleep changes across the lifetime generally reducing with age (Chokroverty, 2010; Hirshkowitz et al., 2015). New-borns have a requirement of approximately 16 hours taken over several episodes each day. This falls to approximately 10 hours per day by the age of 10 years and the average duration in adults is 7.5 to 8 hours. In adults the requirement is usually met through one continuous sleep session during the hours of darkness but this may become biphasic in the elderly.

1.1.3 The regulation of the sleep wake cycle.

The two process model of sleep regulation proposed that sleep length and the circadian pattern of the sleep wake cycle are controlled by two interacting processes, the homeostatic system termed process S and a circadian process termed process C (Borbely, 1982; Daan et al., 1984). This theoretical

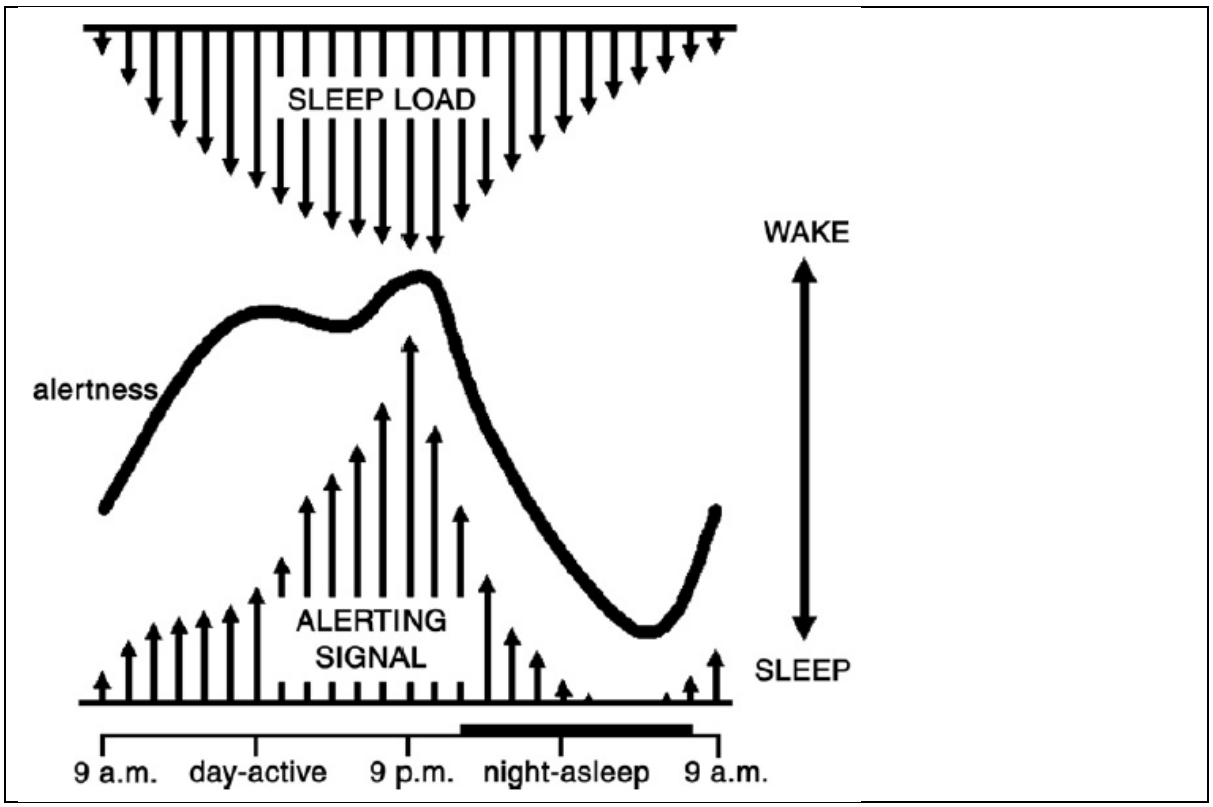


Figure 1.2 The interaction between the homeostatic (sleep load) and circadian (alerting signal) processes over the course of 24 hours (from Beersma and Gordijn. 2007).

mathematical model was developed by observing the effects of sleep length and time awake on slow wave sleep and alertness. The model is able to predict sleepiness and alertness based on prior sleep and time awake. Figure 1.2 demonstrates the interaction between these processes which is described below.

1.1.3.1 The homeostatic regulation of sleep.

Process S mediates a drive for sleep that increases with increasing time awake and dissipates during sleep. Wakefulness is promoted by the ascending reticular activating system (ARAS) originating in the brain stem and via complex relay systems it projects to and activates the cortex. It is opposed by a sleep promoting system containing inhibitory neurotransmitters which arises from the ventrolateral preoptic nucleus (VLPO). The VLPO also receives input from the arousal system which can inhibit VLPO and therefore these two systems can oppose each other to promote sleep or wakefulness (Brown et al., 2012). This has been described as a flip flop switch which controls the transition from sleep to wake depending on the balance of inhibition between the activating and sleep promoting systems (Saper et al., 2001).

1.1.3.2 The circadian regulation of sleep.

Interacting with the sleep homeostat process C regulates the timing of sleep and wake ensuring synchronisation with the light dark cycle. The circadian rhythm of the sleep wake cycle is driven by the central circadian pacemaker or master clock located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus and at a cellular level is controlled by an array of clock genes (Takahashi et al., 2008) which ensure it runs at a period of just over 24 hours. The clocks are entrained to the 24-hour cycle by environmental and endogenous cues called zeitgebers. Light

is the major environmental zeitgeber facilitated by photosensitive retinal ganglion cells which have a direct neuronal link from the retina to the SCN, the retino-hypothalamic tract (Freedman et al., 1999). The SCN influences sleep/wake patterns via bidirectional connections to both the sleep active and wake active neurons of the sleep homeostat (Fuller et al., 2006). As homeostatic sleep propensity increases across the waking day it is increasingly opposed by the circadian drive for alertness. The signal is strongest in the mid to late evening when sleep propensity is at its highest ensuring an individual can maintain wakefulness for around 16 hours per day up until the usual bedtime (Dijk and Czeisler, 1994). For a habitual 11.00pm to 7.00am sleeper this is typically between 8.00pm -10.00pm, a period often referred to as the wake maintenance zone (Gaggioni et al., 2014). The circadian drive for wakefulness then falls during the night as the homeostatic drive for sleep dissipates across the sleep period ensuring that a full 8 hours of sleep can be maintained (Dijk and Czeisler, 1994). As well as regulating the timing of sleep the circadian process also has a strong influence on subjectively and objectively measured alertness and cognition (Dijk et al., 1992) and cognitive performance has been demonstrated to be better during the afternoons and worse in the late evening and early morning when circadian drive is at its lowest (Kleitman and Jackson, 1950).

1.1.3.3 Endogenous circadian rhythm.

There are two important markers that can be measured to estimate the timing of the endogenous circadian signal. The 24-hour profile of melatonin secretion and core body temperature can both provide estimates of the timing of the human SCN and circadian phase (Benloucif et al., 2005; Pevet and Challet, 2011). Core body temperature follows a circadian rhythm over each 24-hour period with a

peak at around 21.00 and nadir at approximately 05.00 hours (Krauchi and Wirz-Justice, 1994), a pattern that is generated by the SCN (Gilbert et al., 2004). The nadir of core body temperature can thus be used as a marker of circadian phase (Benloucif et al., 2005). Melatonin is secreted by the pineal gland and controlled by the SCN. It can be used as a marker of circadian phase by assessing melatonin itself or its metabolite in saliva, plasma and urine over defined time periods. As it is able to entrain the SCN it has also been termed a chronobiotic (Arendt and Skene, 2005). Melatonin secretion does however vary over the lifetime. In new-borns it is almost absent up to 3 months, peaks sometime between one and three years of age, rapidly declines up to adolescence and then there is a steady further decline into old age (Waldhauser et al., 1988). Normally melatonin secretion starts to increase at the end of the wake maintenance zone corresponding to the peak in core body temperature. It continues to increase until about 2-3 hours before the nadir of core body temperature at around 6.00am (Gaggioni et al., 2014) meaning that as melatonin level rises core body temperature declines. The normal profile of melatonin secretion is shown in Figure 1.3. It is worthy of note that there is inter-individual variability in circadian rhythm. Termed circadian chronotypes some people prefer to initiate sleep at an earlier time point and wake earlier in the morning, (morning types or larks) and others prefer to initiate sleep onset at a later time and rise later in the morning, (evening types or owls) (Reid et al., 2011). These phenotypes can be identified with scales such as the Horne-Oestberg questionnaire (Horne and Ostberg, 1976). The chronotypes differ in endogenous phase of their internal biological clock as demonstrated by different timings of peaks and troughs in core temperature and melatonin secretion with

an earlier maximum and nadir occurring in morning types (Duffy et al., 1999; Reid et al., 2011).

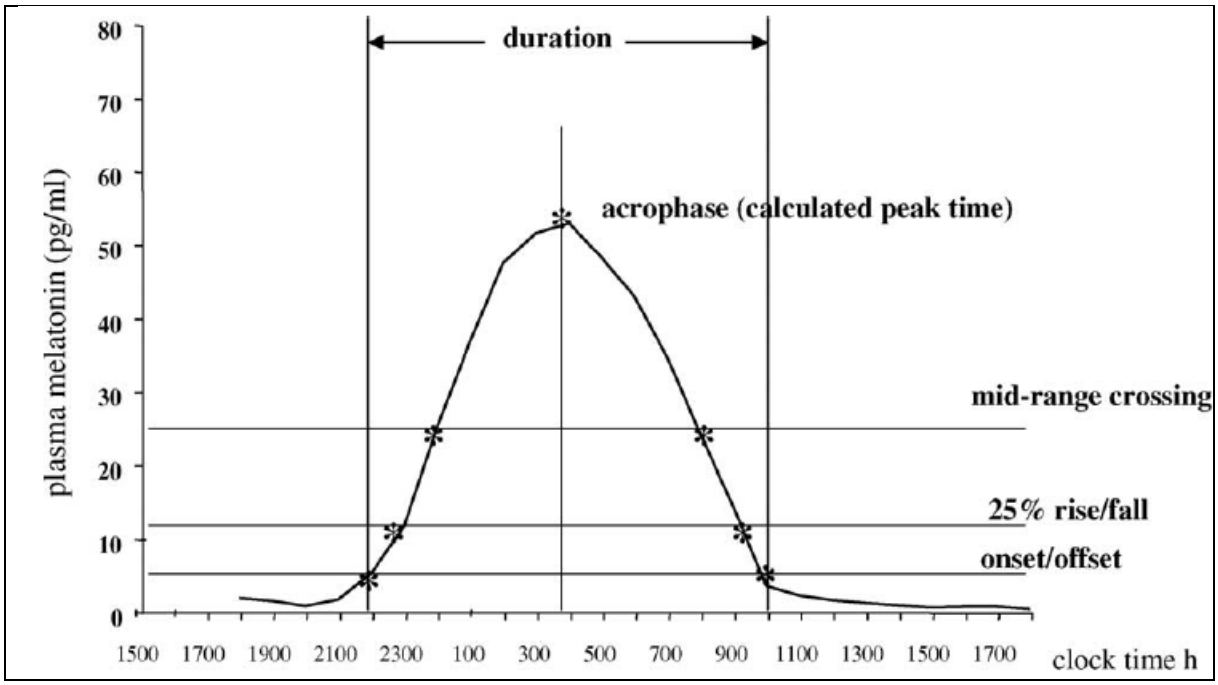


Figure 1.3 The normal profile of plasma melatonin over a 24-hour period (diagram from Arendt and Skene, 2005).

1.2 Assessing sleep and circadian function.

Sleep can be assessed with both objective and subjective methods. Objective methods include polysomnography (PSG) and accelerometry (sometimes referred to as actigraphy). PSG is considered the gold standard to which other methods should be compared and is used to define sleep and its stages and can be used to diagnose sleep disorders (Kirsch, 2012). Subjective methods include sleep diaries and rating scales. Sleep diaries rely on estimations of sleep time and recall of wake during sleep and are therefore open to bias. Studies have tended to demonstrate that people overestimate the time taken to fall asleep (sleep onset latency (SOL)) with sleep diaries and underestimate the number of night time

awakenings compared to PSG (Lichstein et al., 2006; Kaplan et al., 2012). They may also be unreliable for the recording of naps (Martin and Hakim, 2011). The Pittsburgh Sleep Quality Index (PSQI) is a commonly used rating scale that assess subjective sleep quality, quantity and efficiency as well as sleep disturbances and the use of medications to aid sleep (Buysse et al., 1989). The objective measures of PSG and accelerometry correlate more closely with each other than with subjective sleep diaries (Morgenthaler et al., 2007) and are thus preferred methods to measure sleep function. Although PSG is the most accurate method of measuring sleep function it is usually performed in a sleep laboratory limiting its utility in the long-term assessment of sleep function and for this reason was not utilised in this study and will not be further discussed.

1.2.1 Accelerometry to assess sleep wake variables.

1.2.1.1 An introduction to accelerometry.

Accelerometry has been found to be a convenient and cost effective method of monitoring sleep and wake patterns in individuals over 24 hours for periods lasting many consecutive weeks (Ancoli-Israel et al., 2003). Modern accelerometers are usually worn on the wrist and contain an accelerometer to detect movement. Movement is measured multiple times each second and the data stored digitally on the device that at the end of the study period is downloaded onto a computer. An algorithm is then used to estimate sleep and wake periods from the frequency and intensity of movement based on the observation that there is less movement during sleep than wake (Ancoli-Israel et al., 2003). The value of accelerometry depends on its ability to accurately estimate sleep and wake. Validation studies comparing accelerometry to the gold standard PSG, to measure its sensitivity, (the proportion of PSG defined sleep

also identified by accelerometry) and specificity, (the proportion of PSG defined wake also identified by accelerometry) have been performed. Generally, studies have demonstrated that accelerometry is more likely to accurately detect sleep (i.e. has high sensitivity) and less likely to detect wake periods (i.e. has lower specificity). This is not surprising since accelerometry relies on movement to estimate wake and sleep. A poor sleeper may lie still in bed attempting to get back to sleep for long periods of time which accelerometry may identify as a sleep period due to the lack of movement. Validation studies have found that compared to PSG accelerometry performs better at identifying sleep/wake during the night time than daytime period. It is relatively poor at identifying the transition between wake and sleep although useful in identifying circadian sleep/wake rhythms (Pollak et al., 2001). Also accelerometry may be less accurate in more disturbed sleep conditions that involve more transition from sleep to wake where it may over estimate total sleep time (TST) (Paquet et al., 2007). It has been demonstrated that TST can be over-estimated by accelerometry compared to PSG in short sleepers and in those with more fragmented sleep. It may be underestimated in people with sleep disordered breathing (SDB) and excessive daytime sleepiness. This is most likely due to people either lying still and trying to sleep or movements made during sleep that are interpreted as wake (Blackwell et al., 2011).

There are several brands of accelerometer which can be utilised to estimate sleep/wake variables. Much of the technology is now over 20 years old and older devices generally use a single axis accelerometer based motion sensor to detect movement. In addition, the majority of current accelerometry devices use manufacturers specific count values and algorithms to estimate sleep variables

meaning that estimates from different brands of device are not readily comparable and also that the researcher has little control over signal processing (te Lindert and Van Someren, 2013; van Hees et al., 2015). Advances in microelectronics has resulted in the development of high resolution tri-axial accelerometers that record signals in SI units, (raw acceleration), rather than manufacturer specific activity counts, thus allowing more analytical freedom than older accelerometer devices and the potential for comparing raw data collected from different brands of accelerometer. Additionally, the use of raw accelerometer data allows estimates of both sleep and physical activity over each 24-hour period allowing analysis of the relationship between the two (te Lindert and Van Someren, 2013; van Hees et al., 2015). Data collected in this way could also be re-analysed at a later date as more sophisticated and accurate algorithms are developed that utilise raw accelerometry data.

1.2.1.2 Validation of accelerometry in people with sleep disorders and BD.

Accelerometry has been validated in some sleep disorders and BD but it is important to remember that validation studies are specific to the brand of accelerometer and algorithm settings utilised (Johnson et al., 2007). Accelerometry was found to be a satisfactory method to estimate sleep compared to PSG in patients with insomnia (Lichstein et al., 2006) although TST was overestimated and SOL and wake after sleep onset (WASO) were underestimated. Correlations of accelerometry and PSG estimated number of awakenings (nWAK) and WASO weakened as the numbers of these events increased indicating that accelerometry may become less accurate as the severity of sleep disturbances increases. The data also suggested that the use of hypnotics may cause accelerometry to overestimate sleep. A recent study including

insomniacs found accelerometry was reasonably accurate in identifying periods of sleep, (86% accuracy and 90% sensitivity), but specificity was low with a mean of 33% across all the subjects (Marino et al., 2013). Specificity was lower in insomnia patients with low SE (i.e. more WASO) than in insomnia patients with high SE. These studies demonstrate the key weakness of accelerometry in populations with fragmented sleep. A recent review has concluded that although accelerometry provides reasonable estimates of sleep in insomnia patients and can distinguish between groups of individuals with insomnia and controls with reasonable sensitivity it is important to consider that the low specificity of accelerometry may lead to overestimations of sleep (Sadeh, 2011). Accelerometry can also be useful in detecting daytime naps with reasonable accuracy but specificity in detecting wake during daytime rest periods compared to PSG is less reliable and accuracy is dependent on the specific algorithm settings used (Kanady et al., 2011; Cellini et al., 2013).

Given these issues of accelerometry in people with disordered sleep it is important to validate accelerometry in people with BD where sleep is highly variable with both hypersomnia and insomnia frequently reported (Harvey, 2011). To date however only two studies has compared accelerometry to PSG in BD. Kaplan et al. (2012) compared sleep estimates from PSG, accelerometry and sleep diaries between euthymic BD patients and controls and additionally sought to examine the effects of insomnia and psychotropic medications in these populations. Accelerometry agreement with PSG was found to be equally accurate across BD and control groups. A good correlation was found for TST although only modest associations were found for WASO, nWAK, and SE and a non-significant association with SOL. The presence of insomnia in a subset of BD

patients did not significantly affect the results although it must be noted that the number of BD participants with an insomnia diagnosis was very small, (n=6) and it is not reported how fragmented their sleep was during the 2 days of this study. No evidence was found for an influence of psychotropic medication on the concordance of accelerometry and PSG in this sample. One limitation of this study is that only sleep summary data are compared and that no epoch by epoch analysis of accelerometry and PSG was performed. Another study which included 5 BD patients also compared accelerometry to PSG measures and found high intra-class correlation coefficients (ICC's) for TST but poor ICC's for SOL, SE, WASO and nWAK (Baandrup and Jennum, 2015). When patients with PSG estimated WASO > 100 minutes were excluded the ICC values for all sleep continuity variables (except for SOL) improved to a level of moderate agreement between PSG and accelerometry. This demonstrated that in common with insomnia studies, highly disturbed sleep may reduce the sleep variable estimates of accelerometry compared to PSG.

With regards to scoring accelerometer data one study has compared the effect of different methods on sleep estimates in euthymic BD patients (Boudebesse et al., 2013). These methods included utilising sleep diary data, event markers from the accelerometer, the automatic sleep/wake detection from the algorithm alone and supplemented with event markers and visual estimates derived from the actigram by a trained reader. These scoring methods resulted in different sleep estimates. The authors suggested that automated algorithms may have difficulty accurately detecting bedtimes in BD populations who may have low activity levels making a cross check with diary or event marker data a sensible option. They also commented that although an accurately completed diary and event

markers can provide more precise information about bed and rising times there will likely be inconsistencies in recording accuracy and frequency between unmotivated or impaired individuals (possibly such as those with BD) which may bias the results between individuals. Careful consideration should be given to sleep scoring methods and it is likely valuable to cross check patient recorded and algorithm generated data with the visual actigram for general agreement. The study is however limited by a lack of comparison with PSG meaning it was not possible to see which was the most accurate method compared to the gold standard.

Accelerometry has also been compared to subjective sleep assessment. TST estimates were highly correlated between sleep diaries and accelerometry in BD I patients although currently depressed patients tended to underestimate their TST (Gonzalez et al., 2013). Boudebesse et al (2014) compared accelerometry with the PSQI the Composite Scale of Morningness (CSM) and the Circadian Type Inventory in estimating sleep variables in euthymic BD patients for 21 consecutive days. Phase preference assessed by the CSM strongly correlated with accelerometer derived phase markers and sleep duration assessed by the PSQI and by accelerometry were highly correlated. Moderate correlation coefficients were observed between questionnaires and accelerometry for markers of stability of rhythms, sleep quality, SOL and sleep disturbances but these were not significant after correcting for multiple comparisons.

In summary evidence suggests a good correlation of accelerometry estimates with PSG for estimates of sleep duration and sleep/wake activity but it is less accurate for specific measures such as sleep offset, SE, SOL and WASO.

Accelerometry may also be more reliable in healthy adults than in sleep disordered individuals primarily due to its low specificity. Accelerometry has a high sensitivity for detecting daytime naps but a low specificity so may misclassify restful periods during the day as sleep. One study has demonstrated that accelerometry has reasonable concordance with PSG in patients with BD although further validation studies in a larger sample size and in patients with variable sleep performance are required. Finally, it is also important to note that accelerometry has not currently been validated for estimating sleep over the entire 24-hour day/night period which would include voluntary and involuntary naps. However, accelerometry has now been used for research in hundreds of thousands of patients in large cohort studies and is regarded as a robust marker of sleep /wake patterns. It is considered the most reliable method to assess the sleep/wake cycle over several weeks.

1.2.1.3 Accelerometry to assess circadian rhythm.

Another utility of accelerometry is to assess circadian rhythms. Movement data plotted over time in graphical form can be visually inspected to look for changes in 24-hour rest and activity patterns and raw activity levels can be subjected to cosinor analysis to calculate the time of peak activity (acrophase), the difference in peak and lowest activity levels (amplitude) and the mean activity level (mesor) (Ancoli-Israel et al., 2003). It has however been demonstrated that a 24-hour cosine waveform fits poorly to circadian activity and may not be an optimal method for describing circadian rhythms. Other methods such as interdaily stability (IS), intradaily variability (IV) and relative amplitude (RA) have been developed to overcome this issue. IS is a measure of the strength of coupling of the rhythm to stable environmental zeitgebers, IV describes the fragmentation of

the rhythm i.e. the transition between rest and activity within each day and RA is the relative amplitude between the most active 10 hours of a 24-hour period and the least active 5-hour period (Van Someren et al., 1999).

1.3 Bipolar Disorder

1.3.1 Clinical description and diagnosis.

BD is primarily characterised by mood instability ranging from elevated, expansive or irritable mood present during manic or hypomanic episodes to depressed mood and markedly diminished interest or pleasure in activities during major depressive episodes. In the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV), BD is diagnosed by subtype dependant on the occurrence of either full manic or mixed (BD I) or hypomanic (BD II) episodes (American Psychiatric Association, 2000). New DSM criteria were published in 2013 (DSM-V) (American Psychiatric Association, 2013) but as this study began in 2012 DSM-V was not utilised. BD typically follows a chronic recurrent course and sufferers of either subtype are symptomatic approximately 50% of the time with the vast majority of this spent in depressive episodes (Judd et al., 2002; Judd et al., 2003). Even in the absence of major symptoms (euthymia) sufferers often experience residual subsyndromal symptoms (Frye et al., 2006), sleep disturbances (Harvey et al., 2005) significant functional impairment (Judd et al., 2005; Huxley and Baldessarini, 2007) and reduced quality of life (Gutierrez-Rojas et al., 2008) (Figure 1.4). Suicide attempts are common in BD with 25% to 50% of sufferers having at least one lifetime suicide attempt (Jamison, 2000). As a consequence of these features and the early age of onset (see below) BD is ranked 18th in the leading global causes of years lived with disability in the 2010 Global Burden of Disease Study (Vos et al., 2012). BD

also frequently occurs with other DSM-IV axis I comorbidities in particular anxiety and substance misuse disorders (Merikangas et al., 2011).

1.3.2 Epidemiology.

The lifetime prevalence of BD was recently estimated to be 1.0% (0.6% BDI, 0.4% BDII) in the World Mental Health (WMH) Survey Initiative (Merikangas et al., 2011). This study found a lifetime prevalence of bipolar spectrum disorders, which includes BDI and BDII disorders and subthreshold BD defined as people who experience subthreshold hypomania of 2.4% worldwide. Around 50% of BD sufferers have a first onset of illness before the age of 19 and childhood onset is associated with long delays in treatment and a worse prognosis with a greater number of episodes, more severe mania and depression and fewer days well than those with adult onset (Perlis et al., 2004; Leverich et al., 2007)

1.3.3 Pathophysiology of BD.

Although the precise neurobiological causes of BD are poorly understood functional neuroimaging studies of BD support a model of hypo-activation of frontal brain regions, resulting in reduced modulation of limbic regions which demonstrate hyper-activation and together these abnormalities result in dysregulation of mood (Strakowski et al., 2005; Drevets et al., 2008; Kupferschmidt and Zakzanis, 2011). A meta-analysis of functional magnetic resonance imaging (fMRI) studies in BD supported these models as the main findings were that BD patients under-activated the inferior frontal cortex and putamen and over-activated limbic areas including the para-hippocampal gyrus, hippocampus and amygdala (Chen et al., 2011).

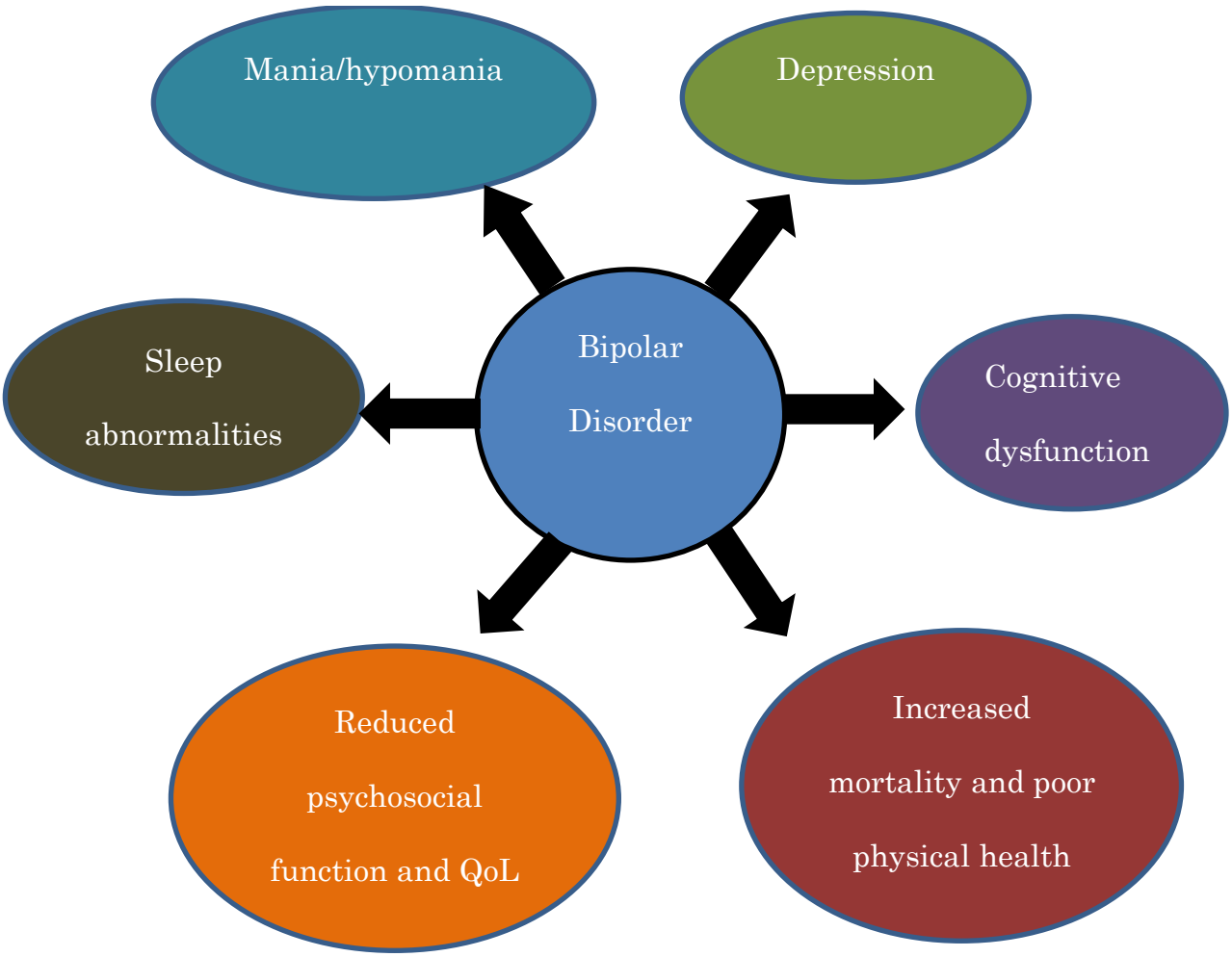


Figure 1.4 Symptoms and consequences of BD

Family, twin and adoption studies have demonstrated that BD is a highly heritable disorder with first-degree relatives of affected individuals being at an approximately 10 fold greater risk of developing BD compared to relatives of unaffected controls (Smoller and Finn, 2003). It is accepted that genetics play a significant part in the pathogenesis of BD and that the genetic risk comes from multiple genes each inferring a small additional risk for the disorder (Geschwind and Flint, 2015). The Psychiatric Genome Wide Association Study (GWAS) combined genomic data from across multiple studies and identified a number of

single nucleotide polymorphisms (SNPs) associated with increased risk for BD (Psychiatric Gwas Consortium Bipolar Disorder Working Group, 2011). A large number of these studies have found that individual risk alleles for BD influence brain structures and functions relevant to the pathophysiology of BD such as the amygdala, prefrontal cortex and white matter integrity (Gurung and Prata, 2015; Dima et al., 2016). The largest GWAS Study to date has identified 30 genetic loci associated with BD with the significant loci containing genes that encode ion channels and neurotransmitter transporters, synaptic components and immune and energy metabolism components (Stahl et al., 2017). Of note genes associated with the regulation of circadian rhythms have also been associated with BD (Etain et al., 2014; Maciukiewicz et al., 2014). This evidence supports the role of sleep and circadian disturbances in the pathophysiology of BD (see section 1.3.4.6 below), although it should be noted others have found no associations between circadian genes and BD after controlling for multiple testing (Byrne et al., 2014) so further work is needed to clarify any role for circadian genes in BD.

In conclusion, the pathophysiology of BD is complex and still poorly understood but is likely to be driven by the interaction of both environmental and genetic factors.

1.3.4 Sleep and circadian rhythm in BD.

Sleep disturbances are a core feature of bipolar disorder and included in the DSM IV diagnostic criteria for major depressive episodes, mania and hypomania (American Psychiatric Association, 2000). They are also reported commonly during euthymia (Harvey et al., 2005). Disturbances in circadian rhythm are also evident in bipolar patients, (Murray and Harvey, 2010) and it has been proposed

that sleep and circadian disturbances rather than being an artefact of mood episodes are a core part of the underlying aetiology and maintenance of bipolar disorder (Harvey, 2011). Sleep function has been assessed in BD with PSG, accelerometry and sleep diaries across all phases of the illness.

1.3.4.1 Sleep in individuals at high risk of developing BD and during the prodrome of relapse.

Multiple studies have examined sleep and circadian rhythm in children and adolescents at high risk of developing BD or during the initial prodrome of BD onset using both subjective measures and accelerometry. Reviews of the literature have concluded that sleep abnormalities commonly emerge during early adolescence, often proceed the onset of illness by several years and are present during the initial prodrome. The nature of these abnormalities is variable with irregular sleep/wake timing and other circadian abnormalities, difficulty getting to sleep, poor quality and fragmented sleep and decreased sleep all being reported (Skjelstad et al., 2010; Ritter et al., 2011; Leopold et al., 2012; Ng et al., 2015; Melo et al., 2016b).

Two systematic reviews have also found that sleep disturbances are common prior to relapse into a mood episode (Jackson et al., 2003; Sierra et al., 2007). Variability was found between studies but sleep disturbances were reported as an early symptom of bipolar depression by 17-57% of subjects, (median 24%) and 53-90% (median 77%) of subjects as an early symptom of manic relapse. Sleep disturbances may therefore be a risk factor for development of BD and relapse or could be an early symptom of disease onset and relapse.

1.3.4.2 Sleep during mania and hypomania.

Decreased need for sleep is a core diagnostic feature of mania (American Psychiatric Association, 2000). A literature review found shortened sleep time and more disturbed sleep identified by PSG and decreased need for sleep reported by 69-100% of subjects with a manic or mixed state by self-report (Harvey, 2008). An accelerometry study in patients with a current manic or mixed episode found decreased circadian amplitude (the difference between daytime and night time activity), more daytime napping, a lower amplitude (activity count per minute) and advanced acrophase (time of peak activity) of 14.00 hours versus 16.00 hours compared to controls (Salvatore et al., 2008).

1.3.4.3 Sleep during BD depression.

Longer SOL, more early morning awakenings and lower SE than controls have been reported with PSG during BD depression (Duncan et al., 1979; de Maertelaer et al., 1987). In contrast another PSG study found no differences were in SOL, TST, number of awakenings or SE between moderately depressed BD patients and controls but in this study participants were woken at 7.00am so restricting the possibility of extended sleep (Thase et al., 1989). In an accelerometry study depressed BD patients were found to have longer time in bed, (TIB) and WASO, lower SE and later morning awakening than controls (Robillard et al., 2013a). A significantly greater proportion of BD patients (60.2%) also had a delayed sleep phase (sleep onset > 1.30am or sleep offset > 10.00am) than controls (10.0%). Self-reported sleep disturbances during bipolar depression also appear to be common but there is variability in study findings. For example in the review by Harvey (2008) the rate of self-reported insomnia was 100% in one study and rates of hypersomnia varied between 23% and 78%.

1.3.4.4 Sleep during euthymia.

Several studies have utilised accelerometry to assesses sleep and circadian rhythm in euthymic BD patients compared to controls and these are summarised in Table 1-1. There are some inconsistencies between findings in these studies which may be due in part to differences in patient populations. For example remission criteria differed between studies and in some participants did not meet conventional criteria for remission. In the study reported by Jones et al. (2005) BD participants had to be euthymic or experiencing only low levels of depressive or manic symptoms and participants had a mean HAMD score of 8.6 which is above the conventional cut off for remission in depressive symptoms of < 7. The study reported by Ritter et al. (2012) used a HAMD-17 cut off of < 15 for remission of depressive symptoms. The duration of accelerometry in these studies also ranged from 3 to 54 days with 6 studies having less than 10 days of assessment. As sleep patterns in BD likely vary over time the short duration of assessment in some studies may not reflect the full extent of any sleep abnormalities and may have limited their ability to detect differences between groups. Collectively however, these studies demonstrated differences in sleep and circadian variables between euthymic BD patients, (or at least in patients with low levels of mood symptoms) and controls. Greater SOL and TST and lower SE in BD patients was demonstrated. Variability in sleep was not assessed in all studies but was generally reported as increased in BD in studies where it was assessed. The majority of this data has been combined in three meta-analyses (Geoffroy et al., 2014b; Ng et al., 2015; De Crescenzo et al., 2017) which report consistent results with respect to greater TST, SOL and WASO in euthymic BD patients with small to moderate effect sizes. Geoffroy et al. (2014b) and De

Crescenzo et al. (2017) also reported lower SE in BD. Ng et al. (2015) reported some additional variables and found no differences in the number of night time awakenings but greater TIB and greater variability in TST, SOL and WASO. There was no difference in SE between controls and BD patients. Both the meta-analyses of Ng et al. (2015) and De Crescenzo et al. (2017) also found lower activity levels in BD patients than controls.

Taking a critical look at the finding in these meta-analyses of increased TST there was moderate heterogeneity between individual study findings with I^2 statistics of 44%, 66% and 42% in Geoffroy et al. (2014b), Ng et al., 2015 and De Crescenzo et al. (2015) respectively. The chi squared statistic was however significant in all these analyses indicating this heterogeneity may be problematic. Individually the studies included in the meta-analyses reported different outcomes. For example in the meta-analysis reported by Geoffroy et al. (2014b) just three of the nine studies found a statistically significant longer TST, four had numerically longer but not statistically significant differences in TST and two had very similar TST between BD and control participants. The relatively small size of sample sizes in these studies (ranging 14 to 36 BD patients) may however have limited the power of these studies. Since this meta-analysis was published the largest accelerometry study reported to date assessing 87 euthymic BD patients and 75 controls over 14 days found no difference in TST between groups and additionally no differences in SOL, SE or WASO (Verkooijen et al., 2017b). The authors performed an updated meta-analysis including their new data alongside that included in the Geoffroy et al. (2014b) meta-analysis. The meta-analysis however found a SMD of 0.52 ($p<0.001$)

Table 1-1 Accelerometer studies assessing sleep and circadian variables in euthymic BD patients

Study	Days of accelerometry	Participants	Mean Age (SD)	% female	Major accelerometry outcomes
Miller et al. (2004)	5	19 BD I 19 Controls	47.3 (10.6) 45.8 (10.5)	58% 58%	Trend towards longer SOL, TST and lower SE in BD. Greater variability in TST and night time wake in BD.
Harvey et al. (2005)	8	20 BD I 20 Insomnia 20 Controls	39.6 (15.2) 39.6 (10.6) 35.0 (13.4)	50% 55% 65%	No significant differences between groups in SOL or WASO. BD greater TST and lower daytime activity than insomnia and controls.
Jones et al. (2005)	7	19 BD 19 Controls	44.4 (13.1) 46.9 (14.8)	74% 74%	Less stable and more variable circadian activity in BD group. BD less active than controls. No differences in TST, SOL, SE, RA.
Salvatore et al. (2008)	3	36 BD I 32 Controls	44.4 (9.8) 42.3 (10.8)	81% 75%	BD greater TST, nocturnal sleep and less nocturnal and daytime activity than controls. BD significantly earlier time of peak activity (acrophase) than controls.
Ritter et al. (2012)	6	19 BD I, 3 BD II 28 Controls	32.7 (10.0) 28.3 (7.2)	41% 43%	Increased TST, TIB, SOL and variability in night time activity in BD patients. No difference in SE or WASO. Note - euthymia was defined as HAMD-17 $\leq$ 15 and $\leq$ 10 on the YMRS which is higher than convention.
Gershon et al (2012)	54	32 BD I 36 Controls	34.7 (10.5) 33.3 (12.6)	63% 53%	Greater SOL in BD. No significant differences in TST, WASO or SE.
St-Amand et al (2013)	14	11 BD I, 3 BD II 13 Insomnia 13 Controls	44.6 (11.0) 42.8 (15.9) 47.2 (10.4)	50% 62% 46%	Insomnia lower SE than BD and controls. No between group differences in TST, WASO or SE. BD patients had lower daytime activity counts than controls.
Geoffroy et al. (2014a)	21	16 BD I,8 BD II, 2 BD NOS 29 Controls	53.5 (11.5) 54.1 (9.1)	65% 45%	Greater SOL, TST, sleep fragmentation and lower SE in the BD group. BD group greater inter daily sleep variability and more variable TIB, TST, SE and fragmentation index than controls.
McKenna et al. (2014)	7	14 BD I 14 Controls	49.1 (11.3) 46.4 (15.0)	79% 71%	BD lower SE and trend to greater TST. BD lower mean activity, longer period and more variable sleep/wake rhythm than controls.
Verkooijen et al (2017b)	14	87 BD 75 Controls	50.3 (11.6) 46.8 (16.3)	56% 51%	No differences in TST, SOL, SE and WASO between BD and controls.

BD = bipolar disorder, SOL = sleep onset latency, TST = total sleep time, TIB = time in bed, SE = sleep efficiency, WASO = wake after sleep onset, RA = relative amplitude between day and night activity.

in TST compared to that of 0.57 in the Geoffroy et al. (2014b) meta-analysis. The I^2 or chi squared statistics were not published. This new meta-analysis also reported SMD's of 0.31 (p=0.001) for SOL, -0.30 (p=0.002) for SE and 0.24 (p=0.009) for WASO between euthymic BD patients and controls. Other factors that could have caused the heterogeneity between findings in individual studies included variability in sleep assessment length (3 to 54 days), variability between study populations in terms of age (mean ages ranged 32.7 to 53.5 years), mood symptoms (remission criteria varied between studies), and the proportion of participants with BDI and BD II diagnoses (although most studies included only BDI populations). As a demonstration of these potential effects of these variables and the need for higher quality better controlled studies Geoffroy et al. (2014) found a larger standard mean difference in TST in studies with greater age differences between BD and controls using meta-regression. They also found that studies with lower residual depressive symptoms in the BD group trended towards finding a longer TST in the BD group. Therefore, further larger scale and more rigorously controlled studies are still required to confirm these reported differences between BD patients and controls and before definitive conclusions can be drawn. One further criticism of these data are that they report the mean of these sleep variables in their respective populations. Although on average there may be differences between BD patients and controls there is also likely large variability in sleep variables between individuals within individuals over time which are not captured in these statistics. Therefore reporting mean values may bear little relevance to individual patients and other methods should also be employed or reporting sleep characteristics of BD patients such as the proportions with short or long sleep.

BD patients subjectively rate their sleep as of poor quality. Harvey et al (2005) reported that 70% of euthymic BD patients scored > 5 on the PSQI which represents the presence of clinically significant sleep disturbance. The mean PSQI score of 7.9 was greater than that in controls (2.3) but lower than that in a group with insomnia (11.5). BD patients also exhibited misconceptions about their actual sleep similar to the insomnia group (such as overestimating SOL and underestimating TST) and had increased levels of anxiety and fear about poor sleep. Geoffroy et al (2014a) also reported lower subjective sleep quality in euthymic BD patients than controls (PSQI 7.38 vs 4.11) with lower scores on individual items of sleep quality, SE and greater sleep disturbances and daytime dysfunction. There were however no differences in daytime sleepiness assessed with the Epworth Sleepiness Scale (ESS) and mean scores were within the normal range. Data from the STEP-BD programme also found BD patients had significantly worse global PSQI scores than controls (4.8 versus 2.8 respectively). Worse scores were found on the individual items of SOL, use of sleep medication and daytime dysfunction (Cretu et al., 2016). Although the mean PSQI score was is in the normal range just over 50% of the BD sample had a PSQI > 5. Greater scores on the PSQI (53.1% scoring > 5) and on the Insomnia Severity Index (ISI) were also reported in euthymic BD patients compared to controls by Gershon et al. (2012). Ritter et al (2012) found BD patients with low levels of mood symptoms reported significantly more frequent and intense sleep disturbances, more non restorative sleep and more frequent episodes of insomnia and hypersomnia than controls. BD patients also reported more frequent and severe episodes of increased need for sleep, greater SOL, more difficulties waking up and getting out of bed and more frequent and longer daytime naps than controls.

In a small study St-Amand et al. (2013) compared euthymic BD patients to insomnia patients and controls. BD patients reported more severe sleep difficulties than controls on the Insomnia Severity Index (ISI) total score but these were less severe than in the insomnia group. Both BD and insomnia groups reported feeling less refreshed after sleep then controls, the BD group took significantly more daytime naps than the insomnia and control groups and BD patients had significantly greater scores on the ESS compared to controls. BD and insomnia patients also demonstrated more circadian variation in the time at which they performed daily activities than controls. Finally a study utilising sleep diaries over 7 days euthymic mostly BD I patients, insomnia patients and controls significant sleep disturbance was found in both the BD and insomnia groups compared to controls (Talbot et al., 2012). Specifically, SOL, nWAK, WASO, total wake time (TWT) and sleep efficiency were significantly different from controls all in the direction of poorer sleep in the patient groups. Insomnia patients were significantly different from the BD group in terms of longer SOL and WASO.

1.3.4.5 Summary of sleep in euthymic BD patients.

In summary objective and subjective assessments demonstrate sleep abnormalities in euthymic BD patients. Accelerometry collectively demonstrates a greater SOL, TST, WASO and variability in sleep than controls but lower SE. BD patients frequently subjectively rate their sleep quality as poor and worse than controls. Complaints of insomnia symptoms are common although the severity of poor sleep quality has not been as severe as in patients with diagnosed insomnia. Similar to people with insomnia BD patients have misconceptions about their sleep when compared to objectively assessed sleep variables. In

addition to insomnia symptoms a proportion of euthymic BD patients report an increased need for sleep, long sleep periods and that their sleep is often non-restorative. Higher rate of daytime sleepiness are also reported compared to controls.

1.3.4.6 The potential relationship between sleep and BD.

The observation that sleep disturbances are common in patients with BD and other mood disorders including in the prodrome of relapse and during euthymic periods led several authors to hypothesise that sleep and circadian disturbances rather than being an artefact of mood disturbance are a core part of the underlying aetiology and maintenance of mood disorders. Wehr and Wirz-Justice, (1982) initially proposed that sleep and circadian rhythm disturbances have a causal role in the development of depression. Their hypothesis was based on several observations of circadian rhythm abnormalities in patients with mood disorders. These included a phase advance in the diurnal rhythm of noradrenaline, a shortened REM sleep latency and early morning awakening indicating a phase advance in the sleep cycle and the diurnal variation in mood indicating that depressed mood may be exacerbated by a factor that exhibits a circadian rhythm. They also noted that depressive symptoms could be temporarily alleviated, or that mania could be induced, by advancing the timing of the sleep period or enforcing SD in mood disordered patients. In addition, antidepressant treatments including lithium, monoamine oxidase inhibitors and tricyclics have been demonstrated to influence the circadian rhythm of the sleep wake cycle or levels of neurotransmitters suggesting this was part of their mode of action. With specific relevance to BD Wehr et al. (1987) proposed that sleep reduction was a final common pathway in the genesis of mania. This hypothesis

was based on observations that manic episodes were often preceded by environmental factors such as long distance travel, emotional reactions to life events and childbirth. These environmental factors disrupt sleep/wake routines and may result in SD. In addition, experimentally induced SD has been demonstrated to precipitate manic episodes in a proportion of people with BD. Wehr et al. (1987) also suggested that since mania itself often results in sleep reduction, mania might become self-maintaining through a perpetual cycle of manic symptoms disrupting sleep/wake cycles which in turn maintain manic episodes.

Since these hypotheses were first proposed further evidence supportive of an association between sleep and mood has appeared resulting in updated hypotheses of a causal role of sleep disturbances in BD and other mood disorders (Harvey, 2008; Harvey, 2011; Gruber and Cassoff, 2014; Watling et al., 2017). Firstly, sleep loss has been demonstrated to effect emotions, emotional control and mood in heathy populations. Experimental studies have demonstrated that sleep loss increases negative mood and negative emotions to neutral and negative stimuli and diminish the ability to control emotions (Gruber and Cassoff, 2014; Palmer and Alfano, 2017; Watling et al., 2017). Evidence also emerged that sleep loss as well as enhancing negative emotions could result in a positive bias in the interpretation of emotional stimuli. Experimentally induced SD resulted in an amplified positive reactivity to pleasure evoking stimuli, so collectively the data demonstrated that sleep loss imposed a bi-directional nature of affective imbalance (Gujar et al., 2011). Underpinning the evidence for a relationship between sleep, emotion and mood, evidence emerged that sleep loss affects the neurobiological processes that underlie mood and emotional control (Ma et al.,

2015; Kaufmann et al., 2016). In one notable fMRI study healthy participants who experienced 35 hours of total SD demonstrated a 60% greater amygdala activation and a 3 fold increase in activated amygdala volume to negative emotional images than a control group who had a normal night sleep (Yoo et al., 2007). There were no differences between groups in amygdala activation when shown neutral images. The increase in limbic activity was also associated with a loss of functional connectivity with the medial prefrontal cortex (mPFC) in the SD group. The mPFC is an area of the brain thought to exert a controlling effect on amygdala function and so this study suggests there was a failure of top-down, prefrontal control of emotional processing in subjects who were sleep deprived. In the study demonstrating amplified positive reactivity following SD, fMRI found an amplification of reactivity throughout the mesolimbic reward brain networks that correlated with the bias in positively rated stimuli (Gujar et al., 2011).

Collectively this evidence supported a role for sleep loss and a mechanism of action in the regulation of emotions and mood. However, in addition to experimental evidence it is important to know if sleep disturbances seen in clinical BD populations are sufficient to be associated with changes in neurobiological function, emotion and mood. As BD is associated with an overactive limbic system and underactive frontal brain areas (Strakowski et al., 2005; Chen et al., 2011), it is possible that patients with BD are more vulnerable than healthy people to the effects of sleep disturbance on brain function. This may mean clinical sleep disturbances are therefore sufficient to have significant effects on emotional regulation and mood people with BD. Studies examining the association of sleep disturbances with mood episodes have been performed in BD but with differing findings on the polarity of mood symptoms. A small study

(n=11) found that decreased sleep duration was the best predictor of manic or hypomanic symptoms the following day but there was no association with between sleep duration and depressive symptoms (Leibenluft et al., 1996). Conversely, a longitudinal study assessing clinical sleep variation and mood found that shorter sleep duration predicted increased depressive symptoms over the following 6 months but not manic symptoms (Perlman et al., 2006). It was noted however that the development of manic symptoms may have been missed as patients were only followed monthly and manic symptoms may increase within hours or days of sleep loss. Eidelman et al. (2010) found that inter-episode sleep was associated with illness course and mood episodes. Lower and more variable sleep efficiency and more variable TWT were associated with a greater number of lifetime depressive episodes. This demonstrated that an unstable sleeping pattern may be a correlate of or contributor to depressive episodes. Additionally variability in SOL was found to be positively correlated with current depressive symptoms and SE was positively correlated with concurrent manic symptoms. This later finding of a positive correlation of increased SE and manic symptoms is contrary to what may be predicted. This relationship was proposed to be due to the fact that patients with manic symptoms may be more likely to leave the bed when awake rather than remain in bed attempting to get back to sleep resulting in better SE. Talbot et al. (2009) explored whether mood could influence sleep in BD patients. In this study PSG was used to assess sleep variables following mood stimulation. Following a happy mood induction euthymic BD patients had longer SOL compared to controls. Controls had a reduction in SOL on happy mood induction nights compared to baseline nights whereas BD patients showed no change in SOL compared to baseline nights. It

was suggested that this demonstrated that BD patients were less able to control the effects of positive stimuli resulting in more difficulty falling asleep thus demonstrating that daily events that affect mood or emotion may have an effect on sleep characteristics. Extending these findings Talbot et al. (2012) found that TWT was associated with next morning negative mood in euthymic BD patients and evening negative mood was associated with next night TWT thus providing evidence for the bidirectional effects of mood and sleep which may be mutually maintaining. A weakness of this study however was that sleep was only assessed subjectively with diaries. In an 8-week longitudinal study utilising actigraphy and sleep diaries to estimate sleep, longer actigraphy estimated SOL was coupled with higher negative affect more strongly in euthymic BD I patients than controls (Gershon et al., 2012). In addition longer TWT after sleep onset and lower SE as assessed by sleep diaries was also more strongly coupled to greater negative affect in BD patients than controls. There was no evidence for a coupling of sleep measures with positive affect. Saunders et al. (2015)(2015) found that poorer sleep quality assessed with the PSQI at baseline predicted increased severity and frequency of depressive episodes, increased severity of manic episodes and increased frequency of mixed episodes over the following 2-year period in women with BD. In men however, baseline depression and neuroticism were stronger predictors of mood outcome than sleep quality. A recent study has also found that sleep loss may have differential effects on mood dependant on gender and BD subtype (Lewis et al., 2018). In this large study, 3140 BD participants were asked during a semi-structured interview whether sleep loss had triggered mood episodes. Sleep loss triggering high mood was associated with female gender and BDI subtype. Women and those with BD II

were more likely to report sleep loss triggering episodes of depression than men but these differences did not reach statistical significance. The findings in this study may explain the different associations found between mood and sleep loss in previous studies dependant of on the differing populations studied. Finally, a study examining the effects of treating insomnia in BD patients has provided evidence that sleep loss may have a causal role in mood disturbance. In this study euthymic BD I patients with insomnia received either cognitive behavioural therapy for insomnia (CBTi) or psychoeducation. Outcomes were assessed at the end of eight treatment sessions and again 6 months later (Harvey et al., 2015). The CBTi group experienced higher rates of insomnia remission than the psychoeducation group and during the 6 month follow up had fewer days in a BD episode (3.3 days vs. 25.5 days). In addition, the CBTi group experienced a significantly lower mania/hypomania relapse rate (4.6% vs. 31.6%) and a lower overall mood episode relapse rate (13.6% vs. 42.1%). The rate of depressive relapse although lower in the CBTi group (9.1% vs. 21.1%) did not reach statistical significance.

In summary there is evidence demonstrating that sleep loss is associated with changes in emotional regulation and mood and evidence of that sleep loss results in neurobiological changes in brain areas that regulate mood and emotions. There is also some evidence of a bidirectional relationship between mood and sleep in BD patients. The evidence base would though benefit from further studies with objective assessment of sleep disturbances as many of the current studies relied on sleep diaries to assess sleep. However, although it has still not been definitively demonstrated that sleep disturbances have a causal role in mood relapses and the maintenance of mood episodes this evidence and the

findings that sleep disturbances are one of the most common symptoms reported during the prodrome of mood relapses suggests a causal role for sleep disturbances in the pathophysiology of BD. That treatment of insomnia in euthymic BD patients led to fewer relapses is supportive of this view. Figure 1.5 illustrates a model connecting sleep, emotional regulation and mood proposed by Watling et al. (2017). In this model there is a direct causal relationship between sleep and both emotion and emotional control whereas the relationship between sleep and mood is bidirectional. Sleep disturbances result in impairments in emotional processing and regulation that lead to mood changes. These mood changes may then lead to further sleep disturbances which then reinforce the emotional and mood changes. Over time this may lead to more significant mood changes and the development of clinical mood disorders.

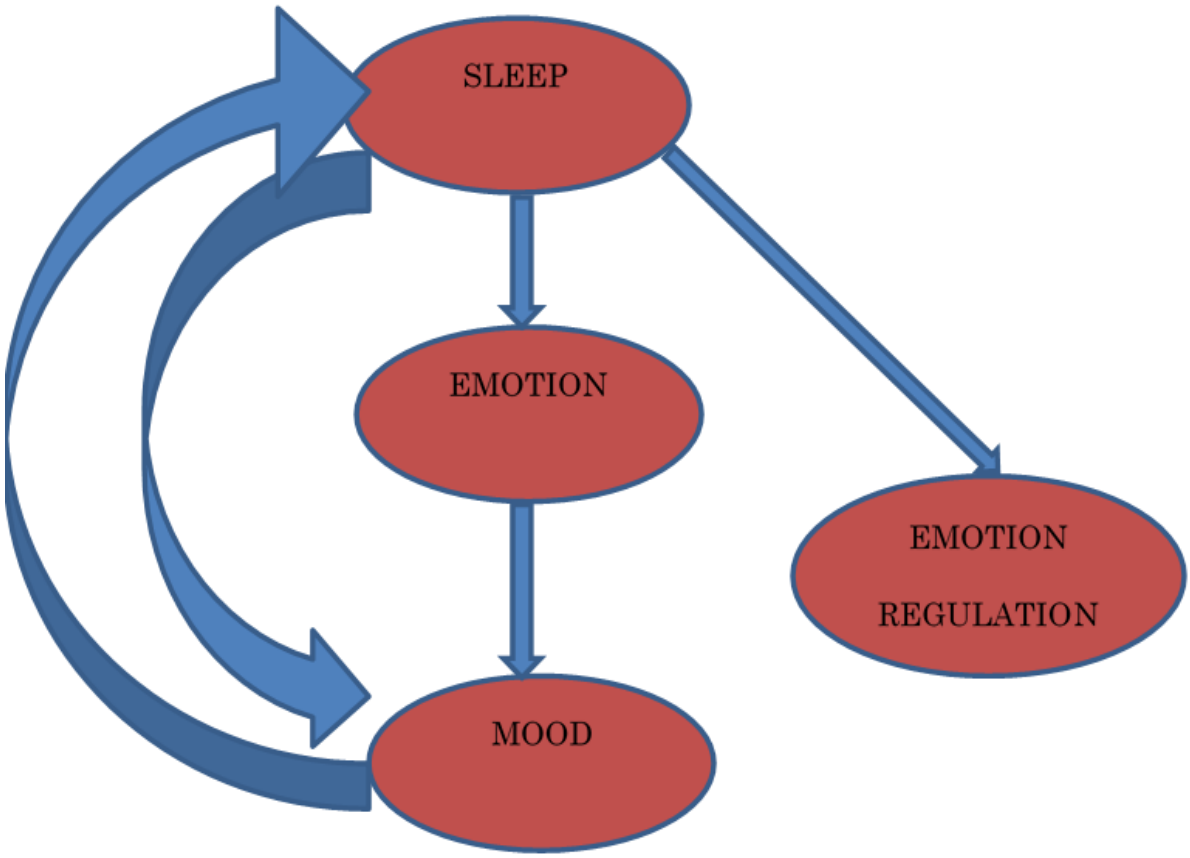


Figure 1.5 Theoretical model of the relationship between sleep, emotion, emotion regulation and mood. (From Watling et al., 2017).

In support of this model a recent study demonstrated that maladaptive emotional regulation mediated cross sectional and prospective relationships between poor sleep quality and depressive symptoms in participants with current or remitted major depressive disorder and healthy controls (O'Leary et al., 2017).

The evidence for a causal relationship between sleep and mood has implications for the investigation of the association of sleep and cognitive function. Cognitive function is also influence by mood (McDermott and Ebmeier, 2009) and therefore it will be important to control for the effects of mood when examining the association between sleep and cognitive function. It is possible that any association between sleep and cognitive function could be mediated by associated changes in mood and emotional processing. In addition, mood and sleep may have separate but additive effects on cognitive function. It is therefore possible that BD patients with mood and sleep disturbances will have greater cognitive impairment than patients with either of these symptoms alone. Finally, it is also possible that there will be an association between sleep disturbances and cognitive function but this may be mediated by other factors. It is possible that patients with a more severe course of illness experience a greater number and severity of mood episodes which they cause a greater degree of cognitive impairment and sleep abnormalities. If possible studies examining the association between sleep and cognitive function should also assess markers of disease severity so that these can be controlled for.

1.3.5 The prevalence of primary sleep disorders in BD.

Although the above data clearly demonstrates the presence of sleep abnormalities in BD patients the question arises as to the prevalence of sleep

disorders such as insomnia, hypersomnia and sleep apnoea that meet diagnostic criteria in BD.

1.3.5.1 Insomnia in BD

The core features of insomnia are difficulty initiating or maintaining sleep and waking up earlier than desired (American Academy of Sleep Medicine, 2014). These symptoms must also be associated with at least one consequence of fatigue, impaired cognitive or social function, mood disturbance/irritability, daytime sleepiness, reduced energy, proneness for accidents/errors or daytime sleepiness. Collectively available data demonstrate that symptoms of insomnia are common in BD and potentially high numbers of patients may meet diagnostic criteria. Harvey at al. (2005) found 55% of a small cohort of euthymic BD I patients met DSM-IV diagnostic criteria whereas St-Amand et al. (2013) found only 2/14 (14%) of euthymic BD patients met diagnostic criteria based on a combination of DSM-IV and International Classification of Sleep Disorders 1st edition (ICSD-1) criteria. Kanady et al., (2015) performed a 5-year retrospective chart review of 51 BD I patients who had comorbid insomnia at baseline, (diagnosis established using the Duke Structured Interview for Sleep Disorders (DSISD). Thirty-eight percent of the months patients spent in the manic phase, 52% in the depressed and 67% during inter-episode periods were spent meeting the insomnia criteria (DSM-IV and ICSD-2) and insomnia persisted over a 5 years period in 59% of the participants. Insomnia symptoms often co-existed with other sleep complaints, for example with reduced sleep need, irregular sleep and hypersomnia. To more accurately estimate the prevalence of syndromal insomnia prospective longitudinal studies including objective sleep assessments such as PSG or accelerometry are required. The need for this is highlighted by the fact that

studies have demonstrated that BD patients have dysfunctional views about their sleep and often overestimate time awake compared with objective measures e.g. Harvey et al.(2005). This may reduce the accuracy of subjective studies. In addition, none of the studies systematically assessed patients for the presence of other sleep disorders such as periodic limb movement in sleep (PLMS) or OSA both of which may lead to an increase in insomnia type symptoms.

1.3.5.2 Hypersomnia in BD.

ICSD-3 diagnostic criteria for hypersomnia associated with a psychiatric disorder requires patients to experience daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months with the symptoms not better explained by another sleep disorder, medical or neurological disorder, or the effects of medications or drugs (American Academy of Sleep Medicine, 2014). Essential features include excessive nocturnal sleep, daytime sleepiness, or excessive napping. Patients with hypersomnia often report poor quality and non-restorative sleep resulting in poor work attendance, full days in bed, social withdrawal, apathy, and feelings of low energy.

Kaplan et al. (2009) reviewed the literature on hypersomnia and BD. They found the reported prevalence ranged from 17 to 78% in BD depression, (at this time there were no studies in euthymic BD patients), but none of the studies reported the criteria for hypersomnia used making it impossible to understand if patients reported symptoms of hypersomnia or met full syndromal criteria. In their review Kaplan et al. (2009) raised the question of whether hypersomnia in psychiatric patients is more a disorder of increased TST or increased TIB. This question was posed as a PSG study found that mood disorder patients with hypersomnia had

shorter TST, only 14% had TST > 9 hours, and longer SOL than patients with idiopathic hypersomnia. However these patients tended to spend a lot of time in bed (Billiard et al., 1994). In addition after finding normal SOL in depressed BD patients i.e. no increase in sleep propensity, Nofziner et al. (1991) had suggested that psychiatric hypersomnia was more likely related to the lack of interest, decreased energy, psychomotor withdrawal and anergia than an increased sleep propensity. Several other lines of evidence support this view. Vgontzas et al. (2000) found a lower sleep propensity and more disturbed sleep in mood disorder patients diagnosed with psychiatric hypersomnia than in patients with primary hypersomnia. A study in euthymic BD also found that of the 25% of patients thought to suffer with hypersomnia, only 2 individuals indicated they slept > 9 hours on a sleep diary while 17 individuals indicated they spent > 9 hours TIB (Kaplan et al., 2011). Kaplan et al. (2015) sought to identify hypersomnia subtypes in euthymic BD patients. The presence of hypersomnia was established with questionnaires and sleep diaries enquiring about typical and maximum sleep lengths and naps, excessive daytime sleepiness. A subset of patients also completed one week of accelerometry which was used to objectively calculate TST and TIB. Two sleep groups were identified, those who reported sleeping over 9 hours per night and those with normal sleep length (mean 7.1 hours) but excessive daytime sleepiness. However, when examining the long sleep and excessive sleepiness subtypes the accelerometry data suggested that the long sleep subtype was actually better characterised by long TIB rather than actual long sleep. In the long sleep subtype mean accelerometry TST was just 7.69 hours whereas accelerometry TIB was 10.05 hours demonstrating participants had overestimated their actual TST subjectively and on the sleep diaries. Collectively

then this data does suggest that hypersomnia in BD may be best characterised by long TIB rather than long TST and a further subtype have normal TST but suffer from excessive daytime sleepiness. Finally, studies have demonstrated that hypersomnia in BD may be more prevalent during depressive episodes and also commonly co-exists with symptoms of insomnia (Soehner and Harvey, 2012; Kanady et al., 2015).

In conclusion symptoms of hypersomnia including long TST and excessive daytime sleepiness are commonly reported in BD but may be more frequent during depressive episodes. However, hypersomnia in BD is probably best described as long TIB or those experiencing excessive daytime sleepiness. It should however be noted that there are no studies using objective longitudinal assessment of sleep to accurately estimate the prevalence of full syndromal hypersomnia.

1.3.5.3 Obstructive sleep apnoea in BD.

Obstructive Sleep Apnoea (OSA) is characterised by intermittent airway collapse which impairs ventilation resulting in intermittent hypoxia and hyercapnea, increased sympathetic nervous activity and sleep distruption (Kapur, 2010). Untreated OSA has many consequences and symptoms including daytime fatigue and sleepiness, impaired cognitive function, social interactions and QoL and increased risk of developing cardiovascular diseases and metabolic syndrome (Kapur et al., 2017). OSA may also contribute to the sleep and cognitive abnormalities in people with BD. A recent meta-analysis found a prevalence of OSA in 681 BD patients objectively tested for OSA of 24.5% and OSA was associated with increasing age and BMI (Stubbs et al., 2016).

1.3.6 Circadian rhythm abnormalities in BD.

Circadian rhythm has been examined in BD patients through a variety of methods including assessment of chronotype, the genetics of the circadian clock system, accelerometry to assess the timing of the sleep wake cycle and biomarkers such as melatonin to assess the core biological circadian rhythm.

1.3.6.1 Chronotype in BD.

In at risk individuals compared to controls no differences in chronotype have so far been reported (Melo et al., 2016b) but in adults with confirmed BD six studies have found a greater prevalence of evening chronotypes in BD than controls and one study no difference (Melo et al., 2016a). It has been reported that evening preference is both persistent and independent of mood symptoms in BD patients and may therefore be a trait marker for BD (Seleem et al., 2015).

1.3.6.2 Accelerometry derived evidence of circadian abnormalities in BD.

Many of the accelerometry studies reported above also provide evidence for circadian rhythm disturbances in BD. Increased variability in night to night TST, TIB, SE, sleep fragmentation and activity and a lower RA has been reported indicating a more variable and less stable circadian rhythm in BD (Millar et al., 2004; Jones et al., 2005; Salvatore et al., 2008; Ritter et al., 2012; Geoffroy et al., 2014a; McKenna et al., 2014). It has also been demonstrated that disruptions in circadian rhythm may develop over time in BD and may be worse during mood episodes (Grierson et al., 2016). Krane-Gartiser et al. (2016) used accelerometry in 43 euthymic BD patients with subjective sleep disturbances to assess circadian rhythm. Unstable circadian rhythm was defined as a diurnal active period duration with variation greater than 2 hours from the mean during one week of

accelerometry. Patients with this pattern had a trend to greater eveningness and went to bed and got up significantly later than those with a stable circadian rhythm. There was also a significantly greater variance in between night go to bed and get up times, minute to minute activity and within and between day variability in activity level in this group. With regards to physical activity several accelerometry studies have reported lower daytime activity in BD than controls (Harvey et al., 2005; Jones et al., 2005; St-Amand et al., 2013; McKenna et al., 2014) and meta-analysis of accelerometry data supports these findings (Ng et al., 2015; De Crescenzo et al., 2017).

1.3.6.3 Circadian rhythm disorders in BD.

Circadian rhythm disorders have been reported in BD. Krane-Gartiser et al. (2016) diagnosed 11/43 (26%) of a cohort of euthymic BD participants with subjective sleep complaints with delayed sleep phase disorder and 21/43 (49%) were identified with unstable circadian rhythms. Delayed sleep phase (the major sleep episode is two or more hours later relative to the desired bedtime) (7%) and irregular sleep patterns (inconsistent and fragmented sleep and an erratic sleep-wake routine) (9%) were also found by Kanady et al. (2015) in a cohort of euthymic BD patients with comorbid insomnia. In young depressed BD patients (mean age 23.2 years) 62% had a delayed sleep phase (defined as sleep onset > 1.30am or sleep offset > 10.00am) which was a significantly greater proportion than those with unipolar depression (30%) or controls (10%) (Robillard et al., 2013a).

1.3.6.4 Subjective assessment of biological rhythm in BD.

Biological rhythms in BD patients have been assessed with the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (Giglio et al., 2009b). The BRIAN is a self-completed semi structured scale designed to assess the regularity of biological rhythms in the domains of sleep, activity, social life and eating pattern in people with BD. In the validation study euthymic BD patients were found to have greater scores than controls across all domains assessed (sleep, activities, social rhythm and eating pattern) indicating greater rhythm disturbance in these domains.

1.3.6.5 Melatonin secretion in BD.

Lewy et al, (1981; 1985) demonstrated that night time melatonin levels declined twice as much in manic and euthymic BD subjects than in controls in response to light, a result replicated by Nathan et al, (1999) in depressed BD patients and Hallam et al. (2009) in euthymic BD I patients. Abnormal suppression of melatonin by light was also reported to be more likely in 18 young people with a parent with BD and 7 young people with a major affective disorder on both sides of the family suggesting it may be an endophenotypic marker for the development of affective disorders (Nurnberger et al., 1988). In contrast, however, neither Whalley et al, (1991) or Nurnberger et al, (2000) found differences in melatonin suppression to light between euthymic BD and controls (although in the Nurnberger study there was a trend to greater suppression in patients with BD I). Lam et al, (1990) found the opposite in that controls had greater suppression than acutely ill BD patients. However, both Nurnberger et al. and Lam et al. did find significant melatonin abnormalities in that BD patients had significantly lower baseline melatonin levels than controls. Kennedy

et al. (1996) found no significant differences in serum melatonin in BD patients across mood states but lower levels of serum melatonin, (but not urinary 6-sulpha-toxymelatonin (aMT6S)) were found in depressed BD patients compared to controls. Souetre et al. (1989) found significantly lower 24-hour mean melatonin levels in 16 depressed patients (n=11 BD, n=5 Major Depressive Disorder (MDD)) compared to controls and night time melatonin and amplitude was significantly lower in depressed patients than recovered patients or controls. Manic BD patients were found to have higher daytime salivary melatonin levels than both controls and depressed BD patients by Novakova et al. (2015). Robillard et al. (2013b) assessed salivary melatonin levels under dim light conditions in young depressed BD and unipolar patients and found abnormalities in secretion timing. Compared to the unipolar group the BD group had a significantly later dim light melatonin onset (DLMO) and a significantly lower melatonin area under the curve. Accelerometry assessed sleep onset and offset times indicated there was an association between DLMO and actual sleep behaviour in the majority but not all patients.

Collectively these data suggest abnormalities in melatonin secretion in at least a subset of BD patients with lower levels of melatonin and delayed DLMO in depressed patients and a possible greater reduction in melatonin secretion due to light exposure in BD patients than controls.

1.3.7 The potential influence of medication on sleep in BD.

In the vast majority of the studies that assessed sleep function BD participants were taking psychotropic medications. Medications can influence sleep in several ways. As they treat both depression and mania, sleep function may improve as a

result of normalisation of mood. Many psychotropic medications also have sedative or alerting properties which could directly influence sleep and daytime activities. Some medications alter sleep architecture e.g. fluoxetine supresses REM sleep (Rush et al., 1998) and others, such as atypical antipsychotics, have been associated with an increased risk for sleep apnoea (Linselle et al., 2016). With regards to melatonin secretion, lithium and sodium valproate have been demonstrated to reduce the sensitivity of melatonin secretion to light in healthy volunteers and it has been claimed that normalisation of melatonin light sensitivity may be part of these drugs mode of action (Hallam et al., 2005b; Hallam et al., 2005a). Monteleone et al. (1989; 1997) also demonstrated that sodium valproate and benzodiazepines reduce nocturnal plasma levels in healthy volunteers and therefore it is possible that medications used to treat BD may influence the circadian system and sleep/wake timing.

There is no easy way of dealing with the effects of medications in sleep studies but Phillips et al. (2008) suggested several methods. These included comparing groups of patients taking each class of medication with other patients not taking that class of medication; converting the dose of each medication within a specific class into dose equivalents of prototypical medications for each class e.g. chlorpromazine equivalents for antipsychotics, followed by correlation analyses to examine the associations of medication load on sleep variables; and a composite score to indicate total medication load which can be used as a covariate in analyses that takes into account the variety, dose and duration of different medications taken. Using this later approach Kaplan et al. (2015) found no association of medication load on either long sleep or excessive sleepiness in BD patients with hypersomnia.

1.3.8 Psychosocial function in BD and the impact of sleep.

In past eras it was believed that mood symptoms in BD were episodic in nature and that long term outcomes including good functional recovery were common (Zarate et al., 2000). Research into functional recovery has however changed that perspective and whilst the severity of functional impairment may increase during acute phases of the illness (Judd et al., 2005; Rosa et al., 2010b) it remains impaired during euthymia with as few as one third of BD patients achieving full social and occupational functioning equivalent to their premorbid levels (Huxley and Baldessarini, 2007). An extensive review of function in BD has identified that social, work and family function were most impaired in BD and that the factors most consistently associated with impaired function were subsyndromal symptoms, comorbid conditions such as substance abuse, anxiety disorders and impaired cognitive function (Sanchez-Moreno et al., 2009). A comprehensive review of the role of cognitive impairment found that cognitive deficits are associated with general and domain specific function across mood states in BD (Baune and Malhi, 2015). A review of prospective studies found that better verbal learning and memory, processing speed, attention and executive functions were associated with better general and occupational function and possibly better predictors of outcome than the severity of affective symptoms. There is also evidence that sleep and circadian rhythm may have a role in the moderation of psychosocial function in BD. In euthymic BD patients Giglio et al. (2009a) found that BD patients with sleep complaints had significantly greater disability on the work, social and family components of the Sheehan Disability Scale and lower scores on the Global Assessment of Functioning (GAF) than BD patients without sleep complaints. In the STEP-BD it was found that short sleepers (< 6hours

sleep per night) and long sleepers (> 9 hours sleep per night) had lower function as measured by the GAF and the LIFE Range of Impaired Functioning Tool (LIFE-RIFT), than normal sleepers (6.5-8.5 hours sleep per night) (Gruber et al., 2009). However, when examining only euthymic patients there were no differences between groups on the GAF although euthymic short sleepers had lower LIFE-RIFT scores than normal sleepers. A 2-year longitudinal study found a positive association between sleep disturbances, mood and psychosocial function in adolescent BD patients (Lunsford-Avery et al., 2012). Walz et al. (2013) found that sleep disturbances and excessive daytime sleepiness, although related, were both independent predictors of function in euthymic BD patients.

The role of circadian rhythm disturbances on function in BD has also been investigated using the BRIAN. Giglio et al (2010) found biological rhythm was a strong predictor of function in euthymic BD patients with greater rhythm disturbance associated with lower function. In a regression model BRIAN along with depressive symptoms and age accounted for 60.5% of the variance in function with BRIAN score being the strongest independent predictor. Another study utilising the BRIAN also found that biological rhythm disturbance was associated with function (Pinho et al., 2015). Greater depressive symptoms were associated with greater biological rhythm disturbance in a dose dependant manner but both were independent predictors of function.

In summary people with BD suffer from impaired psychosocial function and although worse during acute mood episodes the majority of patients do not achieve full functional recovery even during euthymia. Subsyndromal depressive symptoms in particular and cognitive impairments are associated with decreased

function and increasing evidence suggests that sleep and circadian dysfunction may also make a significant contribution. A major limitation of the associations between sleep and psychosocial function are however that all sleep assessments to date have been subjective.

1.3.9 Quality of Life in BD and the impact of sleep.

According the World Health Organisation (1995) QoL refers to a persons perceived well-being across a broad range of domains including areas such as physical and mental health, social and leisure activities, finances, work life and cognitions. Systematic reviews of the literature have demonstrated a significantly reduced QoL in BD patients including in euthymic patients but depressed mood, comorbid anxiety disorders and substance misuse are associated with greater reductions in QoL (Michalak et al., 2005; Ishak et al., 2012b). Cognitive impairment has also been found to be associated with lower QoL in BD. Brissos et al. (2008) found significant negative correlations of performance on executive functions and verbal abstraction with all domains of QoL in euthymic BD patients and Pattanayak et al. (2012) found impairments in cognitive flexibility and set shifting (executive functions) explained 12-32% of the variance in psychological and social domains of QoL. Mackala et al. (2014) found deficits in sustained attention, verbal and working memory and executive functioning explained 15% of the variance in QoL in addition to that explained by mood in euthymic BD patients who had recently recovered from their first manic episode.

Few studies have examined the association between sleep and QoL in BD. In the STEP-BD study short (<6hours per night) and long (>9hours per night) sleepers had poorer life satisfaction compared to normal sleepers (6.5-8.5 hours per night)

(Gruber et al., 2009) and a recent study found lower QoL was associated with greater depressive symptoms, greater biological rhythm disturbance and lower sleep quality (Cudney et al., 2016). However, as in studies assessing the association of psychosocial function and sleep a major limitation is that sleep was assessed subjectively.

1.3.10 Cognitive function in BD.

Clinicians report that people with BD frequently complain of not being able to perform at the level they were preceding the illness onset (Martinez-Aran et al., 2005). Many studies have demonstrated objective cognitive impairment in patients with BD, including euthymic patients, with medium to large effect sizes in domains of attention, processing speed, executive functions and learning and memory (Robinson et al., 2006; Bora et al., 2009).

1.3.10.1 The nature and magnitude of cognitive dysfunction in BD.

Small and selective cognitive deficits most consistently in response inhibition and verbal memory have been found in unaffected first degree relatives of BD patients (Robinson and Ferrier, 2006; Schulze et al., 2011) but these deficits are smaller than those found in BD patients (Arts et al., 2008; Bora et al., 2009). Cognitive deficits in attention, psychomotor speed, executive functions and verbal memory of moderate severity are present early in the course of BD (Lee et al., 2014; Bora and Pantelis, 2015; Daglas et al., 2015) and therefore not solely the result of long term illness or medication use.

1.3.10.1.1 Cognitive function in euthymic BD patients.

Numerous systematic and meta-analytic reviews have found evidence of cognitive impairment in euthymic BD patients (Quraishi and Frangou, 2002; Robinson et

al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009; Kurtz and Gerraty, 2009; Mann-Wrobel et al., 2011; Bourne et al., 2013; Cullen et al., 2016). Despite heterogeneity between individual studies and the differing inclusion criteria of the reviews the findings of these reviews are fairly consistent with the exception of the analysis reported by Mann-Wrobel et al. finding no deficit in intellectual and verbal abilities. Figure 1.6, Figure 1.7 and Figure 1.8 show graphical summaries of the effect sizes for the most commonly used cognitive tests found across the meta-analyses. Effect sizes for executive functions including verbal fluency, working memory, set shifting and inhibition were in the moderate to large range as were the effects sizes for learning and memory. Decrements in tasks of attention and processing speed were of moderate effect size. The meta-analysis reported by Bourne et al. (2013) was an individual patient meta-analysis of the data from the most comparable studies of cognitive function in euthymic BD. Individual patient meta-analyses have the advantage over summary statistic meta-analyses as primary study effect sizes can be adjusted for confounding factors such as age, education, IQ drug treatment and illness severity prior to meta-analysis. It is thought these analyses may therefore produce more accurate results. The authors were able to obtain individual patient data including age, IQ, current mood, age at onset, number of prior manic or depressed episodes (or hospitalisations) and drug treatment history from 25 out of an identified 45 studies and an additional 6 unpublished studies. Data was a priori adjusted for the potential confounders of age, IQ and gender and the confounding effects of residual mood, number of mood episodes and hospitalisations and drug use were explored with further regression analysis. The results found deficits of moderate effect size in the tasks of verbal learning,

TMT-A and TMT-B and digit span backwards. Decrements of small effect size were found for performance on the digit span forwards and WCST in BD patients. These effect sizes are lower than in the previous meta-analyses which the authors considered to be as a result of better control of the confounding effects of age, IQ and gender. The level of residual depressive symptoms and the effects of drug treatment had small effects on the outcome but could not explain the difference between groups. In addition, there were only small correlations of illness variables such as number of mood episodes and hospitalisations on the outcomes with small effect sizes for selected cognitive tests. The most recent systematic review differed from the previous reviews as it attempted to quantify the prevalence of cognitive impairment in euthymic adults with BD and describe the sociodemographic, clinical and other factors associated with cognitive impairment (Cullen et al., 2016). Previous meta-analyses present the mean difference between controls and patients but there are likely within group differences in cognitive performance with some patients having intact cognitions and others deficits compared to controls. Fifteen studies were found that reported prevalence data reported as the proportion of the sample falling below a cut off for cognitive impairment in the assessed domains. In these studies various impairment thresholds were used to describe the proportion of BD patients who were considered cognitively impaired. These were based on comparisons with score distributions based on published test performance norms or from a healthy control group. The thresholds for impairment reported in individual studies ranged from performing 1 standard deviation (SD) below the control or normal mean performance to 2.5 SD below. The primary cut off used as the threshold for cognitive impairment in this review was 1.64 SD below the mean

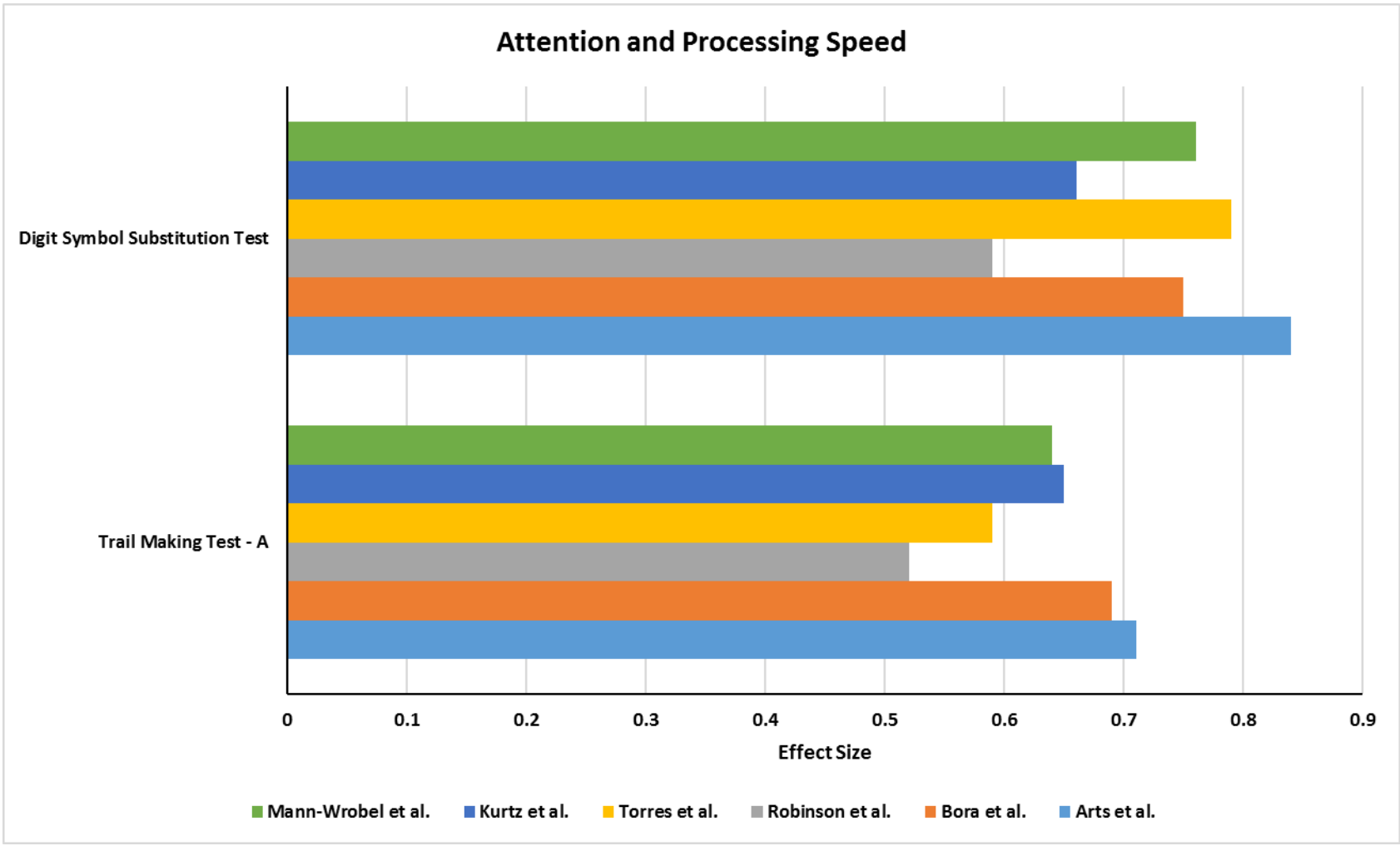


Figure 1.6 Summary of effect sizes (Cohen's d) for tests of attention and processing speed from meta-analyses comparing euthymic BD patients and controls.

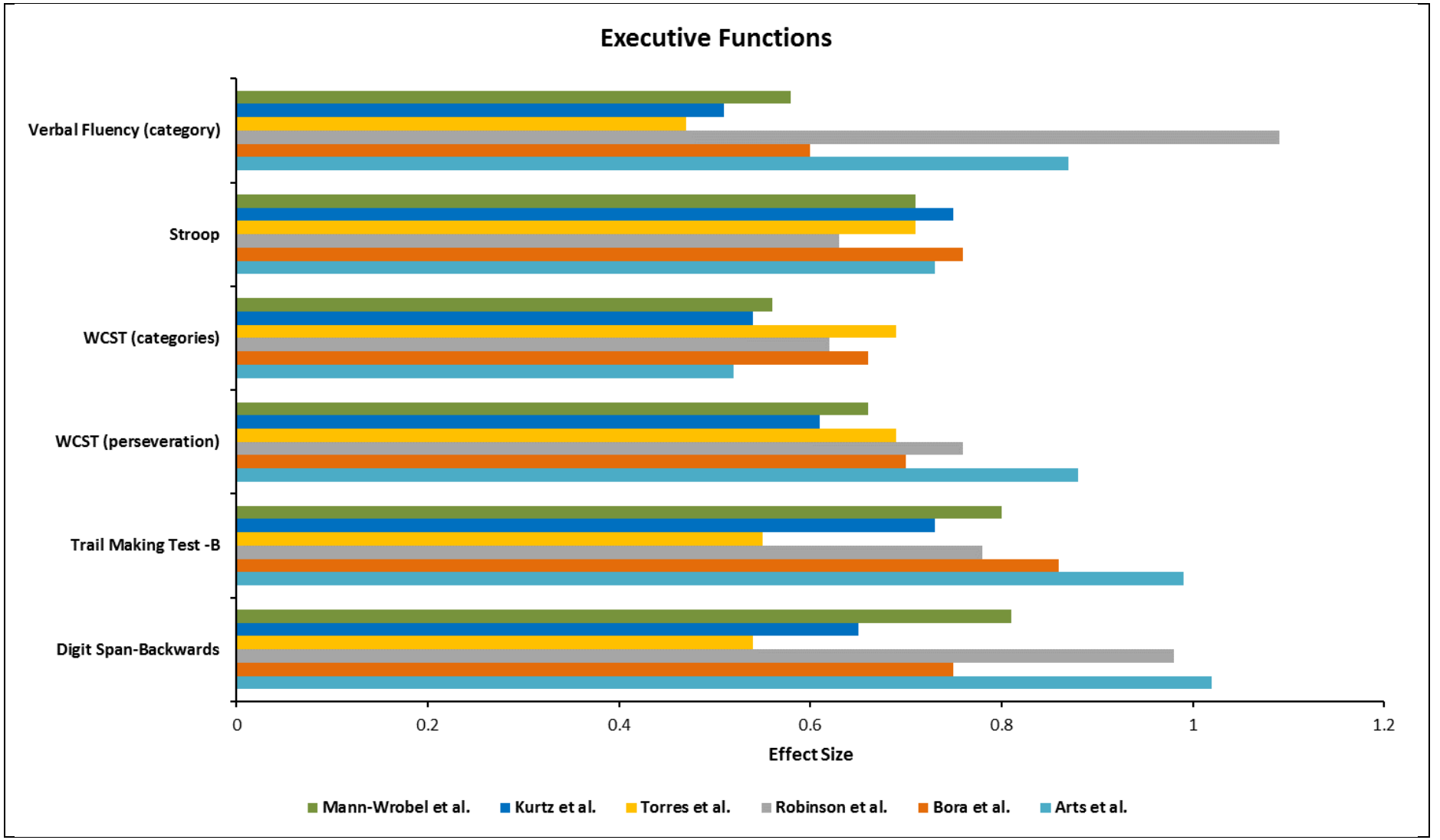


Figure 1.7 Summary of effect sizes (Cohen's d) for executive functions of euthymic BD patients compared to controls.

WSCT = Wisconsin Card Sorting Test

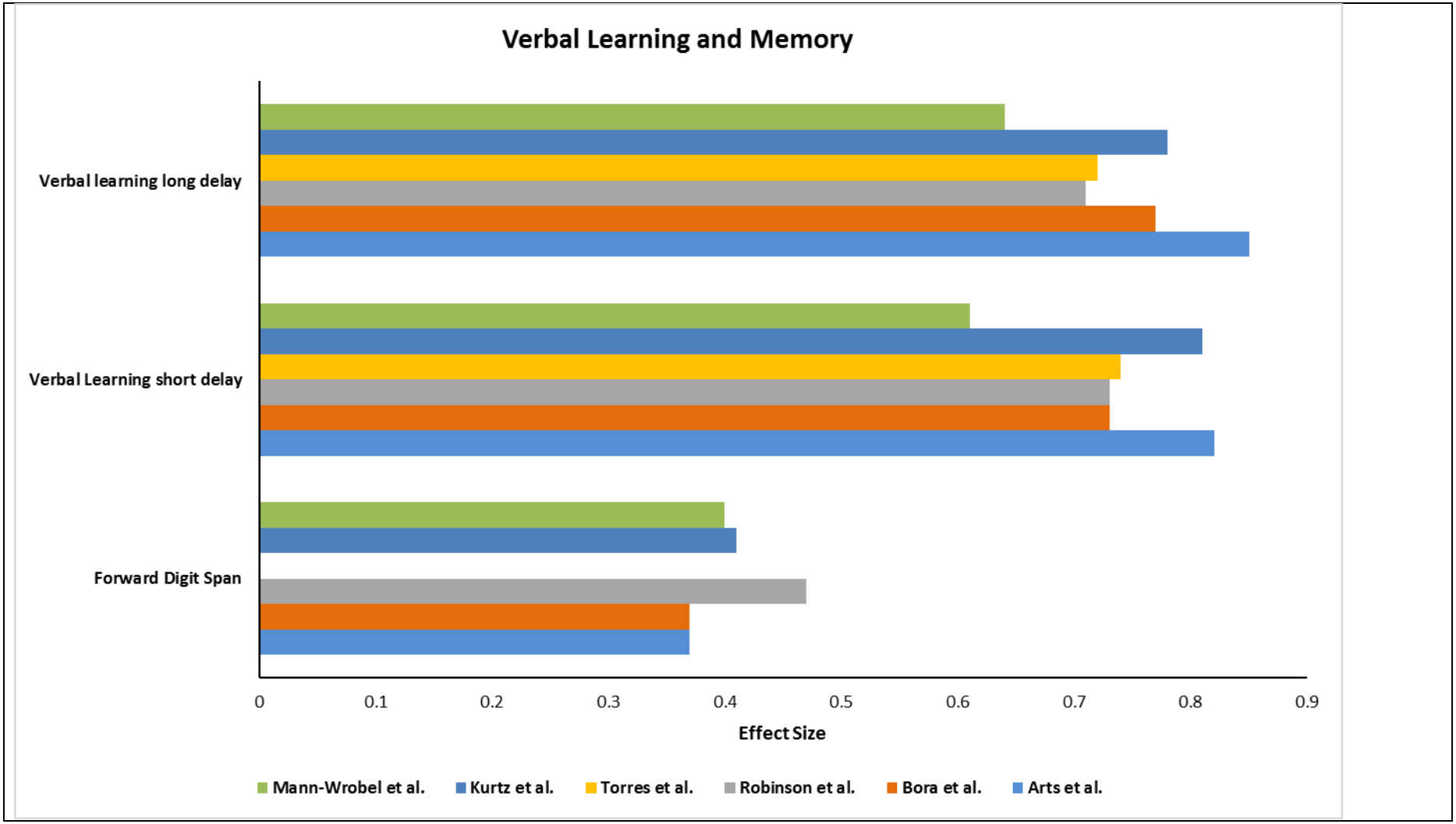


Figure 1.8 Summary of effect sizes for tests of learning and memory from meta-analyses of euthymic BD patients compared to controls.

which equates to the lower 5th percentile of performance in control subjects. BD patients who performed at or below the 5th percentile therefore performed worse on the test than 95% of control subjects or to put it another way as least as bad as the worst 5% of control subjects. At the 5th percentile impairment threshold prevalence rates ranged from 5.3% to 57.7% for executive functions meaning that 5.3% to 57.7% of BD patients performed at a level equal to or worse than the worst performing 5% of the control participants. It should be noted that subjects who did not perform at or below the 5th percentile of controls should not be described as having normal cognition. Normal cognition cannot be defined as there is a distribution of performance in healthy controls and BD patients. The 5th percentile simply represents the proportion of patients who performed at or below this predefined level and is considered to demonstrate impaired cognition. Executive function tests that included a speed component had a slightly greater prevalence of impairment than those without a speed component. The prevalence of deficits in attention/working memory ranged from 9.6% to 51.9%, for speed/reaction time (RT) 23.3% to 44.2%, for verbal memory 8.2% to 42.1% and for visual memory from 11.5% to 32.9% therefore demonstrating cognitive deficits are not uniform across the BD population. Some evidence for sources of variability was found with older age, lower education and premorbid ability and illness severity indices such as number of episodes and hospitalisations being associated with greater decrements in cognitive function. Regarding medication use the strongest evidence was for worse cognition in those taking antipsychotics although this was not a uniform finding across all studies. Mood stabilisers such as lithium and valproate were less frequently associated with cognitive impairment. Previous analyses have also found associations of cognitive

impairment with clinical course and premorbid function. In a narrative review of the literature Robinson and Ferrier, (2006) found that a greater number of manic episodes, number of hospitalisations and length of illness were associated with greater cognitive deficits and the fact that cognitive deficits are greater in patients than first degree relatives also suggests that there may be an impact of the illness on cognitive function (Bora et al., 2009). Anaya et al. (2016) and Martino et al. (2017) recently found evidence that greater premorbid intelligence may be protective against and moderate the cognitive decline found with indicators of increased illness severity such as number of hypo/manic episodes.

Differences in cognitive function between euthymic patients with BD I or BD II have been explored and Sole et al. (2011) performed a systematic review of the literature on this topic. There were fewer studies assessing cognition in BD II than BD I and there were inconsistencies between the studies with some finding greater deficits in BD I patients and some in BD II making it difficult to draw conclusions from the data. Moderators of cognitive function between BD I and BD II that may account for some of the inconsistent findings could be the number of depressive episodes and severity of residual depressive symptoms which may be greater in BD II. Also only BD I patients have experienced a full manic episode. Overall however it was concluded that there were only subtle differences in cognitive function between patients with BD I and BD II with BD II patients mainly demonstrating cognitive deficits in the domains of verbal memory, working memory and inhibitory control. Sustained attention has not been adequately assessed between groups to draw firm conclusions about function in this domain. Further studies with better control for potential confounders are required to draw more firm conclusions.

In conclusion these meta-analyses collectively provide evidence of substantial impairment across a number of cognitive domains in euthymic BD patients which are of generally moderate effect sizes and not entirely due to confounders such as age or IQ. Patients with a more severe course of illness may have slightly worse cognitive function although this may be moderated by pre-morbid IQ. Medication effects were inconsistent but generally found to be small with possibly antipsychotic medication being more frequently associated with worse cognitive function than mood stabilisers.

1.3.10.1.2 Cognitive function during mood episodes in BD.

The meta-analysis reported by Kurtz and Gerraty (2009) also examined cognitive function in patients with current mood episodes. There were far fewer studies of cognition in manic/mixed patients (n=13) and depressed patients (n=5) compared to euthymic patients (n=42) and therefore the results reported will need further confirmation in larger sample sizes. Compared to euthymic patients manic/mixed patients evidenced greater impairment in verbal memory and similar deficits in attention, phenomic fluency, WCST perseverative errors and on the TMT-A and B. During depressive phases greater deficits in verbal memory and phenomic fluency were found whilst a similar deficit on the TMT-A and B was found.

1.3.10.1.3 Are the widespread deficits in cognitive function in BD due to impairment in basic cognitive processes?

An unresolved issue regarding the nature of cognitive deficits in BD revolves around the question of whether the widespread cognitive deficits are due to primary deficits in each specifically impaired domain or these deficits are actually due to selective deficits in cognitive domains such as attention and

processing speed that then impact broader domains such as executive functions. Most if not all tests of cognitive function are not pure tests of specific cognitive domains but require intact function across several cognitive domains for optimal performance. This means that deficits for example in verbal learning could be due to an underlying deficit in for example attention. A failure to sustain attention during a verbal learning test may be the underlying cause of suboptimal performance rather than a primary deficit in verbal learning ability. There is evidence in unipolar polar depression that deficits in executive functions are secondary to deficits in attention. Nilsson et al. (2016) performed tasks assessing executive function and attention in depressed patients with MDD and used regression models to evaluate the role of attention in the executive processes. Deficits in attention and executive functions in MDD patients were demonstrated but regression models found that the attentional deficit persisted after variability in executive function was accounted for. However, the deficit in executive functions in the MDD group was no longer present when deficits in attention were accounted for. Thus, this data suggested that deficits in executive functions could be explained by deficits in attention and that attentional deficits may be the primary cognitive deficit in depression. In BD depressed and euthymic patients it has been demonstrated that deficits in processing speed and attention can between them entirely account for deficits in executive functions and verbal learning and thus may be the core deficits in people with BD (Gray et al. unpublished data). These findings are important as if the broader cognitive impairments found in BD can be reduced down to impairments in basic domains such as processing speed and attention then the aetiology of cognitive

impairment could be better understood and better treatment strategies developed.

1.4 Sleep and cognitive function.

1.4.1 Introduction to sleep and cognitive function.

Subjectively many people find a lack of, or disturbed sleep leads to mental fatigue and poor concentration and there is good experimental evidence that sleep loss has significant effects on normal brain function and the maintenance of daytime cognitive performance (Chuah and Chee, 2008; Waters and Bucks, 2011). In addition to sleep loss there are also performance consequences of altered sleep patterns including those resulting from shift work, prolonged work periods or primary sleep disorders such as sleep apnoea as they lead to accidents and loss of productivity (Akerstedt, 2000; Rosekind, 2005). However, the majority of what we know about the effects of sleep disruption on cognitive function has come from experimental studies in the laboratory which focus on sleep deprivation (SD) and attentional function. These studies have demonstrated the relationship between attentional performance deficits and sleep loss may be best explained by cumulative excessive wakefulness beyond a maximum period during which normal cognitive function can be maintained rather than actual hours of sleep loss (Van Dongen et al., 2003). In this model the critical period of wakefulness beyond which attentional deficits were detected was estimated to be a mean of 15.84 hours resulting in a mean sleep time required to prevent the build-up of attentional deficits of 8.16 hours out of each 24-hour period. This suggests that for the average person who experiences an increase in their hours of wakefulness beyond this time induced by their lifestyle, sleep disorders or psychiatric illness there may be an associated loss in optimum cognitive performance that continues

to accumulate with each additional 24-hour period of reduced sleep/increased wakefulness. It is however important to consider that sleep loss in clinical populations is different from that experimentally induced and may differentially affect individual cognitive domains (Jackson et al., 2013).

Several hypotheses have been put forward to explain the association between sleep loss and cognitive function. The state instability theory (Doran et al., 2001) is based on the observation that performance on sustained attention tasks during SD is interrupted by brief moments of low arousal when subjects are slow to or unable to respond to a stimulus. It is proposed that with increasing time awake and increasing homeostatic pressure to sleep brief moments of wake/sleep instability arise. Subjects experience a brief switch into a sleep state, (micro sleep) and RT increases or no response is made (a lapse) to a stimulus. Another hypothesis (termed the neuropsychological model), proposes that SD also impairs higher cognitive functions that are coordinated by the prefrontal cortex (PFC) in addition to attention (Harrison and Horne, 2000). It is stated that the PFC is one of the hardest working parts of the brain during wakefulness and that as this region of the brain undergoes recovery during slow wave sleep the PFC may be most vulnerable to SD resulting in cognitive deficits in addition to attentional lapses. A further hypothesis termed the controlled attention model (Pilcher et al., 2007) is based on the theory that controlled attention is required to block out distracting stimuli and maintain active attention to the task in hand. Pilcher et al. observed in their studies that SD had less effect on performance in more engaging and interesting tasks and that dull and monotonous tasks were more strongly impaired by SD. This is explained by the fact that the less stimulating tasks require greater top down effort (presumably from the PFC) to maintain

controlled attention whereas the more engaging tasks more readily maintain attention with less top down effort requirement and so performance can be maintained. It should be noted that these hypotheses are not mutually exclusive and that all may be applicable to the behavioural observations following sleep disruption.

As well as reduced sleep it should also be noted that evidence also suggests that cognitive performance may be impaired after extended sleep periods (Taub and Berger, 1976; Taub, 1980) and a shift in the phase of sleep periods without reducing the amount of sleep (Taub and Berger, 1974). Several large population studies have also found that longer sleep duration was associated with poorer cognitive performance in both younger and older adults and these are discussed later in this review. In addition to sleep duration there may also be other associations between sleep and cognitive function. For example it has been demonstrated that circadian misalignment of sleep periods as found in circadian rhythm sleep disorders (CRSD) also leads to decrements in cognitive performance (Reid et al., 2011). It may also be possible that other forms of sleep disturbance without a significant loss of total sleep time may also be a cause of cognitive impairment. For example, some people may experience significant breaks in sleep continuity disrupting normal sleep architecture but may still sleep for more than 8 hours over each 24-hour period by extending their time in bed or by taking daytime naps. It is therefore important to consider all the different types of altered sleep patterns that occur when examining associations of sleep and cognitive function in clinical populations such as BD where the sleep patterns both within and between individuals are so variable.

1.4.2 The nature and magnitude of cognitive impairment following sleep deprivation and sleep restriction in healthy volunteers.

The strongest evidence for an association between sleep and cognitive function comes from experimental studies. Several meta-analyses examining the data on effects of SD and in some cases SR on cognition in healthy subjects have been performed (Koslowsky and Babkoff, 1992; Pilcher and Huffcutt, 1996; Philibert, 2005; Lim and Dinges, 2010; Wickens et al., 2015). The most recent meta-analysis of short term SD (24-48 hours) (Lim and Dinges, 2010) has addressed some of the weaknesses of the previous analyses of SD by separating effect sizes into both speed and accuracy, using "finer grained" definitions of cognitive domains, controlling for study quality and for inter-individual differences found in vulnerability to cognitive effects of SD (Van Dongen et al., 2004). For this reason, this review will focus on the outcomes of this meta-analysis which included 70 studies of short term (24-48hours) SD including 1533 subjects and 147 different cognitive tests. Cognitive tests from the individual studies were grouped by the domains they assessed and the effect sizes for the impact of SD on performance can be found in Figure 1.9. This analysis demonstrated that SD has different effects on specific cognitive domains with the largest effect sizes for simple attention and vigilance tasks and more complex tests (e.g. reasoning) showing the lowest vulnerability to the effects of SD. Both speed and accuracy of cognitive performance were adversely affected to similar degrees in each domain. Lim and Dinges proposed that more complex attention tasks, which include functions such as orientation and inhibition, were only moderately impaired compared to simple attention tasks possibly due to the fact that these tasks are generally more engaging. Greater bottom up stimulation is required during more

monotonous tasks of simple attention, such as RT tasks, making them more vulnerable to the effects of SD. This finding is therefore supportive of the controlled attention hypothesis (Pilcher et al., 2007). Tasks of working memory, an executive function, were moderately impaired by SD for both speed and accuracy and SD had a smaller but still significant effect on short-term memory. A small but significant deficit in tasks involving processing speed was found for RT but not accuracy where the impairment was not significant. The small effect size for accuracy was proposed to be because the majority of processing speed tasks used in these studies were self-paced so participants possibly traded speed for accuracy. Alternatively it was suggested that many processing speed tasks

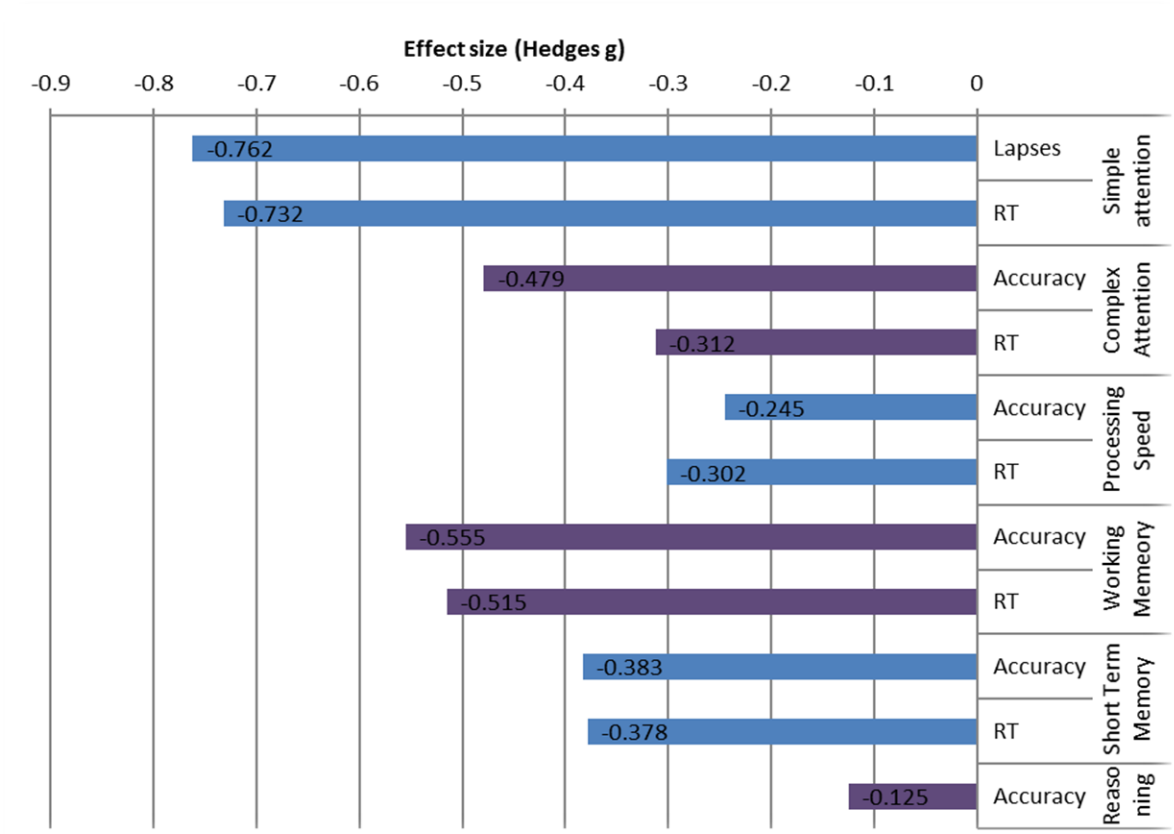


Figure 1.9 Summary of effects sizes (Hedges' g) for the impairment of cognitive domains short term following short term sleep deprivation in healthy participants.

such as the digit symbol substitution test (DSST) involve relatively automated responses which may be relatively unaffected by SD. Lim and Dinges also performed an analysis of potential moderators including time awake and circadian timing of task performance. In this analysis only time awake was found to be a significant moderator and this only for accuracy, not speed, with longer time awake associated with declining accuracy. Despite the lack of interaction in this meta-analysis circadian effects on performance have been noted in individual studies e.g. (Graw et al., 2004; Mollicone et al., 2010). The lack of finding for an effect in the meta-analysis was suggested to be due to the heterogeneity of tests used across studies for each cognitive domain and that there is considerable variation in endogenous circadian phase across individuals.

The effects of SD, SR and circadian phase on complex cognitive tasks were examined in the recent meta-analysis reported by Wickens et al. (2015). This meta-analysis included more studies and a wider range of complex tasks than previous analyses such as decision making, multi-tasking and team performance. The SD analysis included studies of more than 16-hours continuous wakefulness, SR analysis included studies with several consecutive nights of < 6 hours sleep and the effects of circadian timing (morning/afternoon vs. 10.00pm to 6.00am) of tasks during SD was also examined. As most studies did not report outcomes in a form where effect sizes could be calculated the percentage decrement in complex task performance as a function of sleep disruption was calculated. SD was found to impair performance on complex tasks by approximately 10% per day of SD in terms of both time to perform and accuracy. Performance of the tasks during the circadian night caused an additional decrement in performance compared to performance in the daytime particularly for accuracy where the decrement was

twice as large as during the day. Wickens et al. made a comparison to the decline in performance from representative studies of simple attention tasks and found that the decrement in performance in these tasks over 2-3 sleepless days was 2-3 times larger than the finding in this analysis for complex tasks. This finding is in agreement with the conclusions of Lim and Dinges, (2010) who also reported much larger effects of SD on simple than complex tasks as previously discussed. The effects of SR on complex tasks was investigated from five studies that restricted time in bed (TIB) to either 5-6 hours per night (mild SR) or 3-4 hours TIB per night (severe SR) up to a maximum of 7 consecutive nights. The analysis found that mild SR had virtually no effect on complex task performance accuracy but severe SR was associated with an accuracy decrement of 7% for each additional night of severe SR so approaching the 10% decrement after each night of SD. The speed of performance declined only by around 1.2% per day of severe SR.

In summary meta-analysis has demonstrated that SD and SR are associated with significant decrements in cognitive function with the degree of impairment variable between different cognitive domains. The major conclusions to draw are

- Short term SD and SR are both associated with impairment of cognitive function.
- SD has the greatest effect on tasks of simple attention with more complex cognitive tasks such as those involving complex attention, working memory and decision making more moderately affected. Short term memory and processing speed are also affected but to a lesser degree.

- SD has minimal effects on performance of tasks of reasoning and crystalised intelligence.
- Severe SR is associated with greater performance decrements in complex tasks than mild SR.
- There is an interaction between homeostatic and circadian processes evidenced by the fact that there is a greater decrement in complex tasks performed during the circadian night than when performed during the circadian day in studies of SD.

When considering these conclusions it is also important to consider the limitations of meta-analysis. Probably the most important of these is the pooling of different cognitive tasks to assess specific domains of cognitive function. This may be problematic as most cognitive tests involve more than one functional domain and therefore they are never a pure measure of any specific domain. Therefore when interpreting the results of for example tests of executive function, which also rely on other cognitive domains such as attention, the evidence of a deficit on executive function should be considered tentative until studies which are able to control for the effects of different cognitive domains on the overall test outcome are performed (Verstraeten and Cluydts, 2004). In the Lim and Dinges analysis however there was no significant heterogeneity in outcomes between studies for specific domains indicating that the groupings of studies into specific domains was probably appropriate. A further weakness of the meta-analyses is that they report summary statistics at the group level and may miss important differences in performance between individual participants of studies. Differences between individuals would tell us more about the variation in tolerance to or susceptibility to the effects of sleep disruption. One way to

examine this effect would be by performing individual patient level meta-analysis but none has yet been reported.

1.4.3 Observations about the effects of sleep loss on cognitive function from narrative reviews and primary studies.

In this section some of the most salient points to emerge from the primary literature and narrative reviews are discussed that are not identified by the meta-analyses.

1.4.3.1 Sleep loss and attention.

Lim and Dinges, (2008) in their narrative review of the literature on sleep deprivation and vigilant attention noted four main effects mostly derived from performance on the Psychomotor Vigilance Test (PVT) which is a test of vigilant attention and executive control (Unsworth et al., 2010). The key observations Lim and Dinges made from the literature were;

- SD results in a general overall slowing of RTs.
- SD results in increased errors of omission and commission (i.e. increased variability in performance).
- SD enhances the time on task effect (i.e. performance on a specific task worsens over the time it takes to perform the task).
- Tests of vigilant attention during periods of SD are sensitive to both homeostatic and circadian drives (i.e. time awake and time of day).

The observation that attentional performance is sensitive to the time of day suggests care should be taken to standardise the time of day of cognitive testing

between subjects and that an individual's chronotype should be considered in the interpretation of results (Mongrain et al., 2008).

1.4.3.2 Sleep restriction and attention.

SR is a more realistic paradigm of sleep loss in clinical populations than total SD. Van Dongen et al. (2003) demonstrated that chronic SR to 4h and 6h per night for two weeks produced similar deficits in vigilant attention measured by lapses on the PVT as 48h and 24h of total SD respectively. This was despite SR participants reporting significantly lower levels of subjective sleepiness even though they experienced similar cumulative levels of total sleep debt. This suggests people adapt to SR and may therefore underestimate its effects on performance. Dinges et al. (1997), Belenky et al. (2003), Cote et al (2008; 2009), Elmenhorst et al. (2009) and Banks et al. (2010) also found incrementally increasing RT and lapses on the PVT across increasing numbers of nights of SR in a dose dependant manner and performance was dependent on the sleep/wake period extending back over several days. This is an important consideration when examining the association of sleep and cognitive function in people with psychiatric illness as sleep in these populations can be variable suggesting extended periods of sleep assessment may be necessary when examining the association between sleep and cognitive function in clinical populations. Supporting this view, it has been demonstrated that greater amounts of sleep banked in the days and nights prior to SR can protect against decrements in attentional performance associated with SR and also influence the speed of performance recovery from SR suggesting that the physiological mechanisms underlying chronic sleep debt undergo long-term (days/weeks) adaptive changes (Rupp et al., 2009).

1.4.3.3 Recovery in attentional performance following sleep loss.

As sleep is variable in BD patients it is important to understand how people may recover from bouts of SR as periods of good sleep following poor sleep may allow for recovery from any detrimental effects on cognitive function. Data however suggest that several nights of 8 hours TIB recovery sleep are required before full performance in simple attention is restored even after mild sleep restriction of 5-7 hours sleep per night (Belenky et al., 2003). This suggests that BD patients who experience regular nights of poor sleep may not fully recover even if they have the occasional good night of sleep. Lamond et al., (2007) also found that recovery in attentional performance following just 1 night of SD was incomplete even after five nights of 6 hours TIB which was in contrast to full recovery after one night of 9 hours TIB. Banks et al. (2010) found that following five nights of SR to 4 hours TIB full performance to baselines levels on the PVT was not even achieved after one 10 hour TIB recovery night. Collectively this data suggests that patients who never manage to sleep for periods longer than the proposed 8 hours required to maintain full cognitive performance (Van Dongen et al., 2003) may experience a sustained decrement in attentional performance. Considering that even after mild sleep loss recovery periods of several nights are necessary for people to return to full attentional performance it is possible that any sleep loss through illness, travel, work commitments or other reasons in controls in the few days immediately prior to performing cognitive testing may impact their performance. Ideally, therefore control participants should have their sleep monitored in the days prior to cognitive testing to ensure that they are experiencing their habitual sleep times and sleep wake pattern.

1.4.3.4 Individuals vary in their vulnerability to the effects of SD and SR.

Studies using both SD and SR have demonstrated large inter-individual differences in cognitive vulnerability to sleep loss. Van Dongen et al. (2004) found that vulnerability to cognitive impairments assessed with the PVT and DSST following SD was stable within individuals, i.e. was evident at each separate testing in the same individual but was highly variable between individuals, i.e. some individuals were far more vulnerable to the effects of SD on performance. Due to the reliability of this finding, the authors suggested this reflected a trait like phenomenon. Rupp et al. (2012) also found that people who were vulnerable to the effects of SD were also vulnerable to the effects of SR again suggesting vulnerability to cognitive impairment by sleep loss is a trait like phenomenon. Frey et al. (2004) found that intra-individual performance on tasks varied dependent on the task with individuals performing well on some tasks and less well on others. Inter individual variation in performance also differed depending on the task. The best performers on some tasks were the worst performers on other tasks suggesting the SD may have differential effects within individuals on different brain functions. This study demonstrates the importance of using multiple tasks to assess the effect of sleep loss on an individual's performance.

1.4.4 Cognition in clinical sleep disorders.

Experimentally induced sleep loss through SD and SR has clearly been demonstrated to impair a range of cognitive functions but clinical sleep disorders, including those seen in BD, are unlikely to produce the same uniform sleep loss and may therefore have a different association with cognitive function. The fact that SR in addition to total SD is associated with cognitive impairment does suggest that sleep disorders associated with reduced TST such as insomnia,

which is prevalent in BD, may have an effect. In addition, other sleep disorders prevalent in BD such as sleep apnoea, circadian rhythm disorders and hypersomnia may also be associated cognitive impairment.

1.4.4.1 Cognitive function in insomnia.

People with insomnia often complain of fatigue, mood disturbance and reduced QoL (Riedel and Lichstein, 2000) and insomnia has been associated with reduced work function (Sarsour et al., 2011) and increased injury and accidents (Kessler et al., 2012). However a review of the literature concluded that cognitive deficits associated with insomnia are relatively subtle and qualitatively different to those resulting from other sleep disorders such as sleep apnoea and experimental SD (Shekleton et al., 2010). A meta-analysis has quantified the differences in cognitive performance between people with primary insomnia and normal sleepers (Fortier-Brochu et al., 2012) and the effect sizes are shown in Figure 1.10. The most significant findings are moderate deficits in working and episodic memory and problem solving. There were also small to moderate deficits in aspects of attention that approached significance such as complex reaction time, selective and sustained attention. Impairment in processing speed as measured by the DSST although of small effect size also approached significance. The review concluded that the literature base examining cognition in insomnia is small with considerable variance in the number of studies for each domain and that most studies had a small number of participants and therefore a lack of

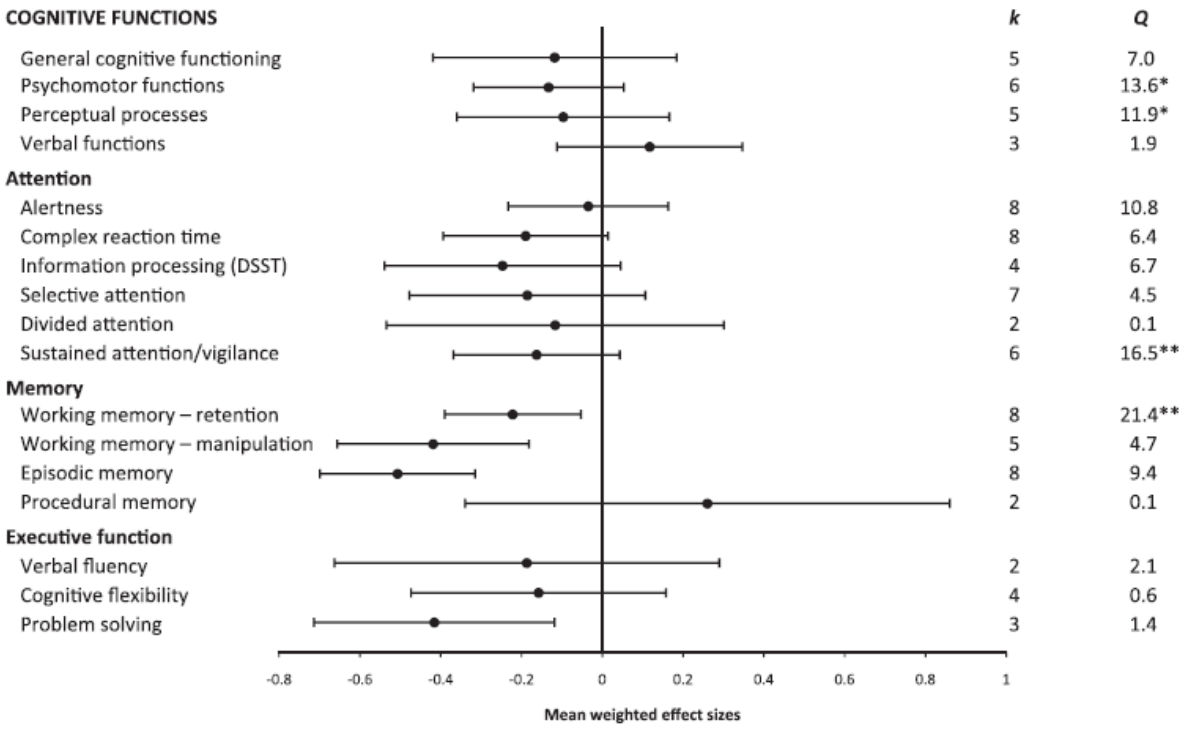


Figure 1.10 Average effect sizes and 95% confidence intervals by cogntive domain for patients with primary insomnia compared to healthy controls. Sample sizes for individual studies included in these analyses ranged from 7 to 122 insomnia participants. K = number of effect sizes available, Q = Q statistic of homogenity, * p<0.05, **p<0.01 (From Fortier-Brochu et al., 2012)

statistical power. Despite this performance was in the same direction as from experimentally induced sleep loss. Fortier-Brochu et al (2012) also noted that insomniacs experience considerable night to night variability in sleep length and quality and therefore a good night sleep before the cognitive testing may mask cognitive deficits present after a poor night sleep.

1.4.4.2 Cognitive function in obstructive sleep apnoea.

OSA has been associated with an increase in accidents and a decline in cognitive function currently thought to be a consequence of sleep fragmentation and/or intermittent hypoxia (Cross et al., 2017). A model has been proposed that sleep disruption and blood gas abnormalities prevent sleep related restorative

processes resulting in chemical and structural damage to the cells within the central nervous system and dysfunction in the PFC and executive dysfunction (Beebe and Gozal, 2002). A recent meta-review of five systematic reviews and meta-analyses has summarised the data relating to objectively measured cognitive function in adults with OSA (Bucks et al., 2013). OSA was found to be associated with deficits in attention, executive functions, visuospatial/constructional ability, verbal immediate and delayed recall but had no association with language ability and psychomotor function. The data supporting deficits in short term memory, working memory and global cognitive function was inconclusive. The severity of sleep fragmentation was also linked with deficits in attention and vigilance.

1.4.4.3 Cognitive function in circadian rhythm sleep disorders.

The available data on cognitive function in subjects with CRSD was reviewed by Reid et al. (2011) who noted that there were very few studies and additionally as CRSDs are also associated with sleep loss it would be difficult to assess if any deficits were due to sleep loss or circadian misalignment. Reid et al. commented that it is likely people with a delayed sleep phase disorder (DSPD) who attempt to maintain socially normal sleep wake rhythms may end up with shortened sleep periods. This would be due to the fact they may have initiated sleep in the early morning hours but are still required to rise in the early morning. This notion was supported in a recent laboratory study comparing 9 people with DSPD and age and sex matched controls (Solheim et al., 2014). When aroused from sleep at 7.00am DSPD subjects found it more difficult to wake and performed worse on a continuous performance test (CPT) with a slowing of RT and more omission errors. They also made more omission errors than controls when the

test was repeated in the afternoon. Reid et al., (2011) were not able to find any studies examining cognitive function in people with advanced sleep phase disorder (ASPD) and my own search did not find any relevant studies. Theoretically people with ASPD would suffer a reduction in cognitive performance later in the evening as their circadian drive for alertness decreases. In addition people may suffer a loss of TST due to going to bed later than their circadian bed time in an attempt to comply with social norms and also as they often suffer from early morning awakening. People with free running or non 24-hour CRSD have a progressively delaying sleep wake cycle usually due to a circadian period that is longer than 24-hours and display intermittent insomnia and daytime sleepiness dependant on the phase of the circadian clock to the time of day (American Academy of Sleep Medicine, 2014). Blind people often suffer from this type of disorder due to a lack of entrainment by light and the circadian period reverting back to the natural 24.2 hours. Lockley et al. (2008) found evidence of cognitive impairment in free running blind people as they performed worse on a 4 choice RT task when it was performed during their biologic circadian night i.e. when melatonin secretion was at its peak. There has also been a number of studies assessing the association of circadian rhythm abnormalities and cognition in elderly people due to the fact that as we age significant changes in the sleep/wake cycle occur enabling the associations of circadian rhythm changes and cognitive function to be examined. This research has generally found that increased variability and lack of stability in the circadian rhythm is associated with worse cognitive function (Carvalho-Bos et al., 2007; Oosterman et al., 2009; Tranah et al., 2011; Luik et al., 2015; Diem et al., 2016). Cognitive vulnerability to irregular sleep/wake cycles has also been

demonstrated in younger people. In a study of healthy male university students, irregular sleepers (defined as those who's bed and wake times varied by 2-4 hours between nights), had longer RTs to an auditory stimulus task than regular sleepers (defined as people who naturally slept between 7-8 hours beween 12.00 and 8.00am each night) (Taub, 1978).

In summary although there are a lack of objective studies of cognitive function in people with CRSD some experimental data and studies in the elderly and blind people suggest it is likely that they are associated with cognitive deficits both due to sleep loss and circadian misalignment between the endogenous circadian clock and the 24-hour day night cycle.

1.4.4.4 Cognitive function in long sleepers and hypersomnia.

A number of population studies have found that excessive sleep may be associated with a decline in cognitive performance. Self-reported long sleep duration (> 9 hours) in the general population and older adults has been associated with both subjective and objectively measured decline in cognitive function (Faubel et al., 2009; Kronholm et al., 2009; Gildner et al., 2014). A recent meta-analysis found that both self reported long and short sleep duration assessed in cross sectional studies in older adults was associated with poorer executive functions, verbal memory and working memory capacity demonstrating an inverted U shaped relationship of sleep duration with cognitive performance (Lo et al., 2016). A similar finding has also been reported in younger subjects where peak performance on tasks assessing working memory and processing speed was found to peak at 7 hours self-reported habitual sleep duration and decline with both shorter and longer sleep durations (Richards et al., 2017). It is

possible that extended sleep may reflect the presence of underlying sleep disorders or age related comorbidities which may be behind the cognitive impairment. However the association of longer sleep duration with poorer cognitive function found by Richards et al., (2017) was as strong or stronger for some tasks in the younger population than in the older population suggesting that there is an effect of long sleep not driven by underlying medical comorbidities. No studies assessing cognitive function in patients diagnosed with hypersomnia were found.

1.4.4.5 Sleep continuity and cognitive function.

The importance of good sleep continuity in preserving cognitive function has been demonstrated in both younger (mean age 23 years) and older (mean age 63 years) healthy adults in a large population study (Wilckens et al., 2014). In the younger age group higher sleep continuity (assessed with WASO) was associated with better working memory and inhibitory control and in the older age group with better inhibitory control, memory recall and verbal fluency. Very short and very long TST was associated with poorer working memory and verbal fluency in the younger group only confirming the inverted U shaped association of TST with cognitive performance in younger people.

1.4.4.6 Summary of cognitive function in clinical sleep disorders.

Overall despite the relative lack of objectively derived data in people with clinical sleep disorders (with the exception of studies in people with OSA), the available evidence suggests that insomnia, short and long sleep duration, circadian rhythm disturbances, fragmented sleep and OSA are all associated with cognitive deficits

in people without mental disorders. This suggests that sleep disturbances in people with BD may be sufficient to impact cognitive performance.

1.5 The potential role of sleep disturbances in cognitive dysfunction in BD.

The review of the literature on sleep in BD and the association between sleep and cognitive function suggests that it is possible there will be an association between sleep and cognitive function in BD. Experimental evidence has demonstrated a clear effect that sleep loss through SD and SR impairs a range of cognitive domains. Clinical sleep disorders including sleep apnoea, insomnia and circadian rhythm disorders are also associated with cognitive deficits. People with both long and short TST from population studies also have worse cognitive performance than those with normal sleep. Comprehensive evidence exists demonstrating a wide range of sleep abnormalities exist in BD including increased rates of OSA, insomnia, hypersomnia and circadian rhythm abnormalities compared to the general population. These are often chronic in nature extending into euthymia and likely of significant magnitude to have a clinical effect on both cognitive and psychosocial function. In addition, some patients may suffer from more than one sleep disorder e.g. CRSD + OSA, which may make it more likely that the sleep abnormality may be sufficient to be a mechanism of cognitive dysfunction. It is also possible that people with BD will be more vulnerable to the effects of sleep abnormalities on cognitive function. BD patients have functional brain abnormalities that are thought to be an underlying mechanism of the disorder perhaps driven by over activity in limbic areas and hypo-activity in frontal brain areas (Strakowski et al., 2005; Chen et al., 2011; Kupferschmidt and Zakzanis, 2011). There is evidence that SD and SR

impair normal brain function during cognitive tasks in healthy individuals (Ma et al., 2015). Therefore, it is possible that sleep abnormalities further disrupt already compromised brain function in BD patients resulting in cognitive deficits. There is also evidence that in healthy individuals cognitive performance can be maintained through the recruitment of additional brain areas not usually utilised during cognitive processing to compensate for those areas that were compromised by SD (Portas et al., 1998; Drummond et al., 2004; Tomasi et al., 2009). It is also possible that as neural pathways are already dysfunctional in BD patients they are less able to recruit additional brain areas in an attempt to maintain cognitive performance than are healthy people again resulting in poorer cognitive performance. For example during attentional tasks sleep loss in healthy individuals is associated with decreased activity in the frontal parietal network and hyper-activation in the thalamus. As the thalamus is a key part of the arousal system and cortical attention network hyper-activation is thought to be to compensate for the dysfunction in the fronto-parietal network to maintain attentional performance (Ma et al., 2015). It has been reported that manic BD patients have lower thalamic activation and poorer performance than controls during a sustained attention task (Fleck et al., 2012) and it is possible that the failure to activate the thalamus could have contributed to this finding. Finally although not the subject of this review sleep disturbances have been demonstrated to impact emotional state and mood (Kahn et al., 2013) and mood state may also influence cognitive function in BD (Porter et al., 2015).

Two recent papers have proposed mechanisms for a role of sleep disturbances in cognitive dysfunction in BD patients. McKenna and Eyler, (2012) focussed on the potential role of the PFC since it is a core structure involved in higher order

cognitive and emotional processing and abnormalities in its function have been highlighted in BD and following sleep disruption. They also cite the similarities in cognitive deficits found in euthymic BD patients and in healthy subjects following SD as suggestive that sleep plays a role in cognitive dysfunction in BD. They propose that the functional and structural changes in the PFC found in BD patients produce trait like cognitive deficits which are then moderated by sleep and circadian variations. As the presence and severity of sleep disturbances change over the course of illness they moderate the severity of cognitive dysfunction and this would help explain the variable findings in the BD literature with regards to cognitive function. In addition, as the SD literature demonstrates a variability in the vulnerability to the cognitive effects of SD this may also explain some of the variability in cognitive function both within BD subjects and between studies. Boland and Alloy, (2013) also suggest that theoretical support for the hypothesis that sleep disturbances contribute to sustained cognitive deficits in BD is evidenced by the fact that SD and additionally clinical sleep disorders such as insomnia and OSA, which are prevalent in BD, are associated with cognitive deficits that overlap with those seen in BD in other populations. They however recognise that this view may be an oversimplification since not all BD patients suffer from sleep disturbances or cognitive impairment so this process cannot be universal to the disorder. They proposed three models with three different cognitive endophenotypes which may exist in the BD population (Figure 1.11). In the first model endogenous cognitive deficits are present which impair occupational and psychosocial function even during euthymia. These cognitive deficits are endogenous to BD and not related in any way to sleep disturbances but may be exacerbated and worsen during

mood episodes and result in an increase in the occupational and psychosocial dysfunction. The second model proposes cognitive deficits in BD are primarily the result of sleep disturbances. In this model there is also a bidirectional interaction between sleep and mood symptoms whereby poor sleep results in mood disturbances and mood symptoms can exacerbate poor sleep. However the cognitive deficits are considered to be driven by the sleep disturbance which therefore may worsen during mood episodes due to the greater level of sleep disturbance experienced during a mood episode. However, the sleep disturbance and mood symptoms both contribute to impaired occupational and psychosocial function. The third model proposes the presence of both endogenous and sleep mediated cognitive dysfunction in BD. As previously discussed there is evidence of a cognitive endophenotype evidenced by the presence of cognitive deficits in first degree relatives of BD patients. This model proposes that mood and sleep disturbances may then further exacerbate cognitive impairment. In addition, sleep and mood also have a bidirectional relationship so that they may worsen and maintain each other thereby maintaining and worsening deficits in cognitive function. BD patients who are susceptible to both endogenous and sleep mediated cognitive impairment perhaps through genetic susceptibility or a common brain lesion that causes both may have the worst outcomes and psychosocial impairment. The hypotheses proposed by both groups of researchers are similar in many respects in that both propose sleep may precipitate mood episodes and cognitive deficits, that individuals may be differentially susceptible to both and that this may help explain some of the variability found in cognitive dysfunction between individuals with BD. Both hypotheses rely to some extent on the

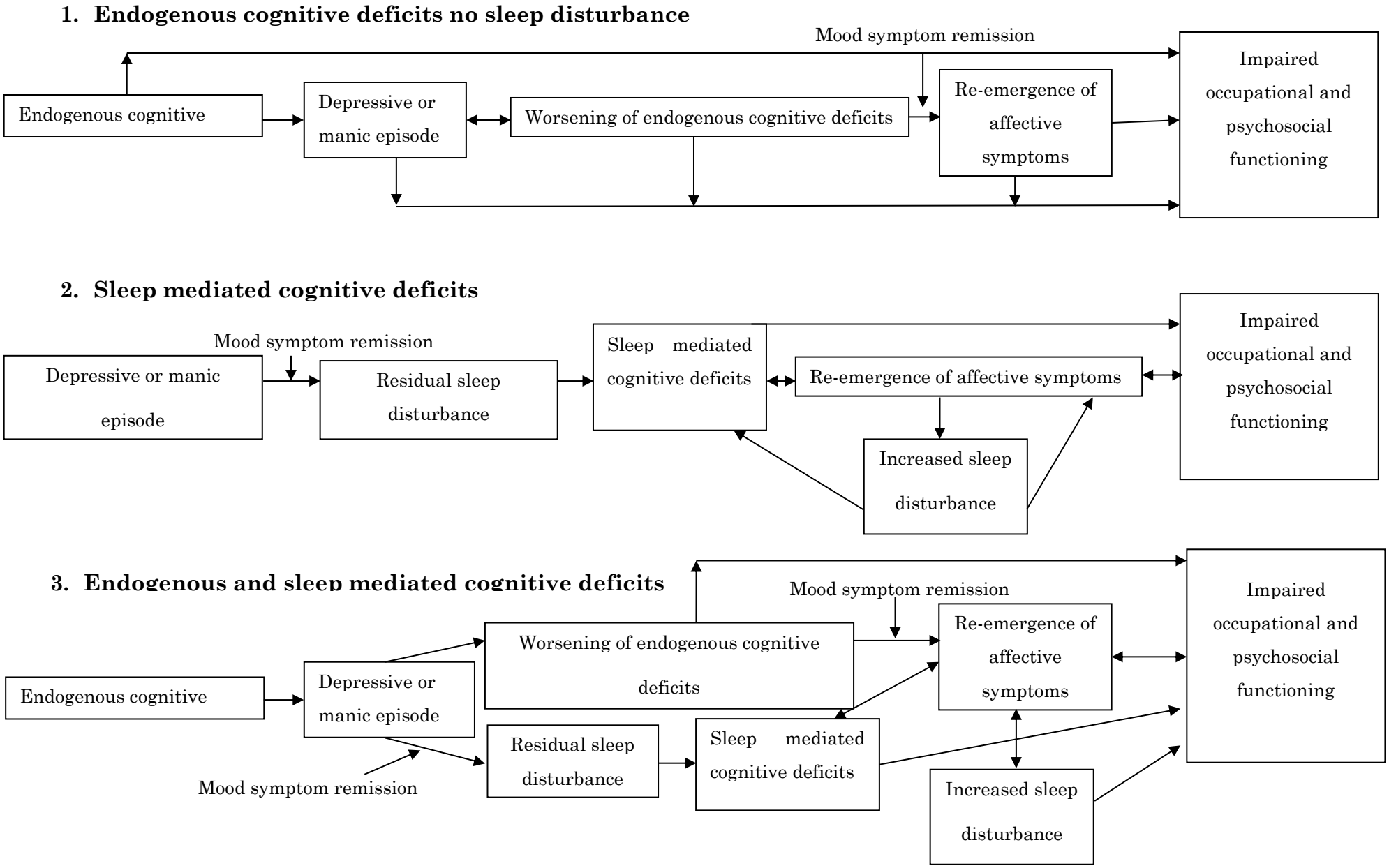


Figure 1.11 Possible roles of sleep and cognitive function in producing poor functional outcomes in BD (from Boland & Alloy 2013)

evidence that SD in healthy individuals results in a similar pattern of cognitive deficits as is found in euthymic BD patients although Boland and Alloy also quote the evidence from people with insomnia and sleep apnoea. Some recent studies have directly explored the association of sleep with cognitive function in BD providing preliminary evidence to support these hypotheses. Volkert et al., (2015) noted the heterogeneity in the level of cognitive impairment between individuals with BD and set out to detect clinical differences between euthymic BD patients with and without cognitive deficits. BD patients were divided into 2 subgroups, those with no clinically significant cognitive impairment (n=29) and those showing deficits in at least one of the 12 cognitive domains tested (n=41). A number of clinical variables were associated with cognitive dysfunction including subclinical depressive symptoms, comorbid anxiety disorder, higher scores on the Montgomery Asberg Depression Rating Scale (MADRS) sleep item and patients who reported persistent initial or middle insomnia were more common in the cognitive deficit group. Multiple regression analysis indicated that in particular processing speed and attention could be explained by the sleep disturbances. A significant weakness of this study however is that the sleep disturbances were subjectively rated represented by a single item on the MADRS and a simple yes/no record of suffering from persistent initial or middle insomnia, neither of which are validated scales for assessing sleep disturbance and could be open to recall bias. Boland et al., (2015) also reported an association between subjective poor sleep, cognitive function and poor work performance in euthymic BD patients. The PSQI daytime dysfunction item had a significant correlation with backwards digit span performance, poor sleep quality assessed with the PSQI and a number of the PSQI sub-scores along with the ISI score were associated

with number of lifetime incidents of quitting one's job and PSQI total score with lifetime unemployment in BD patients. It should however be noted that sleep was also assessed with accelerometry and no differences were found in accelerometer sleep variables between BD and controls and no associations were found between accelerometer sleep variables and function. Russo et al. (2015) reported a relationship between sleep assessed with the PSQI, daytime sleepiness assessed with the ESS and cognitive function in stable BD outpatients. Path analyses revealed social cognition was directly predicted by PSQI sleep disturbance and PSQI daytime dysfunction sub-scores and clinical symptoms only influenced cognition through an indirect pathway via sleep. PSQI total score also had a direct effect on working memory and depression indirectly impacted working memory via effects on PSQI total score. Again this study is limited by the lack of objective sleep ratings and it was also noteworthy that there were no associations of sleep with performance on the continuous performance test which as an attentional task may have been expected to show some relationship to sleep disruption. Kanady et al. (2017) recently reported an association between insomnia related sleep disturbances and cognitive function in euthymic BD patients. They compared euthymic BD patients with an insomnia diagnosis to BD patients without any reported sleep disturbances in the preceding 6 months on tests of working memory and verbal learning. Participants sleep was rated with the ISI, PSQI and a sleep diary which was used to record TST, total wake time (TWT) and the variability in these measures (TWTv, TSTv). Hierarchical linear regression indicated that insomnia diagnosis was not associated with cognition, but regardless of insomnia diagnosis in the whole BD group greater TSTv predicted lower working memory and verbal learning performance. Supporting

the association between sleep and cognitive function, treatment with cognitive behavioural therapy for insomnia (CBTi) and a subsequent reduction of TWT predicted improvement in working memory and a reduction of TSTv predicted an improvement in verbal learning. This study therefore demonstrated that diagnosis of a sleep disorder may not be the driving factor in associations of sleep and cognition but rather the characteristics of the sleep itself such as the day to day variability may drive these associations. Of note there was also a finding that a reduction in TST was associated with an improvement in verbal learning. Given that long sleep has been associated with poorer cognitive function Kaplan et al. noted that the 5 participants with long sleep had the greatest reduction in sleep length (62 mins) and therefore this group may have driven this finding. One major limitation of this study like the others in BD was that sleep variables were estimated subjectively. Finally a recent preliminary study found that accelerometry estimated increased variability in circadian rhythm, activity levels and SE were all significantly associated with the degree of abnormality of brain response in the dorsolateral prefrontal cortex and supramarginal gyri during a working memory task in euthymic BD patients (McKenna et al., 2014). This finding supports the hypothesis that sleep and circadian rhythms are important in normal brain function in BD and may be a mechanism for how sleep abnormalities influence cognitive function.

Although this preliminary evidence demonstrates there is an association between sleep and cognitive function in BD it is important to consider that cognitive and sleep changes may simply be driven by the same lesion. For example if a brain lesion is present in an area of the brain that is involved in regulating both sleep and cognitive function, or there were an abnormality in neurotransmitter

function that was important for both sleep and cognitive function then this lesion would result in impairment in both sleep and cognitive function in the same individuals. The observed association between sleep and cognitive function would then simply reflect the fact that these deficits originated from the same lesion. In order to demonstrate that this is not the case and that sleep abnormalities themselves had a direct impact on cognitive function in BD patients would require a study to demonstrate that the sleep abnormalities and cognitive deficits were independent observations i.e. had different causes. Then it would be required that cognitive deficits were present or became worse only in the presence of sleep abnormalities and improved or resolved in the absence of sleep abnormalities. Currently the precise cause of sleep abnormalities and cognitive deficits in BD is unknown so it is difficult to demonstrate that they have totally independent causes. A study that demonstrated the presence or worsening of cognitive deficits in BD patients during periods of abnormal sleep and an improvement or resolution of cognitive deficits after either natural or interventional resolution of sleep abnormalities would provide stronger evidence that sleep abnormalities had a causal role in cognitive deficits.

1.6 What are the gaps in our knowledge on the association between sleep and cognitive function in BD?

Currently there is no evidence demonstrating an association between objectively assessed sleep disturbances in BD and cognitive and psychosocial function. The little evidence described above is based on subjective sleep assessments. The strongest evidence for an influence of sleep on cognitive function is from studies of SD and SR i.e. a lack of sleep and in people with OSA. Although subjectively BD patients report poor sleep quality and commonly endorse symptoms of

insomnia there is little objective evidence that suggests BD patients suffer from a lack of sleep. Accelerometry studies actually report that TST is on average longer in euthymic BD patients than controls. This may be a true finding or it could be that accelerometry in BD populations overestimates TST as it is relatively poor at correctly identifying periods of actual sleep from restful wakefulness. Therefore, any potential role of sleep in cognitive function in BD is likely to be more complex than simply a lack of sufficient sleep. Objective sleep assessment in BD populations has demonstrated fragmented and variable sleep, high rates of DSPD, irregular sleep/wake cycles, hypersomnia and OSA. However currently we have no objective evidence any of these sleep abnormalities are associated with cognitive deficits specifically in BD populations and if any are which type of sleep abnormality has the strongest association.

1.6.1 Considerations in assessing the association between sleep and cognitive function in BD.

Given the gaps in our current knowledge any study designed to test the hypothesis that sleep and cognitive function are associated in BD should consider a number of factors. Firstly, sleep and circadian rhythm in the BD population under test should be both subjectively and objectively assessed. Objective sleep assessment removes recall bias and misconceptions about sleep but it would be of value to compare objectively assessed sleep with participants subjective assessment of their sleep quality to see how these relate. It is possible that subjective sleep assessments may measure sleep factors that are not picked up with objective measures. Secondly as sleep in BD has been demonstrated to be variable over time and sleep related cognitive deficits may take time to build and indeed recover during periods of normal sleep, sleep function should be assessed

over several weeks so as to more accurately characterise the nature of any sleep abnormalities. Consideration should be given to the method of objective sleep assessment. The gold standard is PSG but this method does not lend itself well to assessment over several weeks. Accelerometry although less accurate is a practical way of assessing sleep over periods of several weeks and has the advantage that is can also assess physical activity and the overall circadian rhythm of the sleep /wake cycle. It has also been demonstrated to have acceptable agreement with PSG. The type of sleep variables assessed should also be carefully considered and should include typical measures such as TST, TIB and SE but also the variability in these measures. In addition another way to assess sleep would be to identify participants with specific sleep phenotypes such as short, long and circadian rhythm disordered sleep and look at the associations between these and cognitive function. Since OSA has an increased prevalence in BD and it is associated with cognitive deficits participants should also be objectively assessed for OSA. Considering the evidence for circadian rhythm disturbances in BD it would also be of benefit to assess circadian rhythm and its association with cognition. Chronotype should be assessed with a standard rating scale and daily functional rhythms can also be assessed with subjective rating scales. Since sleep has been associated with psychosocial function and QoL and these are associated with cognitive deficits these should be assessed alongside cognitive functions.

Cognitive function should be objectively assessed utilising cognitive tests that have demonstrated to be sensitive to sleep disturbances and impaired in BD populations. This should include assessment of sustained attention as this is the domain that is most consistently impaired with the largest effect size by SD and

SR and is also a core deficit in BD. Tests should include those that have been utilised in sleep research and are sensitive to the effects of SD and SR such as the PVT. Considering cognitive function varies with circadian timing the time of cognitive testing should be standardised across participants. In terms of study participants it would be of value to assess BD patients across mood states as well as euthymic patients in order that the interaction of sleep, mood and cognitive function could be assessed.

Consideration should be given to the characteristics of the control group. The control group should be matched on major demographic characteristics such as age, gender and IQ as these may have an effect on cognitive function. With regards to sleep characteristics sleep abnormalities are common in the general population and selection of a control population without any sleep abnormalities could be considered selection for an extra healthy sub-population. It is possible that this extra healthy sub-population may also differ from the general population in other un-measured characteristics and that they may have better cognitive function than the general population. This possibility means that the results of this study should be interpreted as a comparison between good sleeping healthy controls and patients with BD. Any differences in cognitive function found between these groups may therefore be larger than any differences found between BD patients and controls from the general population who were not specifically selected for being good sleepers. However as sleep abnormalities are the subject under investigation it is necessary to ensure that there are clear differences in sleep between the control and BD groups. If sleep abnormalities are associated with cognitive deficits then including controls with sleep abnormalities would make it more difficult to find differences between control

and BD groups. A greater sample size would be required so that sub-populations of controls with and without sleep abnormalities could be compared to BD patients. This would also be useful in order to see if there was a difference in effect size for sleep abnormalities and cognitive deficits between controls and BD patients. An alternative method would be to have an additional control group comprising of participants with clinical sleep abnormalities but no mental health disorder. This would then allow a comparison between healthy controls with no sleep abnormalities, controls with a clinical sleep disorder but no mental health disorder and BD patients with and without sleep abnormalities. This would then provide information on the effect size of any association between sleep abnormalities and cognitive function in people with and without BD.

Ideally, a study would also include assessment of brain function so that associations between sleep, brain function and cognitive function can be explored as this may give insight into potential mechanisms of how sleep may effect cognitive function.

1.7 Hypotheses

Drawing on the information from the literature review hypotheses were generated on sleep and circadian function and their association with psychosocial function, QoL and cognitive function in BD.

1.7.1 Subjective sleep function, psychosocial function and QoL.

1. BD patients will have worse sleep quality, greater circadian rhythm disturbance, poorer psychosocial function and lower QoL than controls.
2. Subjective sleep quality and circadian rhythm will be associated with and predict psychosocial function and QoL.

1.7.2 Objective sleep and circadian function.

3. Objective sleep assessments will demonstrate on average BD patients have a longer mean nocturnal sleep time, lower SE and more night to night variability in their sleep than controls.
4. There will be a higher prevalence of abnormal sleep phenotypes including short sleepers, long sleepers, those with circadian rhythm disturbances (CRD) and OSA.
5. BD patients with objectively defined sleep abnormalities will have lower psychosocial function and QoL than objectively defined normal sleepers.

1.7.3 Cognitive function

6. BD patients will perform worse on tests of sustained attention and executive control of attention including having greater intra-individual variability in RT. BD patients will have worse performance on tasks assessing processing speed, the executive functions of set shifting and working memory and immediate and short-term memory than controls.

1.7.4 The association between sleep abnormalities and cognitive function.

7. Within the BD group
    a) Patients with objectively defined sleep abnormalities will perform worse on the cognitive tasks than patients with objectively defined normal sleep including having greater variability in RT.
    b) Patients with objectively defined sleep abnormalities will have worse cognitive performance than those with only subjective sleep abnormalities.

2. Chapter Two - Methods

2.1 Introduction

This chapter details the methodology of a cross sectional study developed to examine the relationship between sleep and cognitive function in people with BD and to specifically test the hypotheses developed in the section 1.7. Where necessary the rationale for the specific methods chosen will be given.

2.1.1 Contribution of work by the candidate

The original research idea is attributable to Professor Hamish McAllister-Williams (head of Academic Psychiatry at Newcastle University) and Dr Kirstie Anderson (consultant neurologist at Newcastle Upon Tyne Hospitals NHS Trust). Under their supervision I was responsible for the set up and conduct of the study. This included developing the details of the study protocol, developing all study related materials and gaining ethical and research and development approval to perform the study. In addition I acquired the necessary skills to perform patient interviews, utilise specialist equipment, handle biological samples and perform the cognitive tests. I was responsible for the recruitment of study participants and implementing the study protocol with participants. At various times during the study I was supported by one research assistant and four MRES students. I was responsible for training them on the study protocol and methods and supervised them during their time on the study. I personally recruited and ran the protocol with all of the BD participants and approximately 50% of the healthy controls with the MRES students and research assistant recruiting and managing the remaining healthy controls. I personally checked all the data collected by other study personnel. I was responsible for creating the study data sheets, cleaning and inputting all data and creating the statistical database for the study analysis. I performed all the statistical data analysis.

2.2 Protocol design and detailed study methodology.

2.2.1 Overview of study protocol

The study is cross sectional in design with a 21-day assessment of sleep and circadian rhythm (Figure 2.1). The full study protocol and all study documentation can be found in the appendix.

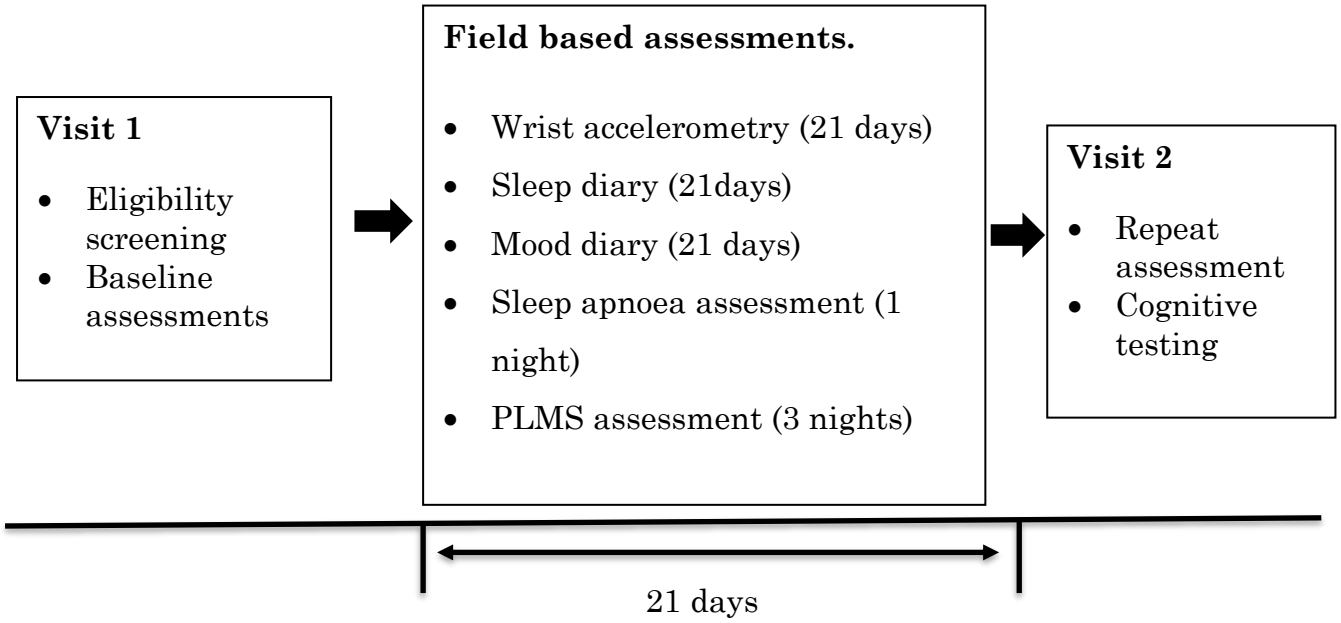


Figure 2.1 Overview of study protocol

2.2.2 Ethical permissions

Ethical approval for this study was granted by the Newcastle & North Tyneside Research Ethics Committee, REC reference 12/NE/0117 on 26/6/2012. Applications to the Research and Development Committees of Newcastle upon Tyne Hospitals NHS Foundation Trust and Northumberland & Tyne & Wear Mental Health Foundation Trust were also made and granted. Northumberland & Tyne & Wear Mental Health Foundation trust acted as study sponsor. After being given full study information and any questions were answered about the study were answered all participants were required to provide written informed

consent before commencing the study protocol. Participants could withdraw from the study at any point. BD participants were reimbursed for all study related travel expenses. Control participants were paid £80 for their time in the study upon completion.

2.2.3 Study Participants

The study aimed to recruit and assess three cohorts of participants. Healthy controls, BD patients and insomnia patients without mental health problems.

2.2.3.1 Calculation of sample size

The sample size calculation was based on the potential effects of sleep abnormalities on attention since this is the cognitive domain most severely impacted by sleep. The effect size of the effects of short term SD on simple attention from the meta-analysis reported by Lim and Dinges (2010) was 0.7 and an effect size of approximately 0.7 was also found for performance on the DSST between euthymic BD patients and controls from the meta-analyses of cognitive function in euthymic BD patients. Assuming the same effect size of 0.7 and a SD of 1.0 then a sample size of 64, 32 per group would have 80% power to detect a difference between groups at an α level of 0.05. With a more conservative effect size of 0.5 and a SD of 1.0 then a sample size of 126 or 63 per group would have 80% power to detect a difference between groups at an α level of 0.05. Based on this information and the practicality of recruitment in the time available this study aimed to recruit a sample size of 50 participants per group.

2.2.3.2 Participant recruitment

BDI or II outpatients in any mood state were recruited from a Medical Research Council (MRC) client database of people with BD II and a patient support group

based in Newcastle upon Tyne. Additionally patients were recruited via direct referral from the Regional Affective Disorders Service in Newcastle upon Tyne, NHS services in Northumberland and Tyne & Wear NHS Trust and the Regional Sleep Disorders Service also based in Newcastle upon Tyne. Healthy volunteers who acted as a control group were recruited from hospital staff such as medical secretaries and Newcastle University and Voice North volunteer databases. These databases contain the names and contact details of registered members of the public who have expressed an interested in taking part in clinical research studies. An email was sent to members of the database asking for volunteers to take part in the study. Volunteers who responded to the email were added to a list of potential participants. Initially controls were recruited into the study in the order in which they responded to the email. Before being invited to attend the first study visit potential controls were firstly screened to ensure they met the major inclusion criteria and did not meet any of the major exclusion criteria to prevent any wasted visits. During course of the study the age and gender of participants from both the BD and control groups who had already entered the study were assessed. The study aimed to recruit age and gender matched BD and control groups and therefore assessing the ages and gender allowed the investigator to assess the similarity of currently recruited control and BD participants for these characteristics. All BD patients who had been referred to or volunteered for the study were entered into the study. Towards the end of the study recruitment period the volunteer database was searched for controls of a specific age and gender in order to ensure the control and BD groups were as evenly matched as possible. When recruitment to the study closed any remaining

control volunteers on the study database were thanked for their interest and informed that the study had closed.

2.2.3.3 Protocol amendment to participant recruitment

The insomnia group was intended to act as an additional control to the BD group in that the effect of a sleep disorder in the absence of a mood disorder on cognitive function could be examined. However, recruitment of the insomnia group proved difficult. This was primarily due to two issues. The insomnia patients identified through the sleep disorder service were primarily in full time paid employment and declined to take part in the study due to work commitments. Many of the insomnia patients also had associated mood and/or anxiety disorders which meant they did not meet the inclusion criteria. After two years only five insomnia participants had been recruited. Therefore, due to insufficient numbers, recruitment of the insomnia group was halted and any data collected was not included in the study.

2.2.4 Inclusion and exclusion criteria

2.2.4.1 General inclusion criteria

- Aged 18 -65 years.
- Able to provide informed consent.
- Fluent in English (due to nature of some of the cognitive tests employed).

2.2.4.2 General exclusion criteria

- Verbal IQ < 90 (assessed with National Adult Reading Test (NART)).
- Any significant medical or neurological disorder that might interfere with sleep or cognition (e.g. Parkinson's Disease, Multiple Sclerosis).

- Current alcohol or substance misuse disorder (defined with DSM IV criteria).
- Current shift work.
- Previous head injury with significant loss of consciousness.

2.2.4.3 Inclusion criteria specific to healthy controls

- Currently psychiatrically well confirmed by Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).
- A current Hamilton Depression Rating Scale 17-item (HAM-D[17]) score < 7.
- A current Young Mania Rating Scale (YMRS) score < 5.
- PSQI < 5.
- Epworth sleepiness scale (ESS) score < 10.

2.2.4.4 Exclusion criteria specific to healthy controls

- A personal or family history (first-degree relatives) of DSM-IV Axis I disorder confirmed by MINI interview.
- Taking psychotropic medication.
- Any self-reported sleep problems.

2.2.4.5 Inclusion criteria specific to BD participants

- Bipolar disorder I or II outpatients in any mood state diagnosed by DSM-IV criteria determined with the MINI.

2.2.4.6 Exclusion criteria specific to BD participants

Any changes to psychotropic medication with the previous 4 weeks.

2.2.4.7 Rationale for inclusion and exclusion criteria

The exclusion of participants with a verbal IQ < 90, medical or neurological disorders, a serious head injury with loss of consciousness or with an alcohol or substance use disorder was because these conditions may have an adverse effect on cognitive function and/or sleep. Shift workers were also excluded as this would artificially alter sleep and circadian rhythm. Psychotropic medication use was excluded in the control group as it may have an effect on both sleep and cognitive function. For the BD population it would be unethical and impractical to withhold medication as this may be associated with illness relapse. Therefore BD participants could enter the study if their medication doses and types had been stable for a at least 4 weeks which was considered a time scale long enough for any associated changes in mood and sleep to have settled.

2.2.5 Rating scales

2.2.5.1 Diagnosis of BD

DSM-IV diagnosis of BD was confirmed at visit 1 of the study using the Mini International Neuropsychiatric Interview (MINI).

2.2.5.2 Assessment of Intelligence Quotient (IQ)

The 50 word NART-IQ (Nelson, 1982) was used to estimate pre-morbid verbal IQ. The participant is required to read the list of 50 phonetically irregular words which would be difficult to sound out and thus checks the number of words already known by the participant. Participants are scored on the number of words correctly pronounced which is checked by the experimenter by using a pronunciation guide. The words in the NART can be found in the appendix.

2.2.5.3 Assessment of handedness

Handedness was assessed with a revised version of the Edinburgh Handedness Inventory (Oldfield, 1971).

2.2.5.4 Assessment of depressed mood

Depressed mood was rated with the 17 item Hamilton Depression Rating Scale ($HAMD^{17}$) (Hamilton, 1960) by utilising the Grid $HAMD^{17}$ (Williams et al., 2008). The Grid $HAMD^{17}$ is scored from zero to a maximum of 52. Scores of seven or below indicate no clinically significant symptoms of depressed mood and a patient is rated as in remission (Keller, 2003). Depressed mood was also rated with the Beck Depression Inventory (BDI) (Beck et al., 1961). The BDI was chosen as a second rating scale as in contrast to the interview led HAMD the BDI is self-administered and examines the severity of depression from a different perspective. The HAMD emphasises somatic and behavioural symptoms of depression whereas the BDI focusses on subjective experiences and cognitive and affective symptoms. It has been demonstrated that depression scores measured with the BDI only moderately correlate with those from the HAMD ($r=0.54$) so the BDI is therefore adding complimentary information about depression severity (Steer et al., 1987). A score of < 8 on the BDI is regarded as indicative of remission (Keller, 2003) and is the cut off for remission used in this study. In this study there was a strong correlation between $HAMD^{17}$ and BDI scores ($r_{(s)(45)} = 0.831$, $p<0.001$) so the BDI was used for comparisons and correlations of mood with other variables. The BDI was chosen in preference to the $HAMD^{17}$ as it contains only 1 sleep variable compared to 3 within the $HAMD^{17}$ and is therefore less influence by sleep which is better assessed with the validated scales for sleep described below.

2.2.5.5 Assessment of manic and hypomanic symptoms

Manic symptoms were rated with the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Altman Self Rating Mania Scale (ASRMS) (Altman et al., 1997). The YMRS is a clinician rated 11-item scale examining behaviour over the past 24 hours. In this study the YMRS was used to rate the participant's behaviour on the day of starting the study since it was not possible to observe participants over a 24 hour period. The scale scores from 0-60 with a score of 13 or greater indicating a possible case of mania or hypomania. Remission is generally accepted as a score of < 12 although others have suggested a more stringent score of < 4 for full remission (Berk et al., 2008). In contrast to the YMRS the ASRMS is self-rated and contains 5 multiple choice questionnaire that the participant answers dependant on how they had been feeling over the past week. Scores on the ASRMS have an excellent correlation with the YMRS. Scores are summed from each individual item and a total score of five or below is thought to indicate no clinically significant symptoms of mania are present.

2.2.5.6 Assessment of anxiety

Anxiety was rated with the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). The STAI consists of two 20 item self-rated questionnaires one of which the STAI-S rates the participants current state i.e. how they feel at the time of completing the questionnaire and the other the STAI-T, their trait symptoms of anxiety i.e. how they generally feel most of the time. The STAI-T will be used as the anxiety variable in correlations with other variables as it had a strong correlation with STAI-S in this study, ($r_{(s)(45)} = 0.822$, $p<0.001$). It is more relevant to measure the association of general anxiety symptoms experienced by

the patients in their usual situation with the other measured variables such as function QoL that also reflect a participants usual situation.

2.2.5.7 Subjective assessment of sleep

Subjective assessments of sleep quality were made with the PSQI (Buysse et al., 1989). The PSQI has been validated in a study comparing good sleeping healthy controls, poor sleepers with major depressive disorder and people with either complaints of insomnia or hypersomnia referred to a specialist sleep clinic. It consists of 19 self-rated items grouped into seven components; sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction. Component scores (range 0-3) are calculated and can be reported individually or combined to give a global PSQI score (range 0-21). A global PSQI score > 5 was found to have a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing between good and poor sleepers.

2.2.5.8 Subjective assessment of daytime sleepiness

Subjective daytime sleepiness was assess with the Epworth Sleepiness Scale (ESS) (Johns, 1991). The ESS is a simple to use self-completed questionnaire consisting of eight items where participants are rate their likelihood of dozing on a scale of 0 (would never doze) to 3 (high chance of dozing) in situations such as sitting and reading or watching TV. The scores for the eight items are added giving a final score ranging from 0-24. The ESS has not been validated in psychiatric populations but was found to have good test-retest reliability and a high level of internal consistency in a study of healthy medical students and patients with obstructive sleep apnoea (Johns, 1992). It has also been shown that

scores on the ESS in patients with various sleep disorders correlate significantly with mean sleep latencies measured with the Multiple Sleep Latency Test (MSLT) (Johns, 1991).

2.2.5.9 Assessment of chronotype and subjective circadian rhythm

A shortened version of the Morningness Eveningness Questionnaire (MEQ) was chosen to assess participants preferred chronotype (Horne and Ostberg, 1976). This is a self-completed questionnaire that assesses a person's time of peak alertness by asking about their preferences for the time to perform certain tasks and how they may perform in certain tasks if they had to perform them at prescribed times. The questionnaire produces a score that relates to one of five chronotypes, definite or moderate morning type, definite or moderate evening type or neither type with no preference for morning or evening.

The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (Giglio et al., 2009b) was chosen to assesses the regularity of biological/circadian rhythms of the domains of sleep, activity social life and eating patterns in the study. The BRIAN was validated in a BD population and was found to have excellent test-retest reliability, internal consistency and highly discriminate between BD patients and controls. It also had a strong correlation to the PSQI. The BRIAN is self-completed and contains 18 questions grouped into four areas; sleep, activity, social and eating pattern. Items are scored from 1, no difficulty, to 4, serious difficulty and can be reported as total scores or individual scores for each of the 4 activities. Use of this scale provides information about difficulties experienced by patients in a broader array of domains than sleep questionnaires so adds additional information to the PSQI.

2.2.5.10 Assessment of function

Function was assessed with the FAST (Rosa et al., 2007). This scale was chosen as unlike other function questionnaires it was developed to measure functions specifically influenced by BD and is also concise and simple for researchers and participants to complete and score. It is an interview led questionnaire containing 24 questions about function grouped into six domains and takes approximately 5-6 minutes to complete. Each question is answered on a scale from 0, no difficulty, to 3, severe difficulty and scores are added to form a total score with higher scores indicating lower levels of function. The six domains are autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal functioning and leisure time. It was validated in a study comparing BD patients with controls and found to have good internal consistency, test-retest reliability and was sensitive to different mood states in that euthymic patients scored significantly lower than manic or depressed patients. It also had a strong correlation with the Global Assessment Functioning Scale (GAF), a commonly used global function questionnaire.

2.2.5.11 Assessment of QoL

The Qol.BD (Michalak and Murray, 2010) was chosen to measure QoL in the study. This scale was chosen as it was specifically developed for use in BD incorporating domains of life that may be specifically important in BD and has good internal validity and test-retest reliability. It is a self-completed questionnaire containing 48 core questions and an additional eight questions relating to work or educational activities if applicable. Participants score each item on a 1 to 5 scale from 1 strongly disagree to 5 strongly agree. The total score is summed and lower scores indicate lower QoL. It also had strong correlations

with other QoL questionnaires such as the short form-36 (SF-36). The QoL.BD is also sensitive to changes in mood state.

2.2.6 Subjective assessment of the sleep wake cycle.

Participants were required to keep a sleep diary for the 21 days of the study period that recorded lights out time, the time participants got out of bed at the end of their main sleep period and the date, time and duration of any daytime naps. A copy of the sleep diary can be found in the appendix.

2.2.7 Objective assessment of the sleep wake cycle

A wrist worn accelerometer was chosen as the primary method of objective assessment of the sleep/wake cycle as it is a practical, convenient and inexpensive method and can be used to measure 24 hour sleep/wake behaviour over prolonged periods of time in a participants natural setting (Martin and Hakim, 2011). In addition to providing numerical estimates of sleep variables accelerometer data can also be displayed visually on what is usually termed an actogram. Visual inspection of sleep/wake cycles is helpful in identifying specific sleep/wake patterns and is useful in the identification of circadian rhythm sleep disorders (Ancoli-Israel et al., 2003). Actograms will be utilised to identify abnormal sleep phenotypes in this study. As sleep patterns and night to night sleep in BD have been demonstrated to be highly variable accelerometry data was recorded over a period of 21 days in order to ensure a representative estimate of the sleep wake cycle was obtained. The ICSD-3 recommends a minimum of at least 14 days of accelerometry to aid diagnosis of circadian rhythm sleep disorders (American Academy of Sleep Medicine, 2014).

2.2.7.1 Choice of accelerometer

Given the potential benefits of utilising a device that records in standard SI units it was decided to utilise a new generation wrist worn accelerometer the GENEActiv (Activinsights Ltd, Kimbolton, UK) tri-axial accelerometer. The GENEActiv accelerometer measures acceleration in three axes within a +/-8g dynamic range and records raw acceleration in SI units. Although this device has only been validated in healthy volunteers it would allow for greater flexibility in data analysis and the possibility of making the data collected open access so that it can be further analysed in the future as more sophisticated algorithms utilising raw accelerometry data become available.

2.2.7.2 Set up of accelerometry device

The accelerometry devices were set up using the propriety GENEactive software. The sampling frequency was set at 30Hz and data were stored in gravity (g) units (1g =9.81m/second^2). Participants were instructed to wear the accelerometer continuously on their non-dominant wrist for 21 days only removing it during activities such as bathing. If the device was removed then participants were instructed to record the time periods and dates of removal. After 21 days at study visit 2 data from the device was downloaded using the proprietary software and saved as .bin and .csv files.

2.2.7.3 Analysis of accelerometer data

The raw accelerometer data from the .bin file was analysed using an open source R package sleep detection algorithm GGIR (van Hees et al., 2015). Compared to polysomnography (PSG) this method has demonstrated high (91%) sensitivity, (correct detection of sleep), high (83%) accuracy, (the proportion of PSG identified

sleep epochs correctly classified by the accelerometer and reasonable specificity (45%), (correct detection of wake), which is comparable to other accelerometer methods. The GENEactive device has not been validated for the detection of daytime nap periods and studies with other accelerometers and algorithms have found that there is low specificity in accurately distinguishing actual sleep periods (naps) from sedentary behaviour during the day and they tend to overestimate sleep time (Kanady et al., 2011; Cellini et al., 2013). In order to help minimise this limitation of accelerometry the sleep diary data was utilised to guide the algorithm in its classification of activity periods as either sleep or wake. Periods of activity that meet the sleep criteria are classified by the algorithm as sleep if they fall between lights out and get up times indicated on the sleep diary and as sustained inactivity bouts daytime (SIBD) if they fall outside of the sleep diary sleep time window. Although the sustained activity periods in the daytime could theoretically be periods of actual sleep it is likely that daytime sleep would be overestimated by this method and therefore in order not systematically overestimate total sleep time in a 24 hour period it was decided to label these activity periods as sustained inactivity bouts rather than definite sleep. In addition other accelerometry studies in BD report nocturnal sleep not 24 hour sleep and therefore naps are not included in other studies.

As it has been demonstrated that sleep diaries can differ significantly from accelerometry recorded data (Martin and Hakim, 2011) an additional step was taken prior to analysis of the data with the algorithm. The data was initially processed without the use of the sleep diary data in order to produce a visual actogram of the participants sleep wake cycle. As the GENEactive device also contains a light meter the actogram also shows periods of light and dark

exposure. The visual actogram was then examined alongside the sleep diary to check for accuracy of the sleep diary in terms of recorded lights out and get up times. If there was a greater than 1-hour difference between lights out time or get up time than that suggested by the actogram then the sleep diary was corrected to within 30 minutes of the times recorded on the actogram. The use of light exposure data although an attractive idea to guide lights out and get up times was only a consideration in determining the accuracy of the sleep diaries. The light meter could be obscured by clothing or bedclothes and therefore provide inaccurate information about lights out times. It was however found that the dark periods generally corresponded with sleep periods giving greater confidence that the majority of sleep diary data was reasonably accurate. Visually scoring the actograms for lights out and get up times has previously been demonstrated as a valid method since a previous study has found that visual scoring of sleep from the actogram has a reasonable correlation ($r = 0.640$) with PSG identified sleep periods (Boyne et al., 2013). Therefore following any necessary adjustment of sleep diary data the data was re-analysed and the data from the algorithms automatic detection of sleep and wake variables was used in the study. The visual inspection of the actograms also allowed verification of any periods when the device was not worn by the participant over the recording period. The algorithm is able to automatically detect periods of non-wear and remove days containing periods of non-wear greater than a time specified by the experimenter. In this study the algorithm was instructed to remove any days with non-wear periods greater than one hour in a 24-hour period from the analysis. That this was correctly performed was checked via visual inspection and corrected if required.

2.2.7.4 Accelerometer defined sleep/wake variables

Sleep variables were calculated across all days of the study period including weekends. Although sleep wake behaviour can change at weekends participants wore the accelerometer for 21 consecutive days of which just 6 would be weekend days which would therefore minimise any effect of weekend changes in sleep wake behaviour in the variables reported. The following accelerometer estimated sleep variables are reported in the study.

- TIB - defined as the mean difference between nocturnal sleep onset and wake times over all days of the recording period measured in hours. TIB includes any periods between these times when the participant did not meet the sleep criteria i.e. had not risen from bed but did not meet the algorithm definition of sleep.
- IV-TIB – Intra subject variability in TIB defined as the standard deviation (SD) in TIB over all nights of the recording period measured in hours.
- Nocturnal sleep time - defined as the mean accumulated nocturnal sustained inactivity bouts that meet the sleep criteria between the nocturnal sleep onset and wake time over all days of the study period measured in hours.
- IV-nocturnal sleep time – Intra-subject variability in nocturnal sleep time defined as the SD in nocturnal sleep time over all nights of the study period measured in hours.
- SE – sleep efficiency defined as the mean nocturnal sleep duration divided by the mean TIB over all days of the recording period.
- IV-SE – Intra-subject variability in SE defined as the SD in SE over all nights of the study period.

- SIBD – sustained inactivity bouts daytime defined as the mean accumulated sustained inactivity bouts outside of nocturnal sleep period over all days of the study period measured in hours. (Note these are activity periods that would have been defined as sleep if occurring between the nocturnal sleep onset and wake period).
- IV-SIBD – Intra-subject variability in SIBD defined as the SD in SIBD over all days of the recording period.
- IV- sleep onset time – Intra-subject variability in sleep onset time defined as the SD in sleep onset time over all days of the study period measured in hours.
- IV- sleep offset time – Intra-subject variability in sleep offset time defined as the SD in sleep onset time over all days of the study period measured in hours.

2.2.7.5 Accelerometer estimated physical activity

Physical activity was estimated from the acceleration of the accelerometer due to arm movement and is expressed in milli-gravitational units (milli-g). Thresholds of activity were set to distinguish between low intensity activity and more moderate and vigorous activity such as walking and running. The outputs used in the study are as follows.

- Mean 24-hour acceleration defined as the mean acceleration over all days of the study period measured in milli-g.
- L5 defined as the mean acceleration during the least active 5-hour time period within each 24-hour period averaged over all study days.

- M10 defined as the mean acceleration during the most active 10-hour time period within each 24-hour period averaged over all study days.
- The relative amplitude (RA) between the most active and least active period calculated by using the formula M10-L5 divided by M10 + L5. The RA ranges from 0-1 with a higher number indicating a greater amplitude between the most active 10-hour and least active 5-hour period. A person with a good circadian rhythm would be expected to have a higher RA than a person with a poor circadian rhythm as a higher RA indicates a larger difference between night time inactivity (sleep) and a the amount of daytime activity.
- MVPA - Moderate and vigorous physical activity expressed in milli-g. Activity of over 100 milli-g of acceleration during any 5 second epoch of time was counted as MVPA as walking at 4km/h has been classified as moderate physical activity and was equivalent to an acceleration of 100 milli-g in a laboratory experiment (Bell et al., 2015).

2.2.7.6 Identification of sleep phenotypes

Using accelerometry derived sleep estimates and inspection of the visual actogram participants were classified as the following objectively identified sleep types.

- Normal sleepers (6-10 hours mean nocturnal sleep over 24 hours with a regular sleep wake cycle), a negative test for OSA (see section 2.2.7.8)
- Abnormal sleepers
    - Short nocturnal sleepers (<6 hours mean nocturnal sleep),
    - Long nocturnal sleepers (>10 hours mean nocturnal sleep),

- Long 24 hour sleepers (>10 hours nocturnal sleep + SIBD within 24 hours).
- Circadian rhythm disturbance (CRD). Patterns of sleep characteristic of CRSD as defined in the ICSD-3 (American Academy of Sleep Medicine, 2014) were identified via visual inspection of the sleep actograms produced by the algorithm.
    - Delayed sleep phase defined as > 2 hours delay (> 1.00am) in usual sleep onset compared to societal norms over the majority of 24 hour periods.
    - Advanced sleep phase defined as > 2 hours advance (< 9.00pm) in usual sleep onset compared to societal norms over the majority of 24 hour periods.
    - Irregular sleepers defined as having a sleep/wake pattern with multiple sleep/SIBD bouts of > 3 hours within the majority of 24 hour periods.
    - Non 24-hour sleepers characterised by a misalignment between the light dark cycle and sleep wake behaviour with a pattern of sleep onset that typically progressively delays each 24 hour period, with a circadian period that is usually longer than 24 hours.
    - CRD not otherwise specified (CRD-NOS) defined as participants with clearly irregular and disrupted sleep wake cycles but who didn't meet the above criteria.
- In addition participants identified with OSA (see section 2.2.7.8) were also classified as abnormal sleepers.

2.2.7.7 Assessment of obstruction sleep apnoea

Participants were objectively assessed for the presence of sleep apnoea with a portable home partial polysomnography device, the Embleta Gold Polygraphy System (Embla Systems, Bllomfield, USA). This device is commonly used in the sleep clinic in Newcastle and has demonstrated good reliability and compliance with patients. Participants were trained in the use of the device at the first visit and asked to perform a sleep study for one night during the 21 day study period. The device assesses respiratory effort, airflow, the presence of snoring, oxygen saturation of arterial blood, heart rate and body position. Details of the all respiratory events were scored according to standard criteria of the American Academy of Sleep Medicine (AASM) (American Academy of Sleep Medicine, 2014). The apnoea hypopnoea index (AHI) and oxygen desaturation index (ODI) were derived. The AHI is the number of apnoeas or hypopnoeas in an hour and the ODI is the number of times the oxygen level drops > 4% of the baseline saturation in an hour. An AHI of > 5 /hr was considered abnormal and indicative of sleep apnoea. Severity was further defined as mild (AHI 6-14), moderate (AHI 15 – 29) or severe (AHI $\geq$30). Those with the obstructive sleep apnoea syndrome were defined as per the 2005 AASM criteria.

2.2.7.8 Assessment of periodic limb movement in sleep

The presence of PLMS was assessed with accelerometry. Participants were instructed to attach an accelerometer (GENEactive) to each foot for three consecutive nights during the study period. Unfortunately an algorithm to estimate PLMS that was in development at Newcastle University was not completed on time for utilisation in this study so although data was collected it

has not been able to be analysed and the presence of PLMS in the study population is not reported.

2.2.8 Assessment of cognitive function

The literature review indicated the cognitive functions most sensitive to short term sleep deprivation and sleep restriction are attention, working memory, short term memory and processing speed. The largest deficits reported in people with insomnia were in working and episodic memory and in patients with sleep apnoea in attention. These cognitive domains have also been demonstrated to be impaired in BD and therefore a cognitive test battery was designed to test these domains. The time of the cognitive testing was standardised to begin at 2.00pm and took between 2 and 2.5 hours to complete depending on break times the participants requested. The tests, the order in which they were administered and the cognitive domains they assess can be found in Table 2-1.

2.2.8.1 The Digit Symbol Substitution Test (DSST)

The DSST originates from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981). The DSST is a pen and paper task with a key at the top of the page containing the numbers 1 to 9 with a unique symbol associated with each number. Below the key are four rows of 25 blank squares each with the number 1 – 9 above the square. The participant is asked to copy as quickly and accurately as possible the correct symbol into the blank square that corresponds with the numbers and matched symbols in the key. A practice of seven blank

Table 2-1 Cognitive Test Battery

Test	Domains Tested
Digit Symbol substitution test (DSST)	Psychomotor Speed
Psychomotor Vigilance Test (PVT)	Sustained attention/executive control
Newcastle Spatial Working Memory	Executive
Verbal learning (immediate recall)	Learning and Memory
Attention Network Test	Sustained attention/executive
Digit Span (forward and backward)	Immediate/executive
Trail making test (A and B)	Processing speed/Executive
Verbal learning (delayed recall)	Learning and memory
Facial Expression Recognition Task (FERT)	Emotional processing
Stroop Test	Executive
Digit Symbol substitution test (DSST)	Psychomotor Speed

Tests were administered to standard protocols in the order listed in the table.

squares is allowed and then the participant is given 90 seconds to complete as many correct responses as possible. The number of correct symbols copied is the outcome measure. The test is reported to assess graphomotor speed, perceptual speed and visual scanning efficiency with small contributions of learning/memory and executive functions (Joy et al., 2003). Additionally, the DSST has been demonstrated to assess executive control in children and older adults but not in young adults (Cepeda et al., 2013). This is hypothesised to be because processing speed tasks are not pure and still rely on executive control for optimal performance. The executive control network in children is not fully developed and in older adults may suffer from cognitive decline. Therefore, interpreting deficits in DSST performance should also consider the possible role of a deficit in the executive control network.

2.2.8.2 The Psychomotor Vigilance Test (PVT)

The PVT (Dinges and Powell, 1985) is a simple reaction time (RT) task reported to assesses vigilant attention and executive control of attention (Unsworth et al., 2010). The participant is required to respond to a stimulus (a digital counter) on a computer screen by pressing the response button as quickly as possible which stops the counter and displays the RT in milli-seconds (ms) for 1 second. The next stimulus appears randomly from 2 sec to 10 sec after the proceeding one and the task duration is typically 10 min, containing approximately 90 RTs per trial. The participant is instructed to respond to the stimulus by pressing the button in the shortest possible time but not pressing the response button before the stimulus has appeared which would be recorded as a false start. The PVT has been included in the test battery as it is the most extensively used cognitive test in studies of SD and SR and has been demonstrated to be highly sensitive to these conditions. Outcome measures from the PVT include mean and median RT and typically in the sleep literature the fastest 10% and slowest 10% of RT's have been analysed to examine if there is a general slowing of RT or just slowing for specific trials. Additionally the first and last 10% of RT's are examined to assess for slowing of RT over the course of the test. RT standard deviations and coefficients of variability can also be calculated to assess variability in RT. Finally the number of lapses (RT's >500ms) and false starts are also recorded.

2.2.8.3 The Newcastle Spatial Working Memory Test (NSWM)

The NSWM is based on the Cambridge Neuropsychological Test Automated Battery (CANTAB) spatial working memory test and assesses spatial working memory an executive function. It is a computer based task completed on a touch screen where participants search through an increasing number of coloured

circles on the screen to find a hidden token. Once a token is found it is placed in a bin and the search repeated until all the tokens have been found. When a token has been found it will not appear behind the same coloured circle again so participants must try and remember behind which circles a token has been found so they do not search there again. The test starts with just four coloured circles and four tokens have to be found The task increases in difficulty as the number of circles and tokens to find increases to a maximum of 12. Performance accuracy is measured as the number of between search errors which is the number of times a participant searches behind a circle where they have already found a circle and the number of within search errors when a participant searches behind a circle they have already searched on the current trial.

2.2.8.4 Verbal Learning Test (immediate and delayed recall)

In this task participants are presented with 30 words consecutively on a computer screen. Participants were asked to read each word and remember as many as possible. They were then asked to recall as many of the words as possible to the investigator who records the number of correct words recalled. Following this task three other cognitive tasks were performed which took approximately 30 minutes and then participants performed the delayed recall. In the delayed recall participants were presented with 60 words consecutively on a computer screen, the original 30 words randomly interspersed with 30 new words. For each word participants had to push a button saying yes if one of the words was one of the original 30 or no if the word was a new word. There was no time limit and the next word only appeared after each response. The total number of errors where participants incorrectly say they have seen the word if it is a new word (foil error) or not seen the word if it was one of the original 30

(target error) are recorded and also the number of target and foil errors. The test assesses immediate memory and short term memory retention including free and cued recall, interference and recognition.

2.2.8.5 The Attention Network Test (ANT)

The ANT uses RT's to quantify the processing efficiency of three attentional networks namely alerting, orienting and executive attention (Fan et al., 2002). Alerting has been defined as achieving and maintaining an alert state; orienting as the selection of information from sensory input; and executive control is defined as resolving conflict among responses. This computer based test takes approximately 15 minutes to complete. Participants are required to determine whether a central arrow of five, points left or right and respond by clicking the left or right mouse button with each RT recorded. The experimental procedure is presented in Figure 2.2. There is a central fixation mark which the participant focusses on and the arrows appear above or below the fixation in the presence or absence of flankers. The alerting component is assessed by the differences in RT when a cue is given just before the appearance of the arrows. There is a no cue condition, a centre cue, double cue and spatial cues. The participant can use the cues to speed up RT as the spatial cue gives information about where the arrows will appear (above or below the fixation mark) allowing the participant to focus on the part of the screen where the arrows will appear. The double and central cues although providing no spatial information still alert the participant to the imminent appearance of the arrows. In the no cue condition there is obviously no alerting or spatial information. The alerting effect is then calculated by subtracting the mean RT's of all the double cue conditions from the mean RT's of the no cue conditions. The orienting effect is calculated bu subtracting the mean

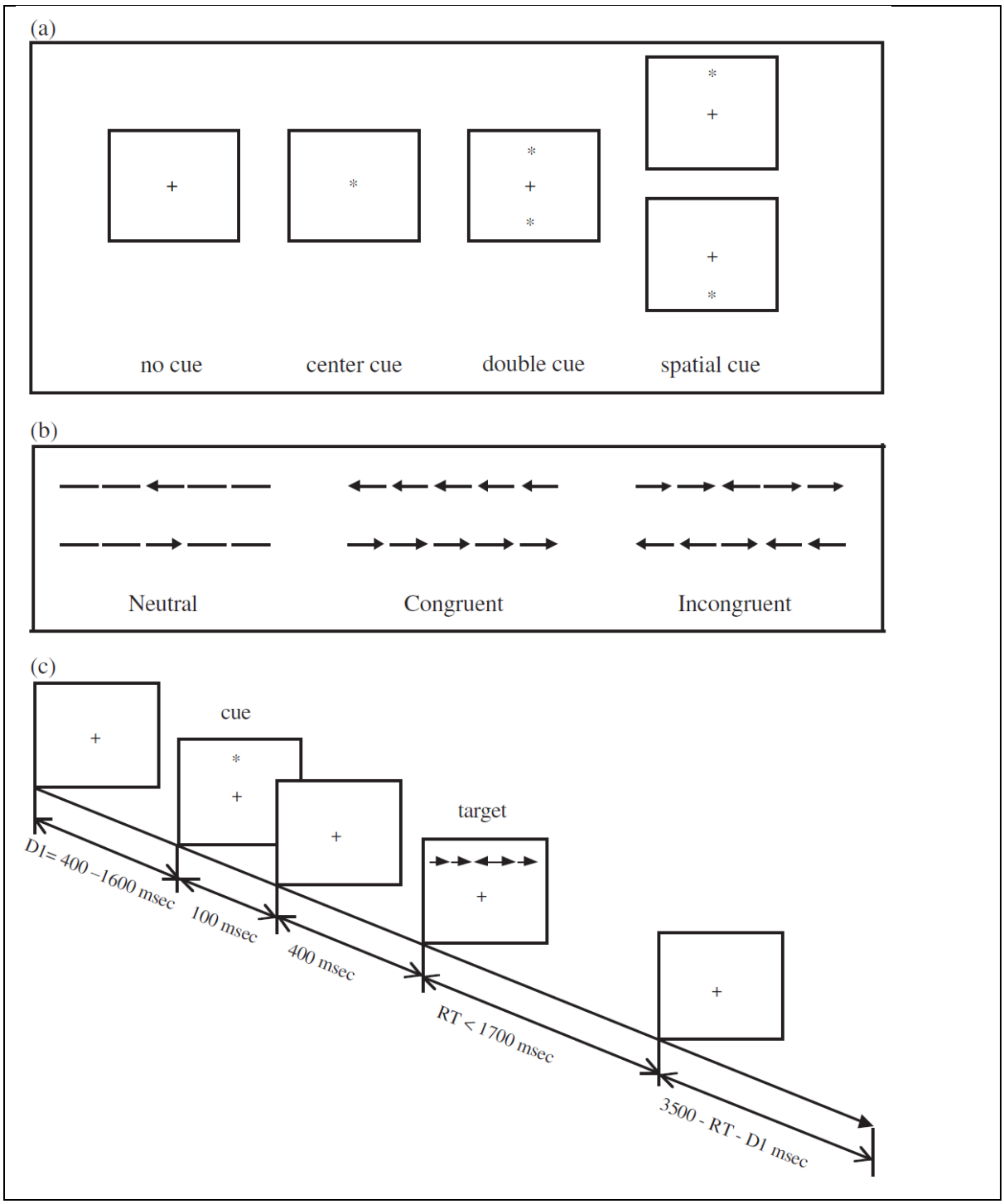


Figure 2.2 Experimental procedure of the ANT. (a) the four cue conditions; (b) the six stimuli used in the test, (c) an example of the procedure. (from Fan et al. (2002)

RT's of the spatial cues from the mean RT's of the central cues. The conflict (executive control) effect is calculated from the RT's to the arrows with or without flankers. Sometimes the arrows have no flankers (neutral condition), sometimes congruent flankers where all arrows point in the same direction and sometimes incongruent flankers where the arrows point in random directions. The conflict

flankers mean it takes more time to calculate which direction the central arrow points due to the conflicting information from the flankers. The conflict effect is then calculated by subtracting the mean RT from the congruent condition (across all cue types) from the mean RT of incongruent flanking conditions. Three main scores are then produced the alerting, orienting and conflict conditions to assess the different attentional networks.

2.2.8.6 Digit Span forwards and backwards

The digit span test assesses verbal working memory an executive function (Lezak et al., 2004). In the digit span the participant is read a series of numbers of increasing length from 3 digits to a maximum of 9. The participant listens and is asked to repeat the numbers in the same sequence. Two number sequences are read for each level of the task. This continues up to a maximum sequence of nine digits or until the participant gets both sets of a level incorrect. The participant gets one point for each correct sequence (maximum of 14). The backwards digit span is identical but the participant has to repeat the number sequence spoken by the investigator backwards and the levels go from 2 to a maximum of 8 digits. The backwards test puts more demands on working memory than the forwards test as the digits have to remembered and then manipulated. One point is scored for each correct sequence (max 14) and the forwards and backwards scores are reported separately or combined to give a total score (max 28).

2.2.8.7 The Trail Making Test (A and B)

The TMT-A is a pen and paper task where a participant is timed how long they take to join a sequence of numbers spread randomly across a sheet of paper from 1-25 in consecutive order. Participants are asked to draw a line between them

with a pen, without lifting the pen from the paper in consecutive order. A practice is given before the test on a shorter span of numbers from 1 to 8 to ensure the participant understands what is expected. The TMT-B is a similar task but this time the participant has to switch between numbers and letters, i.e. join the number 1 to letter A, then letter A to number 2, then number 2 to letter B and so on until the number 13 is reached. The participant is given a short practice first on a short sequence to ensure understanding of the test. The scores are the times in seconds to complete TMT-A, TMT-B and TMT-B minus TMT-A. The TMT-A has been demonstrated to assess mainly visuo-perceptual abilities whilst TMT-B assesses primarily working memory and but also task switching ability. B-A minimizes visuo-perceptual and working memory demands, providing a relatively pure indicator of executive control abilities (Sanchez-Cubillo et al., 2009).

2.2.8.8 Additional cognitive tasks

In addition to these tasks the Facial Expression Recognition Task and a computerised Stroop task were performed but they are not reported in this thesis so will not be discussed here.

2.2.9 Study procedure

2.2.9.1 Visit 1

At visit 1 potential participants were assessed for study inclusion and exclusion criteria with participant specific (control or BD) eligibility screening questionnaires. Eligible participants signed consent forms and then completed the rest of the demographic screening and questionnaires which were recorded on the case report form for visit 1. Participants then received training on data collection and equipment use for the field based 21-day assessment of sleep

function. They left with all necessary equipment and data recording sheets and an appointment for visit 2.

2.2.9.2 Visit 2

After the 21-day field based period participants were instructed to return for visit 2 returning all equipment and data recorded. The time of visit 2 was standardised to begin between 12.00 and 13.00 hours dependent on participant availability in order that cognitive testing during this visit would take place at a similar time of day. Participants had their sleep, mood, anxiety, biological rhythm, function and QoL reassessed. They were also asked if they had experienced any unexpected sleep loss or changes to their habitual sleep pattern or routine. Data from the wrist accelerometer was downloaded to a computer. Participants then completed the cognitive test battery. Following completion of the study protocol participants were asked to inspect the visual actogram of their sleep wake/cycle with the investigator and this was compared with sleep/wake timings from the sleep diary. Any major discrepancies between the actogram and the sleep diary were discussed with the participant in an attempt to understand why they differed. If the participant could provide an explanation for any discrepancies the sleep diary timings were adjusted with the consent of the participant. Following the end of visit 2 all data recorded from the participant was entered into the study datasheet along with the results of the cognitive testing.

2.2.10 Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 22. Data was visually inspected by plotting histograms and box plots to detect

outliers and examined for normality of distribution with the Shapiro Wilk test and for homogeneity of variance with Levene's Test. Log_{10} or square root transformations were used where necessary to normalise the data. Parametric tests were used unless the data remained non-normally distributed despite transformation when equivalent non-parametric tests were used. A significance threshold of $p< 0.05$ was used for all analyses.

2.2.10.1 Treatment of outliers

Data points greater than 3 times the interquartile range were identified as extreme outliers. Extreme outliers in poor performance on specific cognitive tests were excluded from the analysis of that specific cognitive test. This is because it is likely that extreme poor performance would have a disproportionate influence on mean performance on the tests and is unlikely related to a cognitive deficit but due to a different cause such as misunderstanding the test. When performing correlation, analysis of covariance (ANCOVA) and regression analyses scatter plots were drawn to inspect the data and check for outliers that may have had a significant effect on the strength of correlations between variables. Outliers that significantly influenced the strength of correlations were Winsorised.

2.2.10.2 Pre-specified analyses.

For the examination of the association of cognitive function with sleep variables the following analyses were undertaken.

1. BD participants cognitive performance was compared to controls in the following subgroups.
    a. Controls vs. total BD group
    b. Controls vs. euthymic BD patients

c. Controls vs. objective normal BD sleepers
d. Controls vs. objective abnormal BD sleepers
e. Controls vs. objective euthymic abnormal BD sleepers
f. Objective euthymic normal vs. objective euthymic abnormal BD sleepers

2. As SD and BD have both been associated with increased intra-individual variability in RT (Lim and Dinges, 2008; Gallagher et al., 2015). Intra-individual variability in RT data from the PVT and ANT was explored in the subgroups defined in number 2 above by the calculation of the sigma (σ) and tau (τ) statistics with ex-Gaussian analysis. It has been noted that RT distributions typically have a positive skew and contain information that cannot be derived from the distributions mean and variance (Heathcote et al., 1991). RT distributions usually consist of a normal (Gaussian) component but also a tail of longer RTs, an exponential component. Ex-Gaussian analysis calculates the mean (μ) and SD (σ) of the normally distributed component of the distribution and tau (τ) which represents the mean and SD of the exponential component (Whelan, 2008).
3. Correlation analyses was performed between mean PVT RT and the following individual sleep variables.
    a. TIB and IV-TIB
    b. Nocturnal sleep time and IV-nocturnal sleep time
    c. SE and IV-SE
    d. 24 hour TST (nocturnal sleep + SIBD) and IV 24 hour TST
    e. IV sleep onset and IV-sleep offset times

2.2.10.3 Control for multiple comparisons

To control for multiple comparisons subgroup analyses were only performed if there was a statistically significant difference in performance on the cognitive test in the total BD group compared to controls ($p \leq 0.05$).

2.2.10.4 Controlling for potential confounders

The literature review identified that there are a number of potential confounders in cognitive performance including the number of mood episodes, the number of hospitalisations and length of illness. In addition, age, IQ and current mood symptoms may also be associated with cognitive function. In this study as there was no access to BD patients medical notes it was not possible to collect accurate information on the number of prior episodes and hospitalisations or the length of illness and therefore these factors. Therefore it was not known if these factors were equally distributed between BD normal and abnormal sleepers and it will not be possible to control for these potential confounders. This fact should be considered a limitation of the study. The potential confounding effects of age and NART-IQ were controlled using analysis of covariance (ANCOVA). Pearson's correlations were performed between cognitive performance and age and NART-IQ. Where significant correlations existed ANCOVA was performed using age and NART-IQ as the covariates. When performing ANCOVA the data were assessed to ensure it met the assumptions of ANCOVA . Where violations were found they were reported so that the results of the ANCOVA could be interpreted in this knowledge. The results of ANCOVA are only be reported when it had a significant effect on the outcome between groups. In comparisons between controls and BD patients it was not appropriate to use ANCOVA using mood as a

covariate. This is because controls were specifically selected not to have a mood disorder and had to score below the cut off for remission in both depressive and manic symptoms. In contrast, BD patients in any mood state could enter the study. This means that mood will be fundamentally different between the groups and therefore the assumptions of ANCOVA such as homogeneity of regression slopes between mood and cognitive performance would have been violated. I.e. there will be a different relationship between mood and cognitive performance in controls and BD groups. This would make the findings of ANCOVA using either depression or mania scores as covariates unreliable. Therefore, the potential confounding effects of mood were controlled by comparing subgroups of euthymic BD patients with controls. Euthymia was defined as BD patients who meet the remission criteria for both depression and mania. These were defined as a BDI score < 8 and a YMRS score < 11. The BDI was used to define remission rather than the HAMD17 as there is only 1 sleep item on the BDI compared to 3 sleep items on the HAMD17. The BDI remission score will therefore be less likely to be influenced by sleep. It would be theoretically possible for example, for a patient with severe insomnia to score above the remission cut off on the HAMD17 with just one additional depressive symptom.

3. Chapter Three - Results

3.1 Participant recruitment to the study

Following the recruitment procedures 72 controls and 48 BD patients expressed an interest in taking part in the study. The flow of patients through the study protocol can be found in Figure 3.1. Initially controls were enrolled into the study in the order in which they applied to take part but in the later stages of recruitment potential controls from the list of applicants were selected based on their age and gender in order to best match the BD participants. Two controls did not meet the criteria for scoring > 90 on the NART but they were included in the study as their first language was not English. All other controls met all inclusion criteria. All potential BD participants met study inclusion criteria. One BD participant deferred entry into the study for personal reasons and was not able to start the study protocol before the study closed so provided no data for the study leaving 47 BD participants who took part and provided data. The first participant was recruited into the study in October 2012 and the last participant completed the protocol in July 2015.

3.2 General demographics of study participants.

General demographics are presented in Table 3-1. There were no statistically significant differences between the group with regards to age, handedness, NART estimated IQ and years in full time education. BD participants were however on average 4 years older than controls and there was a trend towards a significantly greater NART estimated IQ in the BD group. BD patients had a significantly greater mean BMI than controls and a significantly greater proportion of BD patients than controls were classed as obese (BMI > 30 kg/m2). There was no significant difference in the mean BMI between female and male BD patients

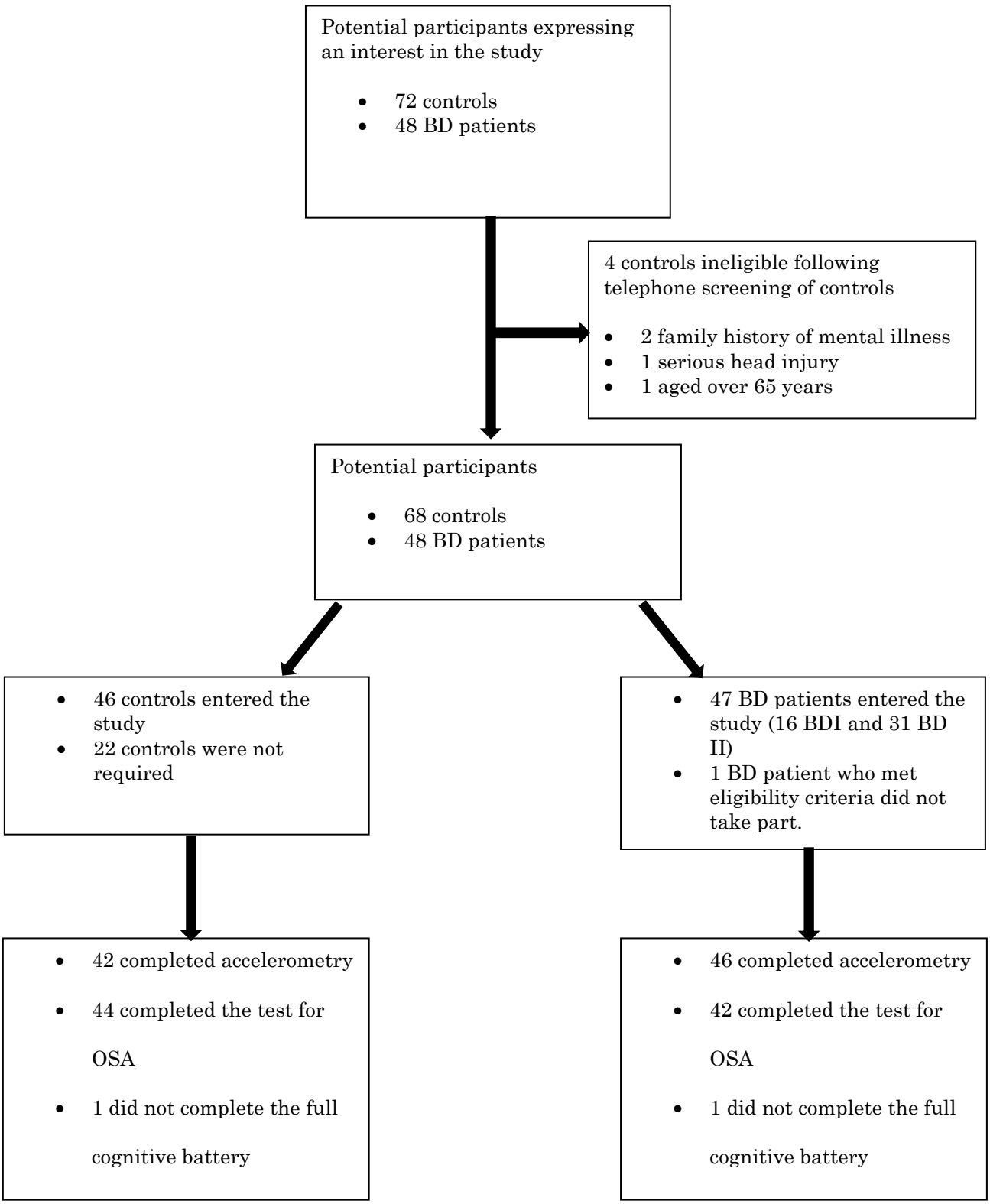


Figure 3.1 Participant flow through the study

Table 3-1 General demographics of study participants

			Statistical Test		
Characteristic	**Controls (n=46)**	**Bipolar Disorder (n=47)**	**X^2 (df)**	**Mann Whitney U**	**p**
Female Gender, n (%)	33 (71.7)	32 (68.1)	0.148 (1)		0.701
Age years: mean (SD) (Range)	42.6 (11.6) (19-64)	46.5 (11.1) (23-64)		869.5	0.104
NART (SD) (Range)	116.7 (7.7) (97-128)	119.4 (7.1) (97-131)		823.5	0.094
Years in full time education (SD) (Range)	15.6 (3.3) (11-24)	15.8 (3.5) (10-24)		1013.5	0.601
BMI mean: kg/m² (SD) (Range)	25.8 (4.7) (19.5-39.7)	29.9 (6.6) (21.0-52.0)		632.0	**0.001**
BMI ≥ 30kg/m², n (%)	9 (20)	19 (40.4)	4.530 (1)		**0.033**
Smoker, n (%)	4 (8.7)	7 (14.9)	0.856 (1)		0.355
Mean alcohol units per week (SD)	7.8 (7.6)	4.8 (9.7)	8.619 (1)	684.0	**0.002**
Currently Employed/student, n (%)	38 (82.6)	23 (48.9)	11.679 (1)		**0.001**
Unemployed, n (%)	4 (8.7)	17 (36.1)	10.038 (1)		**0.002**
Full time employment, n (%)	28 (60.9%)	12 (25.5%)	11.843 (1)		**0.001**
Part time employment, n (%)	3 (6.5%)	8 (17.0%)			
Voluntary Work, n (%)	2 (4.3%)	2 (4.3%)			
Student, n (%)	5 (10.9%)	1 (2.1%)			
Retired, n (%)	4 (8.7%)	7 (14.9%)			
Chronotype, n (%)					
Morning	20 (43.5)	14 (29.8)			
Evening	3 (6.5)	11 (23.4)	5.182 (1)		**0.023**
Neither Type	23 (50.0)	22 (46.8)			

BMI = body mass index, NART = National Adult Reading Test. Chronotype assessed with a modified version of the Morningness/Eveningness Questionnaire. Morning and evening types include both moderate and definite morning and evening types.

(29.1 (SD7.3) kg/m2 vs. 31.6 (SD4.6) kg/m2, $t_{(46)} = -1.592$, p=0.118). Significantly fewer BD patients than controls were in current employment or students and a lower percentage were in full time employment than controls. Smoking rates were not different between groups but BD patients consumed fewer mean alcohol units per week than controls. With respect to chronotype a greater proportion of the BD participants than controls expressed an evening preference (moderate and definite evening types combined).

3.2.1 Psychotropic medication use

Psychotropic medication use by the BD participants is shown in Figure 3.2. Eighty-three percent of the BD patients were taking at least one psychotropic medication.

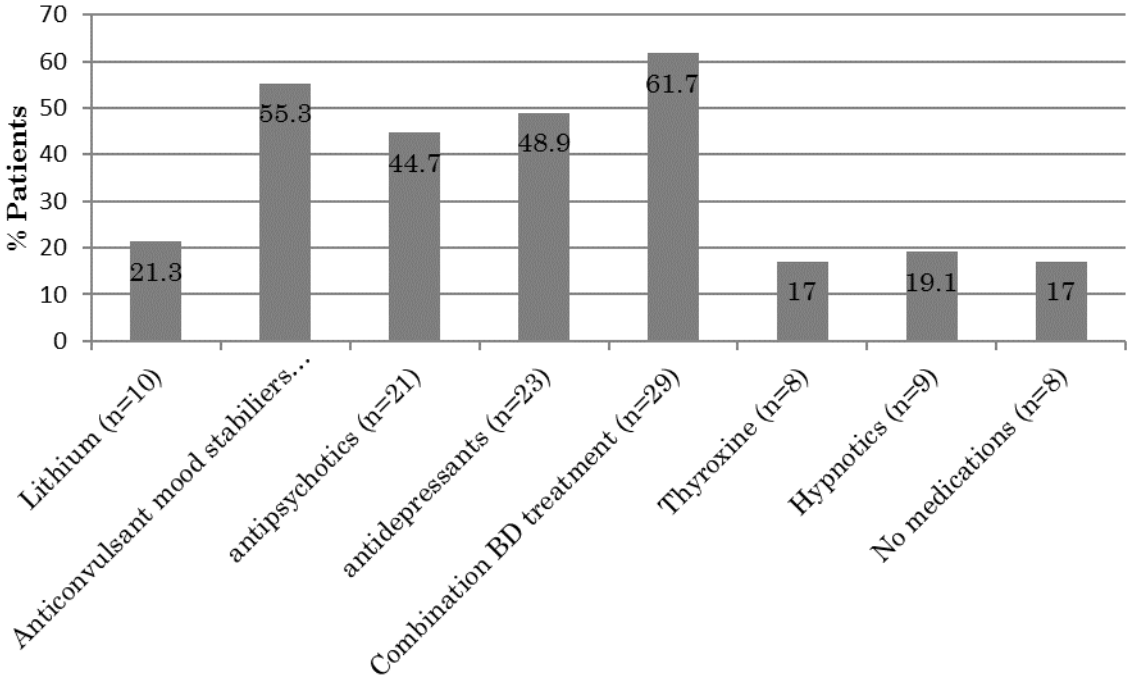


Figure 3.2 Psychotropic medication use in the BD group

Combination BD treatment is defined as a usage of a combination of at least 2 medications from lithium, other mood stabilisers, antipsychotics and antidepressants.

Lithium and other mood stabilisers (sodium valproate, lamotrigine, gabapentin) were the most commonly prescribed medications. Combination treatment with BD medications (lithium, other mood stabilisers, antipsychotics and antidepressants was common. Hypnotics were used by 19.1% of the BD patients.

3.3 Obstructive sleep apnoea

Eighty-six (92.4%) of the participants (44 controls and 42 BD) successfully completed the overnight portable oximetry test for OSA. Seven participants (2 controls; 5 BD) did not complete the OSA assessment due to failure of the device to record correctly. Two of the BD patients were in the obese BMI range and may have been at higher risk for the presence of OSA but both controls had BMI's < 30. A significantly greater proportion of BD patients had an AHI > 5, the usual cut off for a diagnosis of OSA, with the majority of cases being of mild severity (Table 3-2). More depressed than euthymic BD patients also had an AHI >5, 50% vs. 13% ($X^2_{(df)} = 6.662_{(1)}$; p=0.01). Within the BD group there was a statistically significant correlation between AHI and BMI (Pearson's $r_{(47)} = 0.316$, p=0.041) and AHI and ESS (Pearson's $r_{(47)} = 0.332$, p=0.032). Of the 12 BD patients with OSA medication use was as follows; antipsychotics n=5, antidepressants n=7, lithium n=1, other mood stabilisers n=7 and hypnotics n=3.

Table 3-2 Prevalence of OSA, mean AHI and ODI in BD patients and controls.

	Controls (n=44)	Bipolar (n=42)	Chi squared (d.f.)	Mann-Whitney U	p
AHI > 5			5.385 (1)		**0.02**
No, n (%)	40 (90.9)	30 (71.4)			
Yes, n (%)	4 (9.1)	12 (28.6)			
Mild					**0.047***
No, n (%)	42 (95.5)	34 (81.0)			
Yes, n (%)	2 (4.5)	8 (19.0)			
Moderate					0.428*
No, n (%)	38 (95)	37 (90.2)			
Yes, n (%)	2 (5)	4 (9.8)			
Mean AHI (SD) (range)	2.3 (4.5) (0.0 – 25.5)	5.3 (7.1) (0.0 – 28.6)		645	**0.016**
Mean ODI (SD) (range)	1.2 (1.8) (0.0 – 6.2)	4.3 (7.5) (0.0 – 33.8)		592.5	**0.015**

* Fisher's Exact Test. OSA = obstructive sleep apnoea, AHI = Apnoea hypopnoea index, ODI = oxygen desaturation index. Mild = AHI $\geq$ 5 <15, Moderate = AHI $\geq$ 15 < 30, Severe = AHI $\geq$ 30. SD = standard deviation.

3.4 Mood, anxiety, history of psychosis and suicide attempt

Controls and BD patients differed significantly on all subjectively assessed symptoms except manic symptoms (Table 3-3). Just over 50% of the BD patients met remission criteria based on either scale (HAMD < 7 and BDI < 9). Mean scores on both the YMRS and ASRMS were low, in the range for clinical remission and did not differ significantly between BD patients and controls. No BD patients scored > 12 on the YMRS or met DSM IV criteria for current manic or hypomanic episode. From this point forwards as no patients were manic, BD patients will be referred to as euthymic (meet depression and mania remission criteria), or depressed. Anxiety symptoms assessed with the STAI-S/T were significantly greater in the BD group. Co-morbid anxiety disorders diagnosed with the MINI in BD patients were common with 28/47 (59.6%) meeting criteria for at least one anxiety disorder (Figure 3-3). The numbers and percentages of

Table 3-3 Mood, anxiety, subjective sleep biological rhythm, function and QoL in BD patients and controls

			Statistical Test	
	Controls (n=46)	**Bipolar Disorder (n=47)**	**Mann Whitney U**	**p**
HAM-D^{17} mean (SD)	0.3 (0.6)	9.0 (7.3)	53.0	**<0.001**
(Range)	(0-2)	(0-35)		
Remission (HAMD ≤ 7) n (%)	46 (100%)	24 (53.2)		
BDI mean (SD)	0.8 (1.8)	12.6 (11.7)	155.5	**<0.001**
(Range)	(0-8)	(0-49)		
Remission (BDI ≤ 8) n (%)	46 (100%)	24 (51.1)		
YMRS mean (SD)	0.1 (0.4)	0.8 (2.2)	958.0	0.117
(Range)	(0-2)	(0-10)		
ARMS mean (SD)	1.3 (2.2)	2.5 (3.5)	865.5	0.074
(Range)	(0-11)	(0-14)		
STAI-S (SD)	23.5 (3.9)	35.4 (12.8)	368.5	**<0.001**
(Range)	(20-34)	(20-73)		
STAI-T	25.4 (6.2)	44.2 (14.6)	232.5	**<0.001**
(Range)	(20-54)	(21-77)		
PSQI Global score mean (SD)	2.2 (1.2)	8.7 (4.6)	150.5	**<0.001**
(Range)	(0-4)	(1-18)		
PSQI > 5 n (%)	0 (0%)	31 (66.0)		
ESS mean (SD)	3.7 (2.5)	6.2 (4.8)	744.0	**0.009**
(Range)	(0-9)	(0-21)		
ESS ≥ 10	0 (0%)	9 (19.1)		
BRIAN mean (SD)	20.4 (3.1)	40.4 (13.5)	133.0	**<0.001**
(Range)	(18-30)	(18-65)		
FAST mean (SD)	4.0 (6.0)	23.7 (17.5)	236.0	**<0.001**
(Range)	(0-22)	(0-72)		
QoL.BD mean (SD)	214.2 (20.6)	156.5 (39.9)	198.0	**<0.001**
Range	(162-263)	(50-235)		

SD = Standard Deviation; HAM-D^{17} = 17 item Hamilton Depression Rating Scale' BDI = Beck Depression Inventory; YMRS = Young Mania Rating Scale; ARMS = Altman Self Rating Mania Scale; STAI- S/T = State and Trait Anxiety Inventory- State/Trait; PSQI = Pittsburgh Sleep Quality Index; ESS = Epworth Sleepiness Scale; BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry; FAST = Functional Assessment Short Test; Qol.BD = Quality of Life in Bipolar Disorder Questionnaire.

BD patients who had a lifetime history of psychosis and suicide attempt are also shown in Figure 3.3.

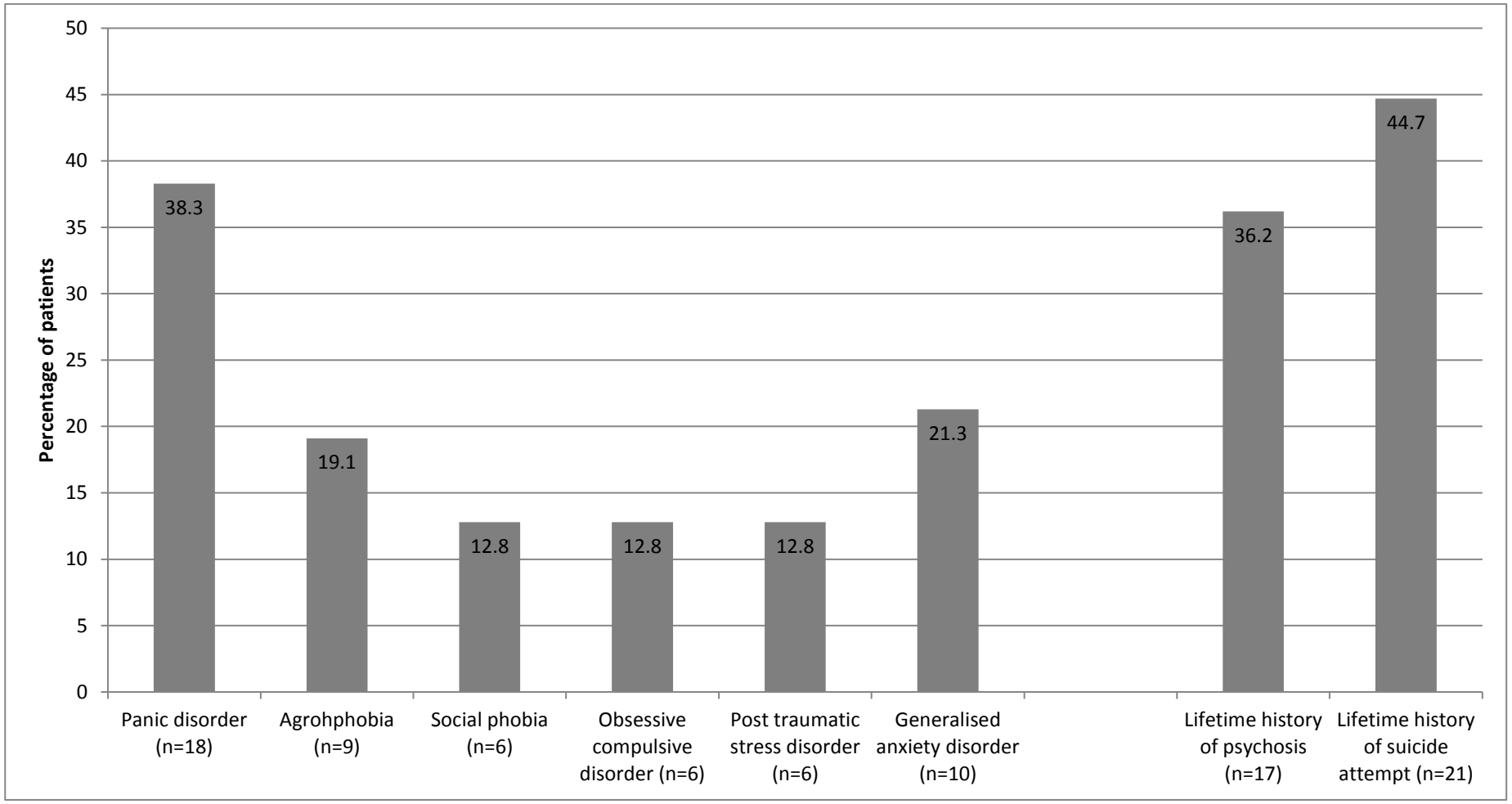


Figure 3.3 Frequency of BD patients with lifetime history or current anxiety disorder and lifetime history of psychosis and suicide attempt.

3.5 Subjective sleep assessments

3.5.1 Pittsburgh Sleep quality index

PSQI score was significantly greater in the total BD group (Table 3-3) and in both euthymic and depressed BD patients (Table 3-4) than controls. In the control group, no participant indicated they had experienced any unexpected sleep loss or changes to their habitual sleep pattern during the sleep assessment period. Mean PSQI scores for controls at the end of the accelerometry assessment period were 2.7 (SD 1.4) (range 0-6). One participant had a PSQI > 5 indicating poor sleep quality (score of 6). This participant had a mean estimated sleep duration of 7 hours per night and an actigraphy estimated mean sleep duration of 7.36 hours per night. Mean PSQI scores were in the clinically significant range for poor sleep quality (PSQI > 5) in the euthymic and depressed BD patients and were significantly greater in depressed than euthymic BD patients. A greater proportion of depressed BD patients 19/23 (82.6%) scored > 5 on the PSQI compared to 12/24 (50%) of euthymic patients ($X^2_{(df)}$ 5.562 $_{(1)}$; p=0.018). There were significant Spearman's correlations between PSQI total score and BDI, STAI-T, ESS, BRIAN, FAST and QoL in the BD group (Table 3-5).

3.5.2 Epworth Sleepiness Scale

BD patients scored significantly more highly on the ESS than controls but the mean score of 6.2 (SD 4.8) was in the clinically normal range (<10). Nine of the BD patients (19.1%) had an ESS score of $\geq$ 10 (range 10-21) indicating excessive daytime sleepiness. There was a relationship between having an ESS $\geq$ 10 and AHI score as there was a weak Spearman's correlation between ESS and AHI (Table 3-5) and having an AHI > 5 was significantly more common in those with

Table 3-4 Participant characteristics in euthymic and depressed BD patients

				Test statistics control vs. euthymic BD			Test statistics euthymic vs. depressed BD			Test statistics control vs. depressed BD		
	Control (n=46)	**Euthymic BD (n=24)**	**Depressed BD (n=23)**	**t (df)**	**U**	**p**	**t (df)**	**U**	**p**	**t (df)**	**U**	**p**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**									
Age, years	42.2 (11.4)	47.1 (11.4)	45.8 (11.1)		399.0	0.075		246.0	0.523		426.	0.235
BMI (kg/m²)	25.8 (4.7)	29.8 (7.1)	30.0 (6.3)	-2.812 (66)		**0.006**	0.128 (45)		**0.899**	-2.598 (65)		**0.004**
BDI	0.6 (1.4)	3.7 (2.3)	21.8 (10.4)		130.0	**<0.001**	10.075 (45)		**<0.001**		0.0	**<0.001**
STAI-T	23.2 (3.6)	28.4 (7.0)	53.5 (13.7)		155.0	**<0.001**	5.478 (45)		**<0.001**		43.5	**<0.001**
PSQI	2.2 (1.1)	6.4 (3.7)	11.0 (4.3)		141.0	**<0.001**	3.967 (45)		**<0.001**		5.0	**<0.001**
ESS	3.6 (2.5)	5.5 (4.4)	6.7 (5.2)		391.0	0.059	0.625 (45)		0.529		323.	**0.011**
BRIAN	20.3 (3.1)	31.2 (9.1)	50.0 (10.4)		125.0	**<0.001**	6.620 (45)		**<0.001**		3.5	**<0.001**
FAST	4.0 (6.0)	12.4 (9.4)	35.6 (16.2)		208.5	**<0.001**	5.852 (45)		**<0.001**		27.5	**<0.001**
QoL.BD	214.9 (20.2)	184.5 (19.9)	127.3 (34.1)		164.5	**<0.001**	-7.051 (45)		**<0.001**		19.5	**<0.001**

Euthymic BD defined as a BDI score $\leq$ 8 and YMRS score $\leq$ 11; Depressed BD defined as BDI score $\geq$ 9; BMI = body mass index, BDI = Beck Depression Inventory, STAI-T = State and Trait Anxiety Inventory – Trait, PSQI = Pittsburgh Sleep Quality Index, ESS = Epworth Sleepiness Scale, BRIAN = Biological Rhythm Interview of Assessment in Neuropsychiatry, FAST = Function Assessment Short Test, QoL.BD = Quality of life in Bipolar Disorder.

Table 3-5 Spearman's correlations Age, BMI, AHI, NART, mood, anxiety subjective sleep, biological rhythm, function and QoL in BD patients

			BMI	AHI	NART	BDI	STAI-T	PSQI	ESS	BRIAN	FAST	QoL.BD
Age	r_s	1.0	-0.146	0.299	0.112	-0.128	-0.140	-0.100	0.329	-0.271	0.014	0.052
	p	-	0.329	0.055	0.454	0.391	0.349	0.506	0.024	0.065	0.924	0.731
BMI	r_s		1.0	0.330	-0.179	0.088	0.142	0.122	0.039	0.196	0.115	-0.181
	p		-	0.033	0.228	0.555	0.341	0.412	0.792	0.186	0.440	0.224
AHI	r_s			1.0	0.148	0.178	0.119	0.158	0.341	0.287	0.193	0.222
	p			-	0.391	0.259	0.452	0.318	0.027	0.066	0.222	0.158
NART-IQ	r_s				1.0	0.187	-0.284	-0.264	0.172	-0.074	-0.306	0.225
	p				-	0.208	0.053	0.072	0.249	0.620	0.036	0.128
BDI	r_s					1.0	0.787	0.605	0.195	0.769	0.730	-0.878
	p					-	<0.001	0.001	0.188	<0.001	<0.001	<0.001
STAI-T	r_s						1.0	0.414	0.264	0.720	0.622	-0.785
	p						-	0.004	0.073	<0.001	<0.001	<0.001
PSQI	r_s							1.0	0.294	0.618	0.586	-0.606
	p							-	0.045	<0.001	<0.001	<0.001
ESS	r_s								1.0	0.309	0.169	-0.171
	p								-	0.035	0.257	0.250
BRIAN	r_s									1.0	0.751	0.783
	p									-	<0.001	<0.001
FAST	r_s										1.0	0.823
	p										-	<0.001
QoL.BD	r_s											1.0
	p											-

n = 47. Significant correlations highlighted from very strong too weak with decreasing shading intensity. Very strong correlations 0.80-1.0, strong 0.60-0.79, moderate 0.40-0.59, weak 0.20-0.39.

an ESS > 10 than in patients with an ESS <10 (75.0% vs. 17.6%, Fisher's exact test p=0.004).

3.5.3 Subjective complaints of insomnia

BD patients scoring > 3 on the HAMD[17] total sleep items with at least one item scoring 2 (indicating persistent mild or marked or frequent marked insomnia symptoms), were deemed to have clinically significant subjective insomnia. Using these criteria 16/47 (34%) BD patients had subjective complaints of insomnia. Fewer euthymic (20.8%) than depressed (47.8%) BD patients had clinically significant insomnia symptoms but the difference just failed to reach statistical significance ($X^2_{(df)}$ $3.811_{(1)}$; p=0.051). There was a strong correlation between the HAMD sleep score and PSQI total score, $r_{(s)(46)} = 0.640$, p<0.001 indicating consistency between subjectively rated sleep disturbances.

3.6 Biological rhythm

BD patients scored significantly more highly on the BRIAN (Table 3-3) including on all the individual domains of the BRIAN; sleep, activity, social and eating pattern (all p=<0.001) indicating a significantly impaired biological rhythm compared to controls. BRIAN score was significantly greater in euthymic and depressed BD patients than controls but was greater in depressed than euthymic BD patients (Table 3-4). In the BD group BRIAN total score had significant correlations with STAI-T, PSQI, FAST and Qol.BD (Table 3-5).

3.7 Psychosocial Function

BD patients had significantly greater scores than controls on the FAST total score indicating impaired psychosocial function (Table 3-3). Function was significantly worse in BD patients across all the domains assessed by the FAST;

autonomy, occupational function, cognitive function, interpersonal relationships, leisure time (all $p<0.001$) and financial issues ($p=0.014$). Function was significantly worse in euthymic and depressed BD patients than controls and worse in depressed than euthymic BD patients (Table 3-4). In the BD group FAST had significant correlations with BDI, STAI-T, PSQI, BRIAN and QoL.BD (Table 3-5).

3.8 Quality of life

BD patients scored significantly lower than controls on the QoL.BD indicating they experienced a significantly lower QoL (Table 3-3). QoL was rated significantly lower by BD patients across all the domains measured by the QoL.BD; physical, sleep, mood, cognition, leisure, social, spirituality, household, self-esteem, independence, identity ($p<0.001$ for all) and finance ($p=0.04$). QoL was significantly lower in euthymic and depressed BD patients than controls and lower in depressed than euthymic patients (Table 3-4). In the BD group QoL.BD had significant Spearman's correlations with BDI, STAI-T, PSQI, BRIAN and FAST (Table 3-5).

3.9 Multiple stepwise hierarchical regression analysis to predict function and QoL.

Multiple stepwise hierarchical regression analysis was performed to see how BDI, PSQI, STAI-T and BRIAN predicted psychosocial function (FAST total score). Scatter plots were first drawn which confirmed a strong linear relationship between the variables with no significant outliers identified. As the primary objective of this study was to investigate the association of sleep and circadian rhythms on cognitive function firstly only PSQI and BRIAN were

entered into the model. The model was a significant predictor of function, $F_{(2,44)}$ = 35.140, p<0.001, r^2 = .615 with both variables contributing significantly to the model. BRIAN accounted for a greater part of the variance in function when added first into the model (BRIAN F change $_{(1,45)}$ = 53.972, p<0.001, r^2 = .545, PSQI F change $_{(1,44)}$ = 7.960, p=0.007, r^2 change = 0.070). When BDI score was added into the model BRIAN became an insignificant predictor of function and the addition of STAI-T to the model did not significantly improve the prediction of function and therefore both STAI-T and BRIAN were dropped. The final model therefore only included BDI and PSQI as significant predictors of function $F_{(2,44)}$ = 53.117, p<0.001, r^2 = .707 (Table 3-6). PSQI score predicted a further 5.3% of FAST score after accounting for the effect of BDI demonstrating subjective sleep quality influenced psychosocial function independently of depression.

Table 3-6 Hierarchical multiple regression model using BDI, PSQI, BRIAN and STAI-T to predict function (FAST total score) in BD patients

Variable	B	t	sr^2	R	R^2	ΔR^2
Step 1				0.809	0.654	0.654
BDI total score	0.809	9.224**	0.654			
Step 2				0.841	0.707	0.053
BDI total score	0.643	6.396**	0.272			
PSQI total score	0.284	2.824*	0.053			

*p=0.007, **p<0.001. BRIAN and STAI-T were dropped from the model.

A similar process was followed to see how PSQI, BRIAN, BDI, STAI-T and FAST were able to predict QoL.BD. Initially only BRIAN and PSQI were entered into the model and these two variables significantly predicted QoL, $F_{(2,44)}$ =48.726, p<0.001, r^2 = 0.689. BDI was added as a third variable and significantly improved the model, $F_{(3,43)}$ = 89.692, p<0.001, r^2 = 0.862 with all 3 variables remaining significant independent predictors of QoL.BD. When STAI-T was entered it did

not significantly improve the model so was dropped. Finally, FAST was entered into the model resulting in a significant improvement but also resulted in both BRIAN and PSQI no longer being independent significant predictors of QoL.BD. When either BRIAN or PSQI were dropped from the model the other variable became a significant predictor in the model. The best final model that predicted the greatest variance in QoL included BDI, FAST and PSQI, $F_{(3,43)} = 99.586$, $p<0.001$, $r^2 = 0.874$ (Table 3-7) demonstrating that subjective sleep quality independently predicted QoL after accounting for depressive mood and function.

Table 3-7 Hierarchical multiple regression analysis using BDI, STAI-T, FAST, PSQI and BRIAN to predict QoL in BD patients

Variable	B	t	sr^2	R	R^2	ΔR^2
Step 1				0.898	0.807	0.807
BDI	-0.898	-13.702***	0.807			
Step 2				0.928	0.861	0.054
BDI	-0.579	-6.049***	0.116			
FAST total score	-0.395	-4.122***	0.054			
Step 3				0.935	0.874	0.014
BDI	-0.556	-6.006**	0.106			
FAST total score	-0.310	-3.101**	0.028			
PSQI total score	-0.157	-2.161*	0.014			

*p<0.05, **p<0.01, ***p<0.001. BRIAN and STAI-T were dropped from the model.

3.10 Summary of subjective sleep, biological rhythm function and QoL

- Euthymic and depressed BD patients reported worse subjective sleep quality than controls but sleep quality was worst in depressed BD patients.
- Approximately one third of the BD patients reported significant symptoms of insomnia but insomnia symptoms were more common in depressed than euthymic BD patients.

- BD patients had a higher incidence of OSA (AHI $\geq$ 5) than controls and an OSA diagnosis was associated with a greater incidence of significant daytime sleepiness (ESS $\geq$ 10).
- Euthymic and depressed BD patients reported a significant disturbance in biological rhythm (BRIAN) compared to controls. Depressed BD patients had a greater disruption of biological rhythm compared to euthymic BD patients even after controlling for the effects of mood.
- Euthymic and depressed BD patients reported a lower level of psychosocial function (FAST) compared to controls. Depressed BD patients had lower function than euthymic BD patients.
- Euthymic and depressed BD patients reported a lower QoL than controls. Depressed BD patients had a lower QoL than euthymic BD patients.
- In BD patients BDI and PSQI scores were independent predictors of function together predicting 70.7% of the variance in function. BDI, FAST and PSQI were independent predictors of QoL together predicting 87.4% of the variance in QoL.

3.11 Objectively assessed sleep and physical activity variables

Compliance with accelerometry was very good with 42 controls and 46 BD patients providing adequate data. The mean number of nights of accelerometry data collected was 20.1 (SD 2.0) for controls (range 10 – 21) and 19.2 (SD 3.6) for the BD group (range 5 – 21) which were not significantly different (U = 790.0, p=0.093). Although 5 days of accelerometery may not be reflective of longer term sleep characteristics the BD participant who provided only 5 days of accelerometry subjectively rated their sleep as good with a normal pattern which was confirmed by the 5 days of accelerometry. They also provided a detailed sleep

diary for 21 days which confirmed a normal sleep wake cycle and so their data was deemed acceptable to include in the analysis of accelerometry variables.

3.11.1 Summary accelerometry sleep variables

Summary accelerometry sleep data comparing controls and BD patients can be found in Table 3-8.

Table 3-8 Summary accelerometry variables in BD patients and controls

			Test Statistic		
All data are means and standard deviations (SD).	**Controls (n=42)**	**Bipolar Disorder (n=46)**	**t-test (df)**	**Mann Whitney U**	**p**
TIB (hours) (range)	7.85 (0.77) (5.54 - 9.21)	8.69 (1.48) (4.48 – 13.04)	-2.973 (86)		**0.004**
IV- TIB (hours)	1.19 (0.44)	1.72 (0.98)		618.0	**0.004**
Nocturnal sleep time (hours) (range)	6.92 (0.70) (4.6 – 8.69)	7.33 (1.20) (3.6 – 9.77)		664.000	**0.012**
IV - nocturnal sleep time (hours)	1.01 (0.35)	1.40 (0.63)	-3.386 (86)		**0.001**
Sleep efficiency (range)	0.88 (0.04) (0.76 – 0.94)	0.85 (0.08) (0.52 – 0.93)		707.000	**0.030**
IV-sleep efficiency	0.05 (0.02)	0.07 (0.04)	-2.960 (86)		**0.004**
SIBD (hours) (range)	1.47 (0.86) (0.32 – 4.88)	1.95 (1.05) (0.36 – 4.33)	-2.246 (86)		**0.027**
IV-SIBD (hours)	0.86 (0.36)	1.10 (0.52)	-2.336 (86)		**0.022**
IV-sleep onset time (hours)	0.99 (0.53)	1.42 (1.27)		730.000	0.056
IV-sleep offset time (hours)	1.29 (1.36)	2.24 (2.55)		694.000	**0.023**

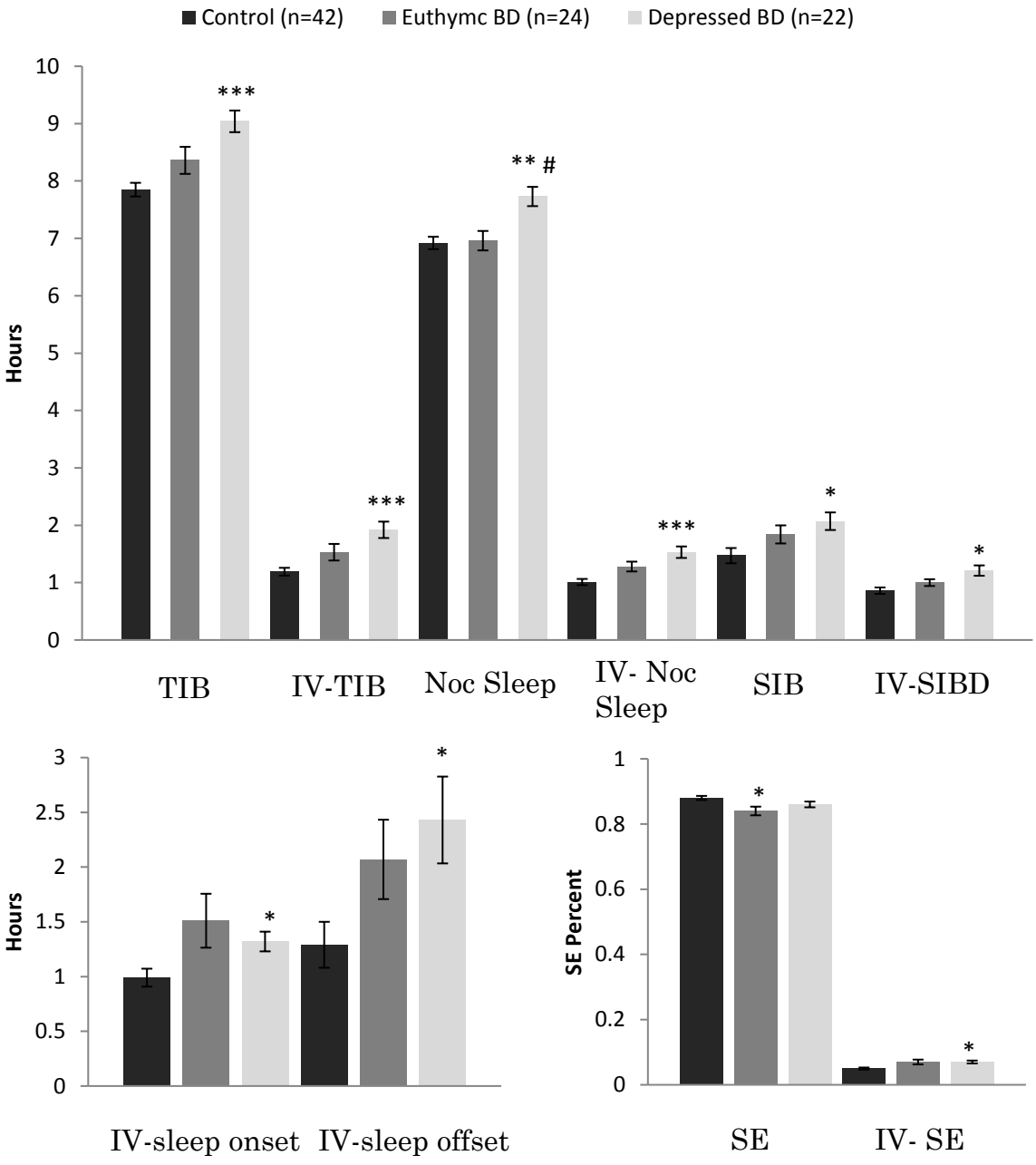
TIB = time in bed, IV = Intra subject variability, SIBD = sustained inactivity bouts during the day and is the sum of all time epochs that meet the algorithm defined sleep criteria but are outside of the nocturnal time window defined by the sleep diary. Intra-subject variability in sleep variables was defined by the between night standard deviation over the assessment period for each subject.

Mean TIB was 50 minutes longer, nocturnal sleep time 25 minutes longer and the night to night variability in these variables, IV-TIB and IV-nocturnal sleep, significantly greater in BD patients than controls. SE was significantly lower and IV-SE significantly greater in the BD group. BD patients spent a greater number of mean hours per day in SIBD (1 hour 57 minutes) compared to controls (1 hour 28 minutes). IV-SIBD was also greater in the BD group. BD patients demonstrated greater variability in the timing of their sleep periods as they had greater IV-sleep onset and IV-wake times than controls. In order to compare the

Table 3-9 Actigraphy estimated variables in controls and BD patients by remission status

				Test statistics control vs. euthymic BD			Test statistics euthymic BD vs. depressed BD			Test statistics controls vs depressed BD		
Actigraphy variables	**Control (n=42)**	**Euthymic BD (n=24)**	**Depressed BD (n=22)**	**t (df)**	**Mann Whitey U**	**p**	**t (df)**	**Mann Whitey U**	**p**	**t (df)**	**Mann Whitey U**	**p**
TIB (hours) (range)	7.85 (0.77) (5.54 - 9.21)	8.36 (1.60) (4.48 - 13.04)	9.04 (1.28) (7.21 -11.77)	-1.121 (64)		0.271	1.596 (44)		0.118	-4.062 (62)		**<0.001**
IV-TIB (hours)	1.19 (0.44)	1.53 (0.98)	1.92 (0.97)		406.0	0.191	1.707 (44)		0.095		183.0	**<0.001**
Nocturnal sleep, hours (range)	6.92 (0.70) (4.6 – 8.69)	6.96 (1.15) (3.60 - 8.62)	7.73 (1.14) (5.64 - 9.77)		429.0	0.317	2.298 (44)		**0.026**		235.0	**0.001**
IV-Nocturnal sleep, hours	1.01 (0.35)	1.28 (0.58)	1.53 (0.68)	-1.837 (64)		0.074	1.521 (44)		0.135	-3.957 (62)		**<0.001**
SE (range)	0.88 (0.04) (0.76 – 0.94)	0.84 (0.09) (0.52 - 0.92)	0.86 (0.06) (0.52 - 0.93)		344.0	**0.033**		240.0	0.598		363.0	0.132
IV-SE	0.05 (0.02)	0.07 (0.05)	0.07 (0.03)	-1.769 (64)		0.086	0.745 (44)		0.460	-3.276 (62)		**0.002**
SIBD, hours (range)	1.47 (0.86) (0.32 – 4.88)	1.84 (1.07) (0.36 - 4.33)	2.07 (1.04) (0.36 - 4.33)	-1.345 (64)		0.183	0.894 (44)		0.376	-2.455 (62)		**0.017**
IV-SIBD	0.86 (0.36)	1.00 (0.40)	1.21 (0.61)	-1.311 (64)		0.194	1.169 (44)		0.249	-2.596 (62)		**0.012**
IV-sleep onset time, hours	0.99 (0.53)	1.51 (1.67)	1.32 (0.61)		425.0	0.292		223.0	0.367		312.0	**0.034**
IV-sleep offset time, hours	1.29 (1.36)	2.07 (2.46)	2.43 (2.69)		407.0	0.196		217.0	0.301		287.0	**0.013**
24 hour acceleration (milli-g)	30.9 (9.1)	24.3 (7.2)	23.2 (5.8)	3.229 (64)		**0.002**	-0.402 (44)		0.690	3.735 (62)		**<0.001**
M10 acceleration (milli-g)	47.7 (14.8)	38.7 (12.9)	36.9 (10.1)	2.639 (64)		**0.010**	-0.523 (44)		0.603	3.092 (62)		**0.003**
L5 acceleration (milli-g)	6.0 (2.8)	5.8 (2.0)	6.0 (1.9)		495.0	0.905	0.529 (44)		0.599		410.0	0.462
Relative amplitude	0.77 (0.10)	0.72 (0.14)	0.70 (0.12)		398.0	0.158		232.0	0.482		300.0	**0.022**
MVPA_E5S_T100 (milli-g)	117.1 (45.3)	79.9 (41.2)	81.1 (31.9)	3.316 (64)		**0.002**	0.109 (44)		0.913	3.319 (62)		**0.002**

TIB = time in bed, IV= intra individual variability, SE = sleep efficiency, SIBD = sustained inactivity behaviour daytime, M10 = most active 10 hours, L5 = least active 5 hours, MVPA = moderate and vigorous physical activity.



*p<0.05 vs. controls **p<0.01 vs. controls, ***p<0.001 vs. controls
# p<0.05 vs. euthymic BD

Figure 3.4 Accelerometry estimated sleep variables in controls and depressed and euthymic BD patients

data with other accelerometry studies which examined euthymic BD patients the comparisons were repeated for euthymic and depressed BD patients (Table 3-9 and Figure 3.4). Euthymic BD patients only differed significantly from controls in SE whereas depressed patients differed significantly from controls on every accelerometry measure except SE. Depressed patients also had significantly longer nocturnal sleep duration than euthymic BD patients, but no other sleep variables differed significantly between BD groups.

Correlation analysis was performed to examine the relationship between sleep log and accelerometry estimated markers of circadian phase (sleep onset, M10 hour and L5 hour) and chronotype assessed with the M/E questionnaire. The analysis found strong to moderate correlations in controls and moderate correlations in the BD group (Table 3-10).

Table 3-10 Pearson's correlations between circadian phase markers and chronotype in BD patients and controls

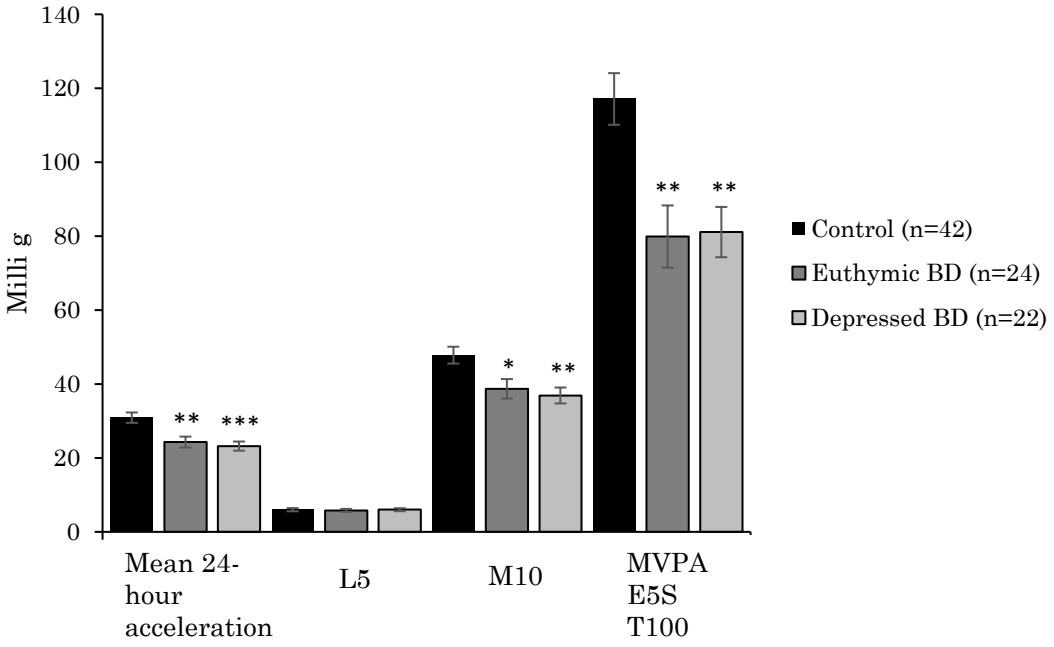
Controls(n=42)		Sleep log onset	Accelerometry onset	M10 onset	L5 onset
M/E Score	r	-0.740	-0.725	-0.561	-0.563
	p	<0.001	<0.001	<0.001	<0.001
BD patients (n=46)					
M/E Score	r	-0.486	-0.399	-0.397	-0.543
	p	0.001	0.006	0.006	<0.001

M/E = Morningness/Eveningness score.

3.11.2 Summary accelerometry physical activity variables

The summary physical activity data can be found in Figure 3.5 and Table 3-9. BD patients performed significantly lower levels of physical activity demonstrated by the lower mean 24 hour acceleration, lower mean acceleration during the most active 10 hour period (M10) and lower levels of MVPA than the control group.

Physical activity was significantly lower in both depressed and euthymic BD patients than controls but the BD groups did not differ significantly from each other (Table 3-9). It is possible that the reduced physical activity is a driver of poor sleep in the BD group. There were no differences between BD and control groups in the mean acceleration in the least active 5-hour period of each 24-hour time period (L5). The RA between L5 and M10 was significantly lower in the BD group but was only significantly lower in depressed BD patients than controls (Figure 3.6).



*p=0.01, **p<0.01, ***p<0.001 controls vs. BD

L5 = mean acceleration in the least active 5 hour period, M10 = mean acceleration in the most active 10 hour period, MVPA E5S T100 = moderate and vigorous activity measured in 5 second epochs at a threshold of 100 milli g. Error bars represent standard error of the mean.

Figure 3.5 Accelerometry estimated physical activity variables in BD patients and controls

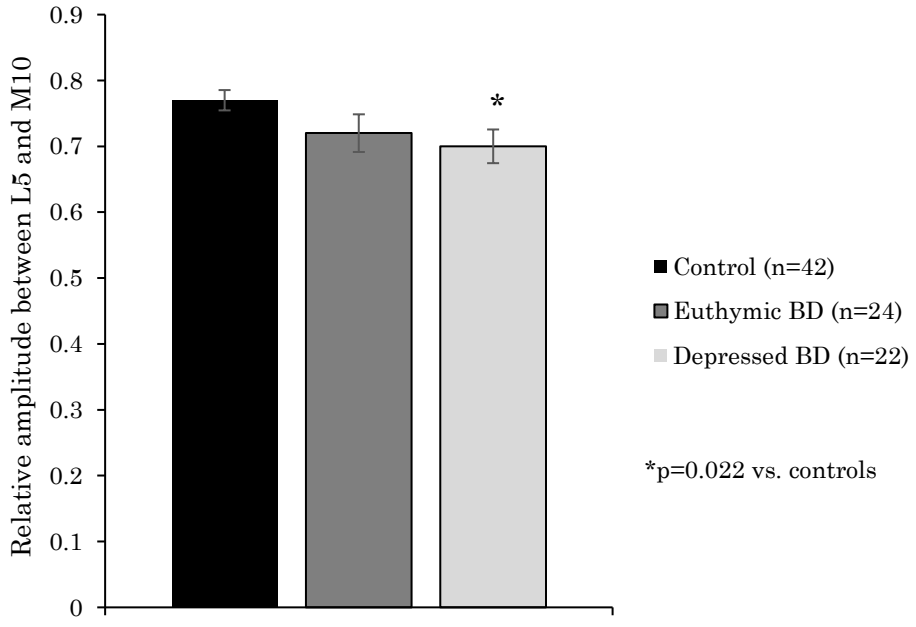


Figure 3.6 Relative amplitude between L5 and M10 in BD patients and controls

3.11.3 Sleep phenotypes

Sleep phenotypes were identified using the accelerometry data and visual actograms as described in the methods. Of the 42 controls with accelerometry data four had an AHI > 5 and 2 did not complete the test for OSA so were not included as normal sleepers, leaving 36 objectively defined normal sleepers. Of the 46 BD patients with accelerometry data 24 (52.2%) had normal actograms and accelerometry variables. Sixteen of these 24 BD patients also had a confirmed AHI < 5 so had no detectable sleep abnormality and met the criteria for objective normal BD sleepers. There were 28 BD patients who met the criteria for abnormal sleepers. Example actograms for a normal, long, short and irregular sleeper are shown in Figure 3.7. The three largest groups of abnormal sleepers in the BD group were long sleepers (n=14, 30.4%) those with a CRD (n=12, 26.1%) and those with OSA (n=12). Of those with a CRD one had advanced sleep wake

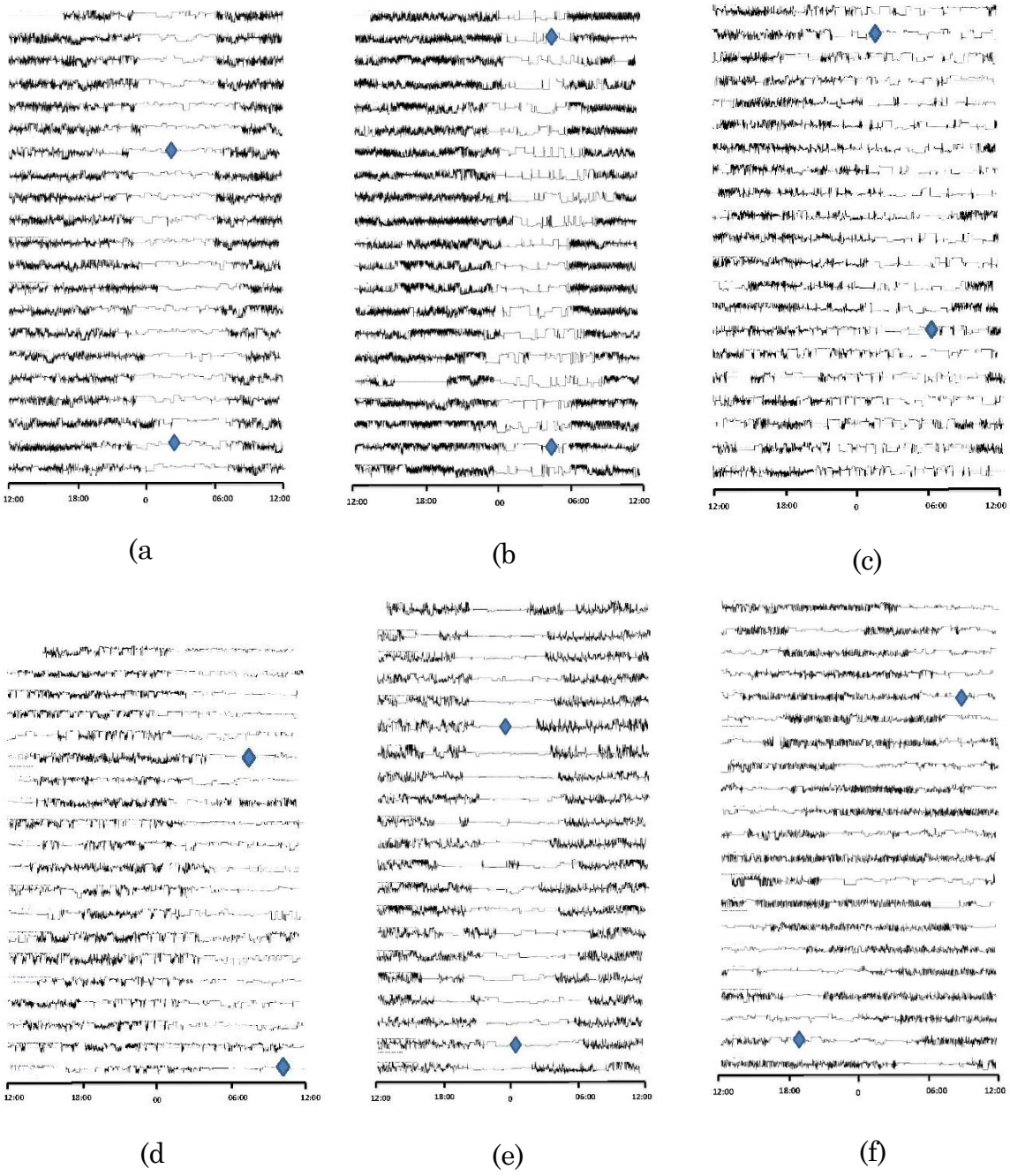
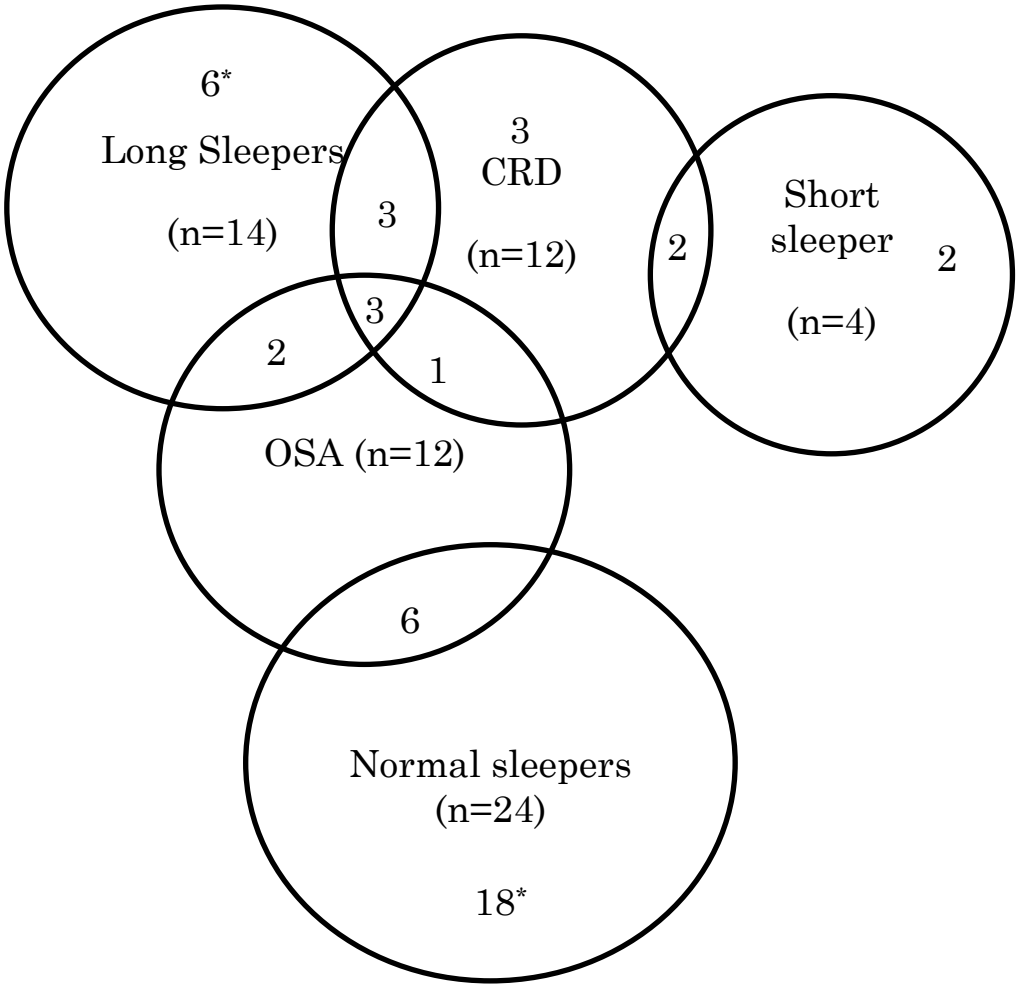


Figure 3.7 Representative 21-day actograms from BD normal and abnormal sleepers

Data are successive days on vertical axis starting at midday. The diamonds represent the timing of the acrophase of aMT6s taken at two different time points over the 21 days of accelerometry. (a) Normal sleeper with a well entrained circadian rhythm, mean nocturnal sleep duration = 6.9 h. (b) Short sleeper with a well entrained circadian rhythm, mean sleep duration = 5.7 h. (c) Long 24-hour sleeper, mean sleep duration = 10.9 h. Note mildly irregular sleep–wake times and aMT6s period length = 24.40 h. (d) Delayed sleep phase with well entrained circadian rhythm, mean sleep onset time = 01:43, mean nocturnal sleep duration = 08.6 h. (e) Advanced sleep phase with well entrained circadian rhythm, mean sleep onset time = 20:25, mean nocturnal sleep duration = 7.23 h. (f) Non-24-h sleep–wake rhythm. Actogram demonstrated an irregular sleep–wake cycle with evidence of free-running sleep onset during the final 8 days. aMT6s period length = 24.4 h.

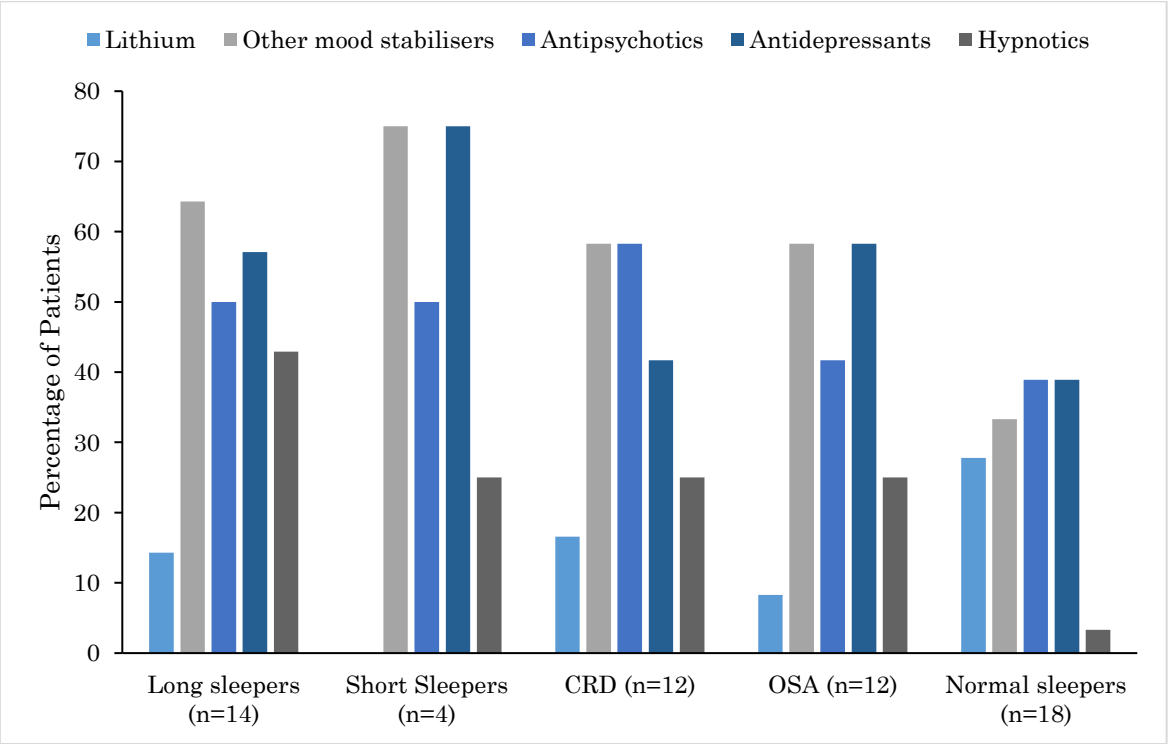
phase, three delayed sleep/wake phase, four non 24-hour sleep wake rhythms, three irregular sleep/wake phase and 1 CRD not otherwise specified. Only four (8.7%) of the BD patients were short sleepers and no BD patients were long nocturnal sleepers. Some BD patients had more than one sleep abnormality as a number of those with short or long sleep also had a CRD or OSA. A Venn diagram showing the overlap of sleep phenotypes and their relationship with OSA (AHI > 5) can be found in Figure 3.8.



Normal sleepers = > 6 & < 10 hours nocturnal sleep and no CRD; Long sleepers = total 24 hour sleep > 10 hours; Short sleepers = nocturnal sleep < 6hours; CRD = circadian rhythm disorder; OSA = obstructive sleep apnoea.

*3 of the participants in the long sleep only cohort and 2 of the normal sleepers did not complete the test for sleep apnoea.

Figure 3.8 Venn diagram showing sleep phenotypes and their overlap in BD patients



CRD = circadian rhythm disturbance, OSA = obstructive sleep apnoea. Other mood stabilisers includes sodium valproate, lamotrigine and gabapentin.

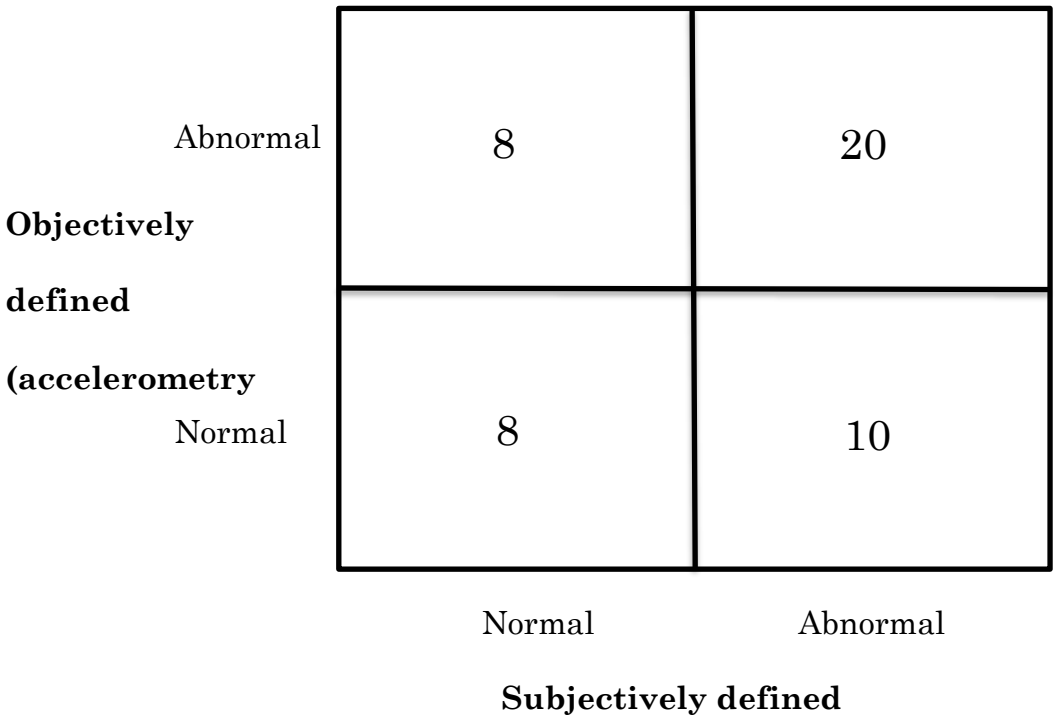
Figure 3.9 Psychotropic medication use in sleep phenotypes

3.11.3.1 Psychotropic medication use and sleep phenotypes

Figure 3.9 shows the percentages of each sleep phenotype prescribed a drug from each of the major psychotropic medication groups. A greater proportion of abnormal sleepers (67.9%) than normal sleepers (33.3%) (Fisher's Exact Test, p=0.034) were prescribed mood stabilisers (sodium valproate, lamotrigine, gabapentin) and there was a trend towards a greater proportion of abnormal sleepers (28.6%) than normal sleepers (5.6%) prescribed hypnotics (Fisher's Exact Test, p=0.069). A greater proportion of long sleepers (42.9%) than non-long sleepers (9.4%) were prescribed hypnotics (Fisher's Exact Test, p=0.015). There were no other significant differences between groups in medication use.

3.11.4 Comparison of subjectively and objectively defined abnormal sleepers

A comparison was made to identify if the same participants were classified as abnormal sleepers by subjective and objective methods. Subjective normal/abnormal sleepers were identified using baseline PSQI > 5 for subjective abnormal sleeper and objective abnormal sleepers were those as previously described using accelerometry variables. As can be seen in Figure 3.10 twenty BD patients with objective abnormal sleep had a PSQI > 5 (abnormal/abnormal) but eight BD patients with objective abnormal sleep subjectively rated their sleep as normal (PSQI < 5). Ten BD patients subjectively rated their sleep as abnormal but objective assessment could find no sleep abnormality and eight BD patients had both objective and subjective normal sleep.



Subjective normal sleepers scored ≤ 5 on the PSQI and subjective abnormal sleepers scored > 5 on the PSQI. Objective normal and abnormal sleepers were defined by accelerometry.

Figure 3.10 Comparison of subjectively and objectively defined normal and abnormal sleep in BD patients

3.12 Comparison of mood, biological rhythm, function and QoL between controls and objectively defined normal and abnormal BD sleepers.

In this section the objectively assessed BD normal and abnormal sleepers and the main individual sleep phenotypes (long, CRD and OSA) will be compared to controls on mood, biological rhythm, function and QoL. Comparisons between subjectively defined normal and abnormal sleepers are also made.

3.12.1 Controls vs. objective normal and abnormal BD sleepers

Comparisons were made on mood, subjective sleep quality, biological rhythm, function and QoL between controls and objective normal and abnormal BD sleepers. In addition to minimise the effects of mood, euthymic abnormal BD sleepers were also compared to controls (Figure 3.11). It should be noted that the mean BDI score for normal sleepers was in the range for remission and that 13/16 (81.3%) normal BD sleepers were in BDI remission at week 3 compared to 11/28 (39.3%) of abnormal sleepers. (Comparisons of all variables can be found in **Error! Reference source not found.**). Normal and abnormal BD sleepers (including euthymic abnormal sleepers) had lower mood, function and QoL, worse subjective sleep quality and greater biological rhythm disturbance than controls all with large effect sizes. The differences were greatest between abnormal BD sleepers and controls with effect sizes approximately double those between normal sleepers and controls. The euthymic abnormal sleeper group was intermediate in effect size between normal and abnormal sleepers. Of note euthymic abnormal BD sleepers also had greater biological rhythm disturbance,

lower function and lower QoL than euthymic normal BD sleepers (Table 3-12) demonstrating that the worse

Table 3-11 Characteristics of controls, normal and abnormal BD sleepers

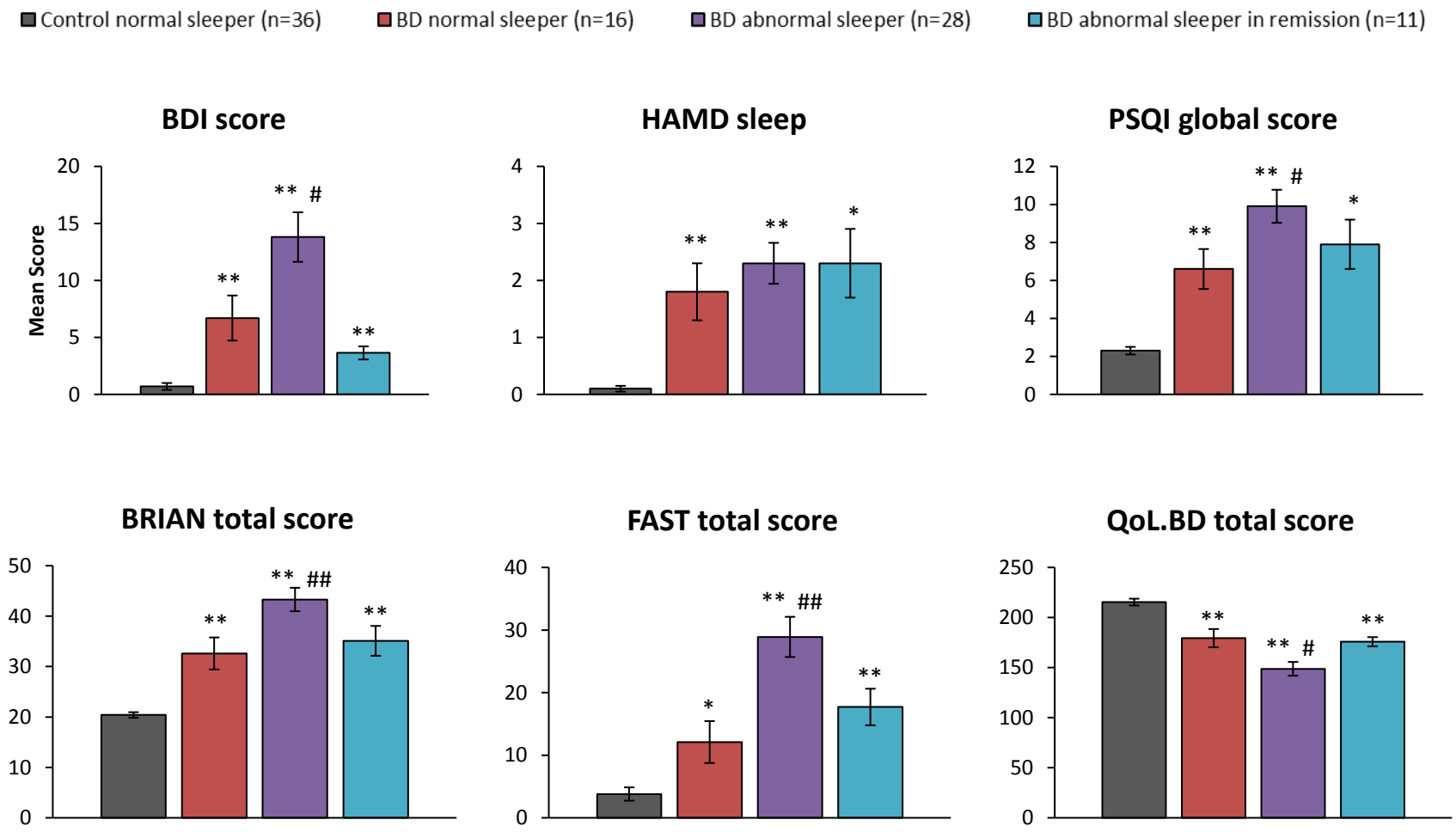
	Control no OSA (n=36)	BD normal sleepers (n=16)	BD abnormal sleepers (n=28)	t (df)	U	p	t (df)	U	p	t (df)	U	P
	Mean (SD)	Mean (SD)	Mean (SD)	Test statistics control vs. BD normal sleepers			Test statistics controls vs. BD abnormal sleepers			Test statistics BD normal vs. abnormal sleepers		
Age, years	42.8 (11.9)	44.1 (10.3)	49.2 (10.8)		276.0	0.812		343.0	**0.029**		155.5	0.094
BD II diagnosis, n (%)	N/A	10 (62.5%)	20 (71.4%)							$X^2 = 0.374$ (1)		0.541
BMI, kg/m2	25.1 (4.4)	28.3 (4.2)	31.0 (7.8)		61.0	**0.016**		255.0	**0.001**	-1.220 (42)		0.229
BDI	0.7 (1.8)	6.7 (7.9)	13.8 (11.5)		72.5	**<0.001**		44.0	**<0.001**	-2.464 (42)		**0.018**
STAI-T	25.5 (6.4)	39.2 (12.9)	45.3 (14.7)		93.5	**<0.001**		92.5	**<0.001**	-1.371 (42)		0.178
HAMD sleep	0.1 (0.3)	1.8 (2.0)	2.3 (1.9)		120.0	**<0.001**		141.0	**<0.001**		186.0	0.342
PSQI	2.3 (1.2)	6.6 (4.2)	9.9 (4.6)		86.0	**<0.001**		39.0	**<0.001**	2.360 (42)		**0.023**
ESS	3.8 (2.4)	5.4 (3.6)	7.1 (5.4)		207.5	0.107		307.0	**0.007**	-0.914 (42)		0.366
BRIAN	20.4 (3.3)	32.7 (12.7)	43.3 (12.3)		84.5	**<0.001**		20.5	**<0.001**	-2.748 (42)		**0.009**
FAST	3.8 (6.4)	12.1 (13.4)	28.9 (17.0)		127.5	**0.001**		49.5	**<0.001**	3.919 (42)		**<0.001**
QoL.BD	215.4 (20.3)	179.4 (36.4)	148.8 (36.4)		100.5	**<0.001**		42.0	**<0.001**	2.691 (42)		**0.010**
Psychosis, n (%)	N/A	7 (43.8%)	8 (28.6%)							$X^2 = 1.044$ (1)		0.307
Suicide attempt (n (%)	N/A	6 (37.5%)	14 (50%)							$X^2 = 0.642$ (1)		0.423

Only actigraphy defined normal sleepers without OSA are included. Two normal sleepers did not complete the test for OSA and are excluded from the normal sleeper group. Abnormal sleepers includes those with normal actigraphy sleep but with confirmed OSA. BMI = body mass index, HAMD-Sleep = Hamilton depression rating scale sleep items, BDI = Beck depression inventory, STAI-T = state and trait anxiety inventory – trait, PSQI = Pittsburgh sleep quality index, ESS = Epworth sleepiness scale, BRIAN = biological rhythm interview in assessment of neuropsychiatry, FAST = function assessment short test, QoL.BD = quality of life bipolar disorder scale, N/A = not applicable.

Table 3-12 Characteristics of objectively defined euthymic normal and abnormal sleepers in the BD group

	Euthymic BD normal sleeper (n=13)	Euthymic BD abnormal sleeper (n=11)	Normal vs. abnormal test statistics		
	Mean (SD)	Mean (SD)	t (df)	Mann Whitney U	p
Age (years)	44.5 (10.5)	50.2 (12.1)		43.0	0.098
BMI (Kg/m²)	27.8 (4.5)	32.2 (8.9)	-1.481 (22)		0.161
HAMD Sleep	1.0 (1.1)	2.3 (2.0)		45.0	0.109
BDI	3.8 (2.7)	3.6 (1.9)		69.0	0.883
STAI-T	34.8 (9.3)	35.9 (8.3)	-0.312 (22)		0.758
PSQI	6.6 (4.2)	7.9 (4.3)	-1.852 (22)		0.082
ESS	5.2 (2.7)	6.8 (5.7)	-1.368 (22)		0.185
BRIAN	27.9 (7.2)	35.1 (9.8)	-2.084 (22)		**0.049**
FAST	7.9 (6.3)	17.7 (9.7)	-2.686 (22)		**0.013**
QoL.BD	191.9 (21.0)	175.8 (15.3)		37.0	**0.045**

Only actigraphy defined normal sleepers without OSA are included. Two normal sleepers did not complete the test for OSA and are excluded from the normal sleeper group. Abnormal sleepers includes those with normal actigraphy sleep but with confirmed OSA. BMI = body mass index, HAMD-Sleep = Hamilton depression rating scale sleep items, BDI = Beck depression inventory, STAI-T = state and trait anxiety inventory – trait, PSQI = Pittsburgh sleep quality index, ESS = Epworth sleepiness scale, BRIAN = biological rhythm interview in assessment of neuropsychiatry, FAST = function assessment short test, QoL.BD = quality of life bipolar disorder scale.



*p<0.01 vs. controls, **p<0.001 vs. controls. # p<0.05 vs. normal BD sleepers, ## p<0.01 vs normal BD sleepers. Error bars represent standard error of the mean.

Figure 3.11 Mood, subjective sleep biological rhythm function and QoL in controls and objectively defined normal and abnormal sleepers

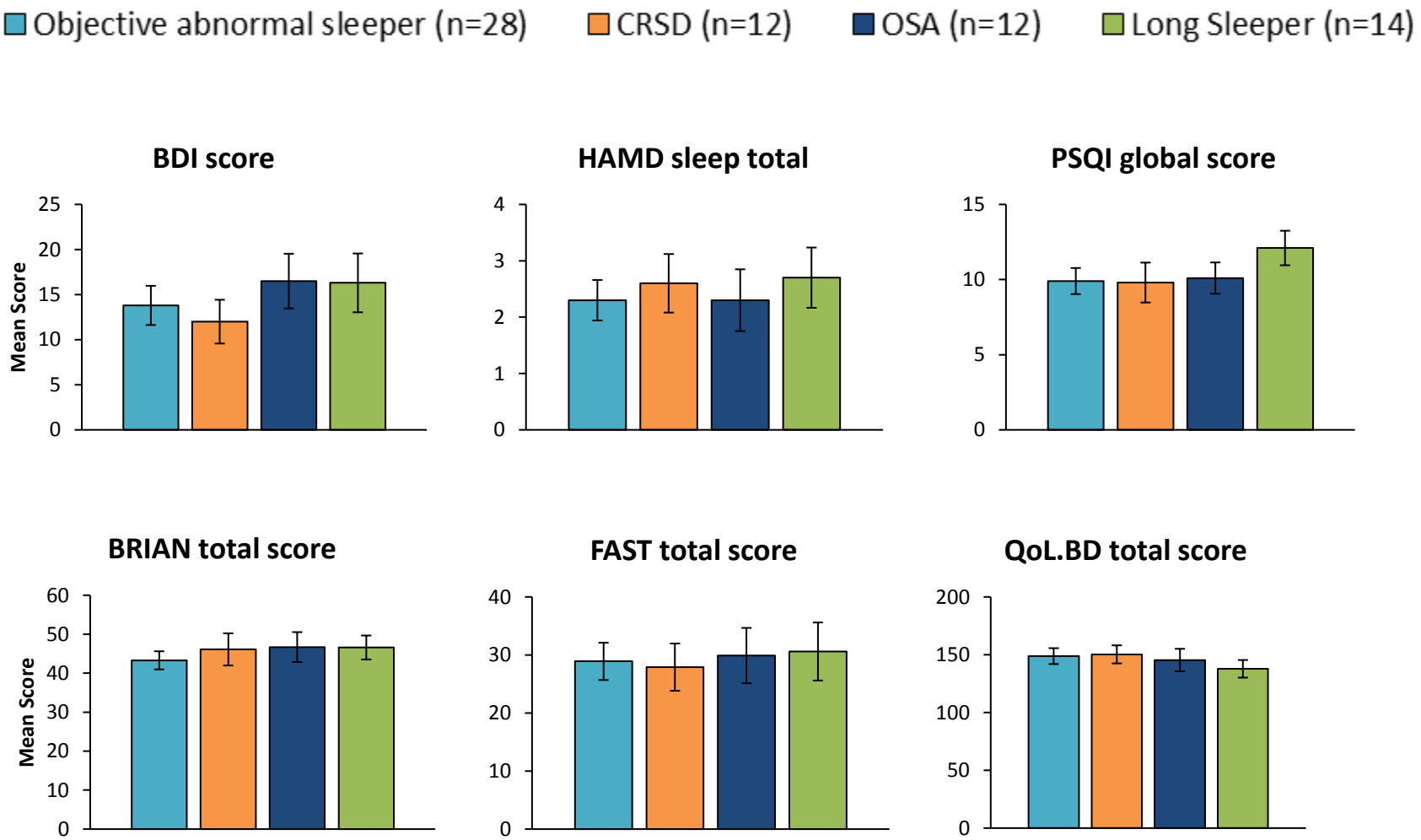
Table 3-13 Effect sizes comparing biological rhythm, function and QOL in controls and objectively defined normal and abnormal BD sleepers

BD sleep group	Hedges g (95% CI)
Biological rhythm (BRIAN) compared to controls (n=36)	
Normal sleepers (n=16)	1.61 (0.94-2.27)
Abnormal sleepers (n=28)	3.10 (2.26-3.94)
Euthymic abnormal sleepers (n=11)	2.65 (1.79-3.51)
Function (FAST) compared to controls (n=36)	
Normal sleepers (n=16)	0.90 (0.29-1.51)
Abnormal sleepers (n=28)	2.30 (1.57-3.04)
Euthymic abnormal sleepers (n=11)	1.88 (1.11-2.66)
QoL (QoL.BD) compared to controls (n=36)	
Normal sleepers (n=16)	-1.35 (-2.0 to -0.71)
Abnormal sleepers (n=28)	-2.50 (-3.27 to -1.74)
Euthymic abnormal sleepers (n=11)	-2.02 (-2.81 to -1.23)

outcomes in abnormal sleepers were independent of mood. There were no differences in the proportions of normal and abnormal sleepers in BD II diagnosis, history of psychosis or history of suicide attempt.

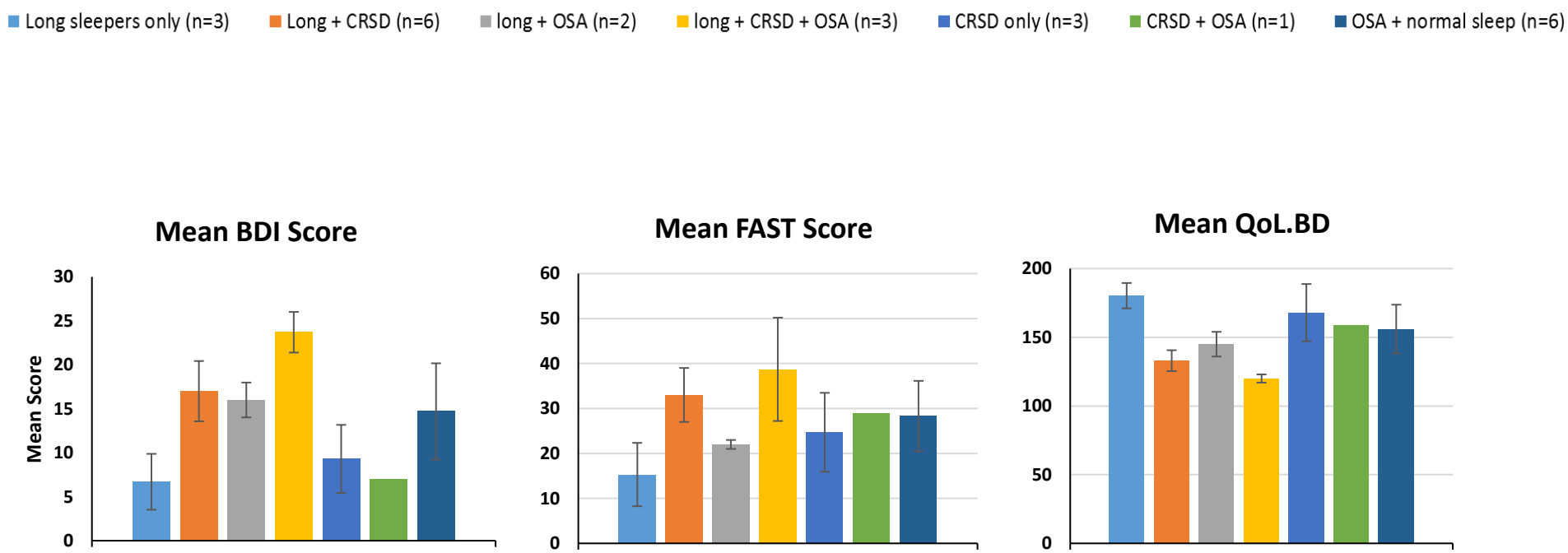
3.12.2 Characteristics of BD abnormal sleep phenotypes

A comparison between the individual sleep phenotypes (CRD, OSA and long sleepers) revealed similar scores on the BDI, HAMD sleep, PSQI, BRIAN, FAST and QoL.BD (Figure 3.12). Comparisons were also made between BD patients with single and multiple sleep abnormalities (Figure 3.13). Statistical comparisons were not made between groups due to the very small sample sizes in each subgroup. The lowest function and QoL was in the group with long sleep, a CRD and OSA suggesting that there may be an additive effect of multiple sleep abnormalities. This conclusion however should be taken very cautiously due to the very small numbers in each subgroup and the fact that BDI score was also greatest in this group. Larger samples will be required to explore this issue further.



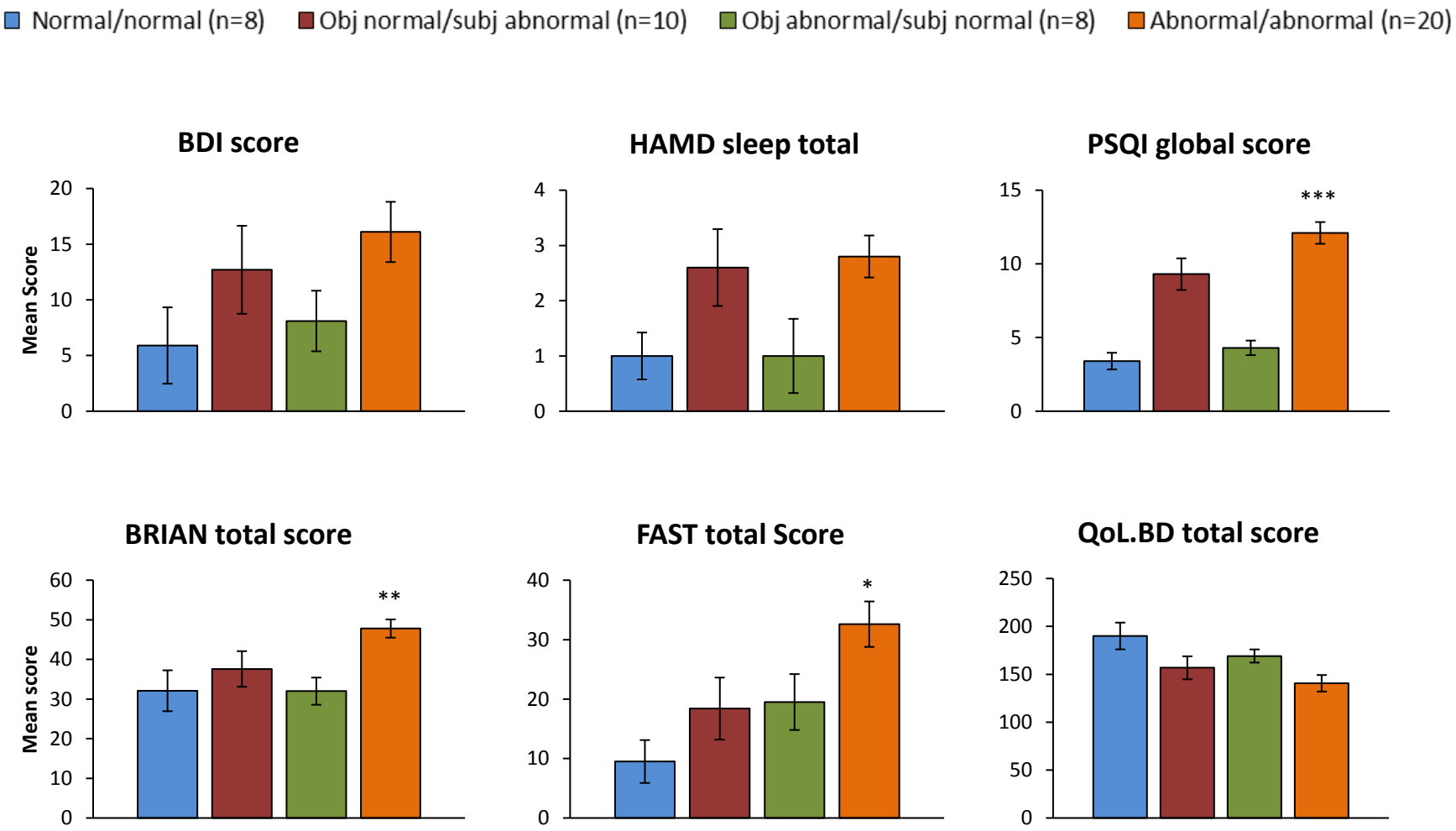
Error bars represent standard error of the mean. No statistical comparisons were made between groups due to small sample sizes.

Figure 3.12 Characteristics of abnormal BD sleepers and individual sleep phenotypes



Error bars represent standard error of the mean. No statistical comparisons are made due to small sample sizes.

Figure 3.13 Mean BDI, FAST and QoL scores in BD patients with multiple sleep abnormalities



Subjective normal = PSQI $\leq$ 5, subjective abnormal = PSQI > 5, objective abnormal defined by accelerometry as described in the methods. *p=0.01 vs. other abnormal/normal groups combined, **p<0.01 vs. other abnormal/normal groups combined, ***p<0.001 vs other abnormal/normal groups combined.

Figure 3.14 Characteristics of subjectively and objectively defined normal and abnormal BD sleepers

Table 3-14 Characteristics of objectively and subjectively defined normal and abnormal sleepers

	Normal normal (n=8)	Obj Normal Subj Abnormal (n=10)	Obj abnormal subj normal (n=8)	Abnormal abnormal (n=20)	Statistical Tests of abnormal/abnormal sleepers vs. other abnormal/normal groups combined.		
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**t (df)**	**Mann Whitney U**	**p**
Age (years)	44.9 (9.3)	41.4 (11.9)	55.4 (6.0)	46.8 (11.4)		164.0	0.640
BMI (Kg/m2)	26.5 (4.7)	29.9 (2.7)	30.2 (4.4)	31.2 (8.9)	-0.114 (36)		0.910
HAMD sleep	1.0 (1.2)	2.6 (2.2)	1.0 (1.9)	2.8 (1.7)		124.0	0.095
BDI	5.9 (9.7)	12.7 (12.5)	8.1 (7.7)	16.1 (12.1)	-1.423 (36)		0.163
STAI-T	36.8 (13.1)	45.7 (14.7)	42.5 (15.1)	46.4 (14.9)	-0.434 (36)		0.667
PSQI	3.4 (1.6)	9.3 (3.4)	4.3 (1.4)	12.1 (3.3)	-4.468 (36)		**<0.001**
ESS	4.0 (3.1)	5.6 (4.1)	5.9 (4.4)	7.6 (5.8)	-0.934 (36)		0.357
BRIAN	32.1 (14.6)	37.6 (14.2)	32.0 (9.7)	47.8 (10.3)	-3.440 (36)		**0.001**
FAST	9.5 (10.2)	18.4 (16.5)	19.5 (13.3)	32.6 (17.1)	-2.731 (36)		**0.010**
QoL.BD	190.0 (39.5)	156.8 (38.0)	169.1 (19.4)	140.6 (38.6)	1.903 (36)		0.065

Objective normal and abnormal sleepers defined by actigraphy as defined in the methods. Subjective normal sleepers = PSQI $\leq$ 5, subjective abnormal sleepers = PSQI > 5.

3.12.3 Comparison of mood function and QoL in objectively and subjectively defined normal and abnormal sleepers.

In order to assess if the association of abnormal sleep with poor function and QoL were driven by actual (objective), or perceived (subjective) abnormalities in sleep, comparisons were made between patients assessed by both objective and subjective methods as described in section 3.11.4. The characteristics of these groups can be found in Figure 3.14 and Table 3-14. Due to small numbers in each group statistical comparisons were only made between the abnormal/abnormal group (n=20) and the two abnormal/normal groups combined (n=18). Numerically the group with the worst scores on each measure were those with both objectively and subjectively defined sleep abnormalities. Compared to those in the groups with either only objectively or subjectively defined sleep abnormalities combined the scores on the PSQI, BRIAN and FAST were all statistically significantly worse. However, BDI scores were also highest in the abnormal/abnormal group so ANCOVA was performed using BDI as a co-variate. The differences between groups in PSQI ($F_{(1,35)} = 17.380$, $p<0.001$), BRIAN ($F_{(1,35)} = 10.254$, $p=0.003$) and FAST ($F_{(1,35)} = 5.284$, $p=0.028$) remained significant.

3.12.4 Comparison of BD sleep phenotypes with and without OSA

As OSA as a sleep disorder has a different aetiology than other sleep abnormalities such as circadian rhythm disturbances or short and long sleep the data was also analysed with respect to the presence of OSA. Table 3-15 shows the clinical characteristics of BD patients with and without OSA. BD patients with OSA had significantly more daytime sleepiness as demonstrated by significantly greater scores on the ESS. Although this would be expected in people with OSA due to the sleep disruption, the mean score of 8.6 in the OSA group is still within

Table 3-15 Clinical characteristics of BD patients with and without OSA

				Test statistics control vs. BD (No OSA)			Test statistics control vs. BD OSA			Test statistics BD OSA vs BD no OSA		
	Control (n=36)	**BD (No OSA) (n=29)**	**BD (OSA) (n=12)**	**t (df)**	**U**	**p**	**t (df)**	**U**	**p**	**t (df)**	**U**	**p**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**									
BD II, n (%)		19 (65.5%)	9 (75.0%)							$X^2 = 0.352$ (1)		0.553
Female, n (%)	25 (69.4%)	19 (65.5%)	10 (83.3%)							$X^2 = 1.301$ (1)		0.254
Age, years	42.8 (11.9)	45.0 (11.1)	51.6 (9.6)		469.0	0.484		121.5	**0.024**		111.0	0.073
BMI, kg/m²	25.1 (4.4)	29.0 (6.0)	32.3 (7.9)		299.0	**0.005**		81.0	**0.002**	-1.464 (39)		0.151
BMI > 30kg/m²	6 (16.7%)	10 (34.5%)	7 (58.3%)							$X^2 = 1.989$ (1)		0.158
BDI	0.5 (1.9)	9.1 (9.5)	12.8 (10.0)		87.7	**<0.001**		10.0	**<0.001**	-1.100 (39)		0.278
STAI-T	26.1 (8.8)	41.0 (13.3)	48.0 (14.5)		160.0	**<0.001**		42.0	**<0.001**	1.487 (39)		0.145
STAI-S	23.5 (4.5)	34.1 (11.6)	37.7 (11.5)		188.0	**<0.001**		44.0	**<0.001**	-0.895		0.376
PSQI	2.8 (1.4)	6.8 (3.7)	8.3 (2.5)		189.5	**<0.001**		16.0	**<0.001**	-1.319 (39)		0.195
ESS	3.6 (2.6)	4.4 (3.4)	8.6 (3.5)		466.5	0.460		54.5	**<0.001**	-3.599 (39)		**0.001**
BRIAN	20.2 (3.5)	33.6 (11.3)	40.9 (12.9)		114.0	**<0.001**		34.0	**<0.001**	-1.827 (39)		0.075
FAST	2.6 (5.5)	15.9 (13.5)	30.2 (14.9)		136.0	**<0.001**		12.0	**<0.001**	-2.995 (39)		**0.005**
QoL.BD	212.2 (20.7)	169.7 (40.7)	143.4 (40.6)		194.0	**<0.001**		28.5	**<0.001**	1.879 (39)		0.068
Psychosis , n (%)		10 (34.5%)	2 (16.7%)							$X^2 = 1.301$ (1)		0.254
Suicide attempt, n (%)		11 (37.9%)	9 (75.0%)							$X^2 = 4.668$ (1)		**0.031**
Any anxiety disorder, n (%)		16 (55.2%)	10 (83.3%)							$X^2 = 2.901$ (1)		0.089

Only actigraphy defined normal sleepers without OSA are included. Two normal sleepers did not complete the test for OSA and are excluded from the normal sleeper group. OSA = obstructive sleep apnoea, BD II = bipolar II disorder, BMI = body mass index, HAMD-Sleep = Hamilton depression rating scale sleep items, BDI = Beck depression inventory, STAI-T = state and trait anxiety inventory – trait, PSQI = Pittsburgh sleep quality index, ESS = Epworth sleepiness scale, BRIAN = biological rhythm interview in assessment of neuropsychiatry, FAST = function assessment short test, QoL.BD = quality of life bipolar disorder scale.

the normal range as it is less than 10. A significantly greater proportion of patients with OSA had a history of suicide attempt than those without OSA. Function was also significantly worse in the OSA group with nearly double the score on the FAST as those without OSA. There were no further differences in any of the clinical characteristics.

Table 3-16 shows the clinical characteristics of abnormal BD sleepers with and without OSA. There was a trend to a greater proportion of BD abnormal sleepers with OSA having a history of suicide attempt (p=0.066). Epworth sleepiness scores were significantly greater in the OSA group but was still within in the normal range (<10).

Table 3-16 Characteristics of abnormal BD sleepers with and without OSA

			Test statistics BD OSA vs BD no OSA		
	Abnormal Sleepers (No OSA) (n=13)	**Abnormal sleepers (with OSA) (N=12)**	**t (df)**	**U**	**p**
	Mean (SD)	**Mean (SD)**			
BD II, n (%)	9 (69.2%)	9 (75%)	$X^2 = 0.103$		0.748
Female, n (%)	7 (53.8%)	10 (83.3%)	$X^2 = 2.493$		0.114
Age, years	46.2 (12.5)	51.6 (9.6)		56.5	0.242
BMI, kg/m²	29.9 (7.8)	32.3 (7.9)	-0.768 (23)		0.450
BMI > 30kg/m²	4 (30.8%)	7 (58.3)	$X^2 = 2.493$		0.165
BDI	15.1 (10.6)	16.5 (10.5)	0.564 (23)		0.579
STAI-T	50.2 (10.6)	46.8 (14.6)	0.441 (23)		0.663
PSQI	8.5 (3.4)	10.1 (3.6)	0.171 (23)		0.866
ESS	3.6 (2.9)	8.9 (3.7)	-3.858 (23)		**0.001**
BRIAN	40.4 (9.1)	46.7 (13.3)	-0.120 (23)		0.906
FAST	23.2 (11.3)	29.9 (16.5)	-1.334 (23)		0.195
QoL.BD	145.9 (33.8)	145.4 (33.7)	0.168 (23)		0.868
Psychosis , n (%)	3 (23.1%)	2 (16.7%)	$X^2 = 0.160$		0.689
Suicide attempt, n (%)	5 (38.5%)	9 (75%)	$X^2 = 3.381$		0.066

Three BD patients who did not complete the test for OSA are excluded. OSA = obstructive sleep apnoea, BD II = bipolar II disorder, BMI = body mass index, HAMD-Sleep = Hamilton depression rating scale sleep items, BDI = Beck depression inventory, STAI-T = state and trait anxiety inventory – trait, PSQI = Pittsburgh sleep quality index, ESS = Epworth sleepiness scale, BRIAN = biological rhythm interview in assessment of neuropsychiatry, FAST = function assessment short test, QoL.BD = quality of life bipolar disorder scale.

3.12.5 Summary

In summary the following conclusions can be drawn from the sleep assessments.

- BD patients had a longer duration of TIB, nocturnal sleep, SIBD and lower SE than controls as estimated by accelerometry. These differences were primarily driven by the depressed BD patients with only SE being significantly worse in euthymic BD patients than controls.
- BD patients had more variable sleep than controls but this was only the case in depressed BD patients with euthymic patients not differing from controls.
- BD patients, both depressed and euthymic had lower levels of physical activity than controls.
- Evidence of mild OSA, long 24-hour sleep/sedentary behaviour and evidence of CRD was common in the BD patients. There was significant overlap between these sleep abnormalities.
- There was disagreement between objectively and subjectively defined abnormal sleep in approximately 40% of BD patients.
- Objectively defined BD normal and abnormal sleepers including euthymic abnormal sleepers had lower mood, more subjective sleep disturbance, greater biological rhythm disturbance and lower function and QoL than controls with a large effect size. Euthymic abnormal BD sleepers had greater biological rhythm disturbance and lower function and QoL than euthymic normal BD sleepers.

3.13 Cognitive function in controls and BD patients and its association with sleep abnormalities

Only participants with accelerometry data allowing objective assessment of sleep phenotypes were included in the analysis of cognitive function. Two BD participants did not complete the full battery of cognitive tests, one who became

anxious and asked to stop and the other for undisclosed reasons. One aged 55 years, was a normal sleeper and had a BDI score of 8. The other aged 25 years, was a normal sleeper with a BDI of 28. Their data will be included for the tests they completed.

3.13.1 Performance on the Attention Network Task

The ANT was completed by 35 controls and 44 BD patients. One control was omitted from the analysis as their mean RT and conflict RT were more than 3 times the interquartile range and they were considered an extreme outlier. Mean RT was significantly longer in the total BD group than controls but subgroup analysis found this was only the case in objective abnormal BD sleepers, including those in euthymia (Table 3-17). Euthymic abnormal BD sleepers also had significantly longer mean ANT RT than euthymic normal BD sleepers with a large effect size.

Mean RT's for the alerting, orienting and conflict components and effect sizes between groups can be found in Table 3-18 and mean RT for the conflict component in Figure 3.15. The data demonstrate that the BD patients had an intact alerting network as there was no difference in the alerting component compared to controls. BD patients however had deficits in the orienting and executive attentional networks as they had significantly longer orienting and conflict RTs with moderate effect sizes. These deficits in performance were also evident in the euthymic BD patients compared to controls although the difference with controls for conflict RT was not significant. In the subgroup analyses there was only a significant performance deficit in the orienting component in normal BD sleepers compared to controls with a moderate effect size. Regarding the

Table 3-17 Mean ANT RT in controls and BD normal and abnormal sleepers

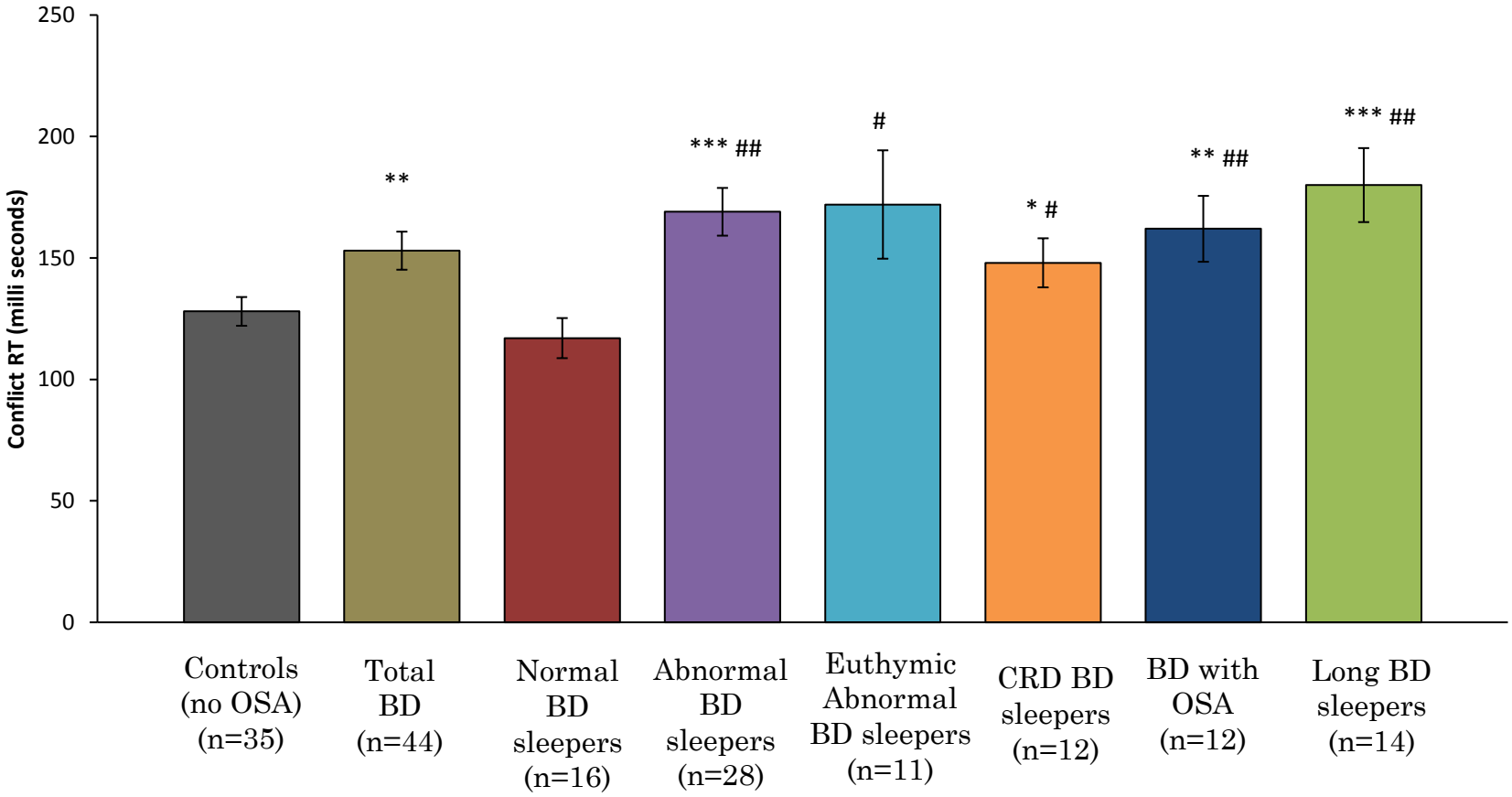
	Controls (n=34)	Total BD group (n=44)	T test (df)	p	Hedges g (95% CI)
Mean RT	566 (83)	614 (102)	-2.246 (76)	**0.028**	0.50 (0.05-0.96)
	Controls (n=34)	**Euthymic BD (n=25)**	**T test (df)**	**p**	**Hedges g (95% CI)**
Mean RT	566 (83)	604 (116)	-1.498 (57)	0.140	0.38 (-0.14-0.90)
	Controls (n=34)	**Normal BD sleepers (n=16)**	**T test (df)**	**p**	**Hedges g (95% CI)**
Mean RT	566 (83)	548 (64)	0.761 (48)	0.451	-0.23 (-0.82-0.37)
	Controls (n=34)	**Abnormal BD sleepers (n=28)**	**T test (df)**	**p**	**Hedges g (95% CI)**
Mean RT	566 (83)	652 (102)	-3.680 (60)	**0.001**	**0.92 (0.40-1.45)**
	Controls (n=34)	**Euthymic abnormal BD sleepers (n=11)**	**T test (df)**	**p**	**Hedges g (95% CI)**
Mean RT	566 (83)	676 (128)	-3.328 (43)	**0.002**	**1.13 (0.41-1.85)**
	Euthymic Normal BD sleepers (n=13)	**Euthymic abnormal BD sleepers (n=11)**	**T test (df)**	**p**	**Hedges g (95% CI)**
Mean RT	547 (69)	676 (128)	-3.136 (22)	**0.005**	**1.24 (0.37-2.12)**

RT data are mean and standard deviation (SD). ASC090 (control) is excluded as mean RT > 3 times interquartile range and considered an extreme outlier.

Table 3-18 Comparison of mean component RT data from the ANT in controls and normal and abnormal BD sleepers

	Controls (n=34)	Total BD group (n=44)	T test (df)	Mann-Whitney U	p	Hedges g (95% CI)
RT alerting	39 (32)	41 (33)	-0.302 (76)		0.763	0.06 (-0.39-0.51)
RT orienting	43 (25)	56 (27)	-2.087 (76)		**0.040**	**0.49 (0.04-0.95)**
RT Conflict	124 (23)	153 (52)	-2.937 (76)		**0.005**	**0.68 (0.22-1.14)**
	Controls (n=34)	**Euthymic BD (n=25)**	**T test (df)**		**p**	**Hedges g (95% CI)**
RT alerting	39 (32)	34 (28)	0.655 (57)		0.515	-0.16 (-0.68-0.35)
RT orienting	43 (25)	57 (26)	-2.083 (57)		**0.042**	**0.54 (0.02-1.07)**
RT Conflict	124 (23)	141 (60)	-1.371 (57)		0.181	0.39 (-0.13-0.91)
	Controls (n=34)	**Normal BD sleepers (n=16)**	**T test (df)**		**p**	**Hedges g (95% CI)**
RT alerting	39 (32)	35 (30)	0.416 (48)		0.679	-0.13 (-0.72-0.47)
RT orienting	43 (25)	59 (26)	-2.013 (48)		**0.050**	**0.62 (0.02-1.23)**
RT Conflict	124 (23)	126 (40)	- 0.210 (48)		0.836	0.07 (-0.53-0.66)
	Controls (n=34)	**Abnormal BD sleepers (n=28)**	**T test (df)**		**p**	**Hedges g (95% CI)**
RT alerting	39 (32)	45 (34)	-0.660 (60)		0.512	0.18 (-0.32-0.68)
RT orienting	43 (25)	54 (28)	-1.605 (60)		0.114	0.41 (-0.09-0.92)
RT Conflict	124 (23)	169 (52)	-4.555 (60)		**<0.001**	**1.14 (0.61-1.68)**
	Controls (n=34)	**Euthymic Abnormal BD sleepers (n=11)**	**T test (df)**		**p**	**Hedges g (95% CI)**
RT alerting	39 (32)	32 (25)	0.743 (43)		0.462	-0.23 (-0.91-0.46)
RT orienting	43 (25)	51 (27)	-0.840 (43)		0.406	0.31 (-0.37-0.99)
RT Conflict	124 (23)	172 (74)		83.0	**0.006**	**1.15 (0.43-1.87)**
	Euthymic Normal BD sleepers (n=13)	**Euthymic Abnormal BD sleepers (n=11)**	**T test (df)**		**p**	**Hedges g (95% CI)**
RT alerting	36 (33)	32 (25)	0.342 (22)		0.735	-0.13 (-0.93-0.67)
RT orienting	65 (25)	51 (27)	1.311 (22)		0.204	-0.52 (-.134-0.30)
RT Conflict	111 (27)	172 (74)	-2.628 (22)		**0.015**	**1.10 (0.24-1.96)**

RT data are mean and standard deviation (SD). ASC090 (control) is excluded as mean RT > 3 times interquartile range and considered an extreme outlier.



*p<0.05 vs. controls; ** p<0.01 vs. controls, ***p<0.001 vs. controls, # p<0.05 vs. normal BD sleepers, ##p <0.01 vs. normal BD sleepers. Error bars represent standard error of the mean.

Figure 3.15 ANT conflict RT in controls and BD normal and abnormal sleepers

conflict component only abnormal BD sleepers, including those in euthymia had a performance deficit compared to controls with a large effect size. Euthymic abnormal BD sleepers also had a deficit in the conflict component compared to euthymic normal BD sleepers also with a large effect size. This finding suggests that abnormal BD sleepers have an impaired executive attentional network compared to controls and BD normal sleepers independent of mood state. There was no effect on the outcomes when considering the potential confounders of age or NART-IQ. The difference in the conflict component compared to controls was also evident in all three BD sleep phenotypes (Table 3-19). There were no statistically significant differences in ANT performance between BD patients prescribed antipsychotics, antidepressants, mood stabilisers or hypnotics and those not taking these medications.

Table 3-19 Mean ANT component RT's in controls and BD sleep phenotypes

	Controls (n=34)	BD long sleepers (n=14)	T test (df)	p	Hedges g (95% CI)
RT alerting	39 (32)	46 (42)	-1.084 (46)	0.285	0.20 (-0.43-0.82)
RT orienting	43 (25)	57 (30)	-1.655 (46)	0.105	0.52 (-0.11-1.15)
RT Conflict	124 (23)	180 (57)	-4.358 (46)	**<0.001**	**1.53 (0.84-2.22)**
	Controls (n=34)	**CRSD BD (n=12)**	**T test (df)**	**p**	**Hedges g (95% CI)**
RT alerting	39 (32)	43 (33)	-0.526 (44)	0.602	0.12 (-0.54-0.78)
RT orienting	43 (25)	55 (30)	-1.358 (44)	0.181	0.45 (-0.22-1.11)
RT Conflict	124 (23)	148 (35)	-2.704 (44)	**0.010**	**0.89 (0.21-1.57)**
	Controls (n=34)	**BD OSA (n=12)**	**T test (df)**	**p**	**Hedges g (95% CI)**
RT alerting	39 (32)	54 (30)	-1.170 (44)	0.249	0.47 (-0.20-1.13)
RT orienting	43 (25)	58 (25)	-1.755 (44)	0.081	0.59 (-0.08-1.26)
RT Conflict	124 (23)	162 (47)	-3.008 (44)	**0.004**	**1.21 (0.51-1.92)**

RT data are mean and standard deviation (SD). ASC079 (control) is excluded as mean RT > 3 times interquartile range and considered an extreme outlier.

3.13.2 Performance on the Psychomotor Vigilance Task

The PVT was completed by 36 controls and 46 BD patients. One BD patient was omitted from the analysis as the number of lapses committed was more than 3 times the interquartile range and they were deemed an extreme outlier. The results comparing controls and BD patients including normal and abnormal sleepers on the PVT can be found in Table 3-20. BD patients differed from controls on all variables assessed with the PVT with moderate to large effect sizes. Mean RT was slower, more lapses (RT > 500ms) were committed and BD patients demonstrated a general slowing of RT as both the fastest and slowest 10% of RT's were longer in the BD group. Evidence for a slowing of RT's over the course of the test, which may indicate fatigue, was found as BD patients last 8 RT's compared to their first 8 RT's slowed to a greater amount than the control group, although this difference just failed to reach statistical significance ($p=0.056$). Some of these differences were also present in euthymic BD patients but with smaller effect sizes. In the subgroup analyses no significant differences were found between normal BD sleepers and controls but abnormal sleepers differed on all variables generally with large effect sizes and there was a similar finding for euthymic abnormal sleepers demonstrating an effect independent of mood state. Within the BD group euthymic abnormal sleepers performed worse than euthymic normal sleepers in a similar pattern as they did to controls except few of the differences reached statistical significance possibly due to reduced statistical power as the magnitude of the difference was only marginally lower than the difference with controls. The differences with controls were consistent across each of the three main BD sleep phenotypes (Table 3-21) and controlling for age or NART-IQ with ANCOVA when they were associated with the

Table 3-20 PVT variables in controls and normal and abnormal BD sleepers

	Controls (n=36)	Total BD (n=45)	t (df)	Mann Whitney U	p	Hedges g (95% CI)
Mean RT	325 (32)	360 (50)	-3.657 (79)		**<0.001**	**0.81 (0.35-1.26)**
Median RT	312 (27)	342 (45)	-3.657 (79)		**<0.001**	**0.78 (0.33-1.23)**
Lapses	1.8 (2.8)	5.1 (6.4)		470.5	**0.001**	**0.64 (0.19-1.09)**
Fastest 8	262 (20)	278 (29)	-2.775 (79)		**0.007**	**0.62 (0.17-1.07)**
Slowest 8	453 (108)	539 (144)		458.0	**0.001**	**0.66 (021-1.11)**
First 8	331 (54)	354 (60)		604.0	**0.050**	0.40 (-0.05-0.84)
Last 8	329 (40)	374 (65)		442.5	**<0.001**	**0.81 (0.35-1.26)**
1st - last 8	1 (49)	-20 (51)	-1.942 (79)		0.056	0.41 (-0.03-0.86)
	Controls (n=36)	**Euthymic BD (n=26)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**
Mean RT	325 (32)	353 (54)		329.0	**0.047**	**0.65 (0.13-1.17)**
Median RT	312 (27)	336 (49)		341.0	0.070	**0.63 (0.11-1.14**)
Lapses	1.8 (2.8)	4.4 (6.7)		337.0	**0.050**	**0.53 (0.02-1.05)**
Fastest 8	262 (20)	275 (31)		346.0	0.082	**0.51 (0.00-1.02)**
Slowest 8	453 (108)	526 (163)		397.0	0.311	**0.54 (0.03-1.05)**
First 8	331 (54)	351 (51)		348.0	0.087	0.37 (-0.13-0.88)
Last 8	329 (40)	369 (76)		325.0	**0.041**	**0.68 (0.16-1.20)**
1st - last 8	1 (49)	-17 (56)		407.0	0.384	0.34 (-0.17-0.85)
	Controls (n=36)	**Normal BD sleepers (n=16)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**
Mean RT	325 (32)	338 (49)	-1.045 (50)		0.301	0.34 (-0.25-0.93)
Median RT	312 (27)	322 (37)	-1.009 (50)		0.318	0.32 (-0.27-0.92)
Lapses	1.8 (2.8)	2.7 (3.8)		240.0	0.312	0.28 (-0.31-0.87)
Fastest 8	262 (20)	270 (27)	-1.110 (50)		0.272	0.35 (-0.24-0.95)
Slowest 8	453 (108)	497 (173)		254.5	0.507	0.33 (-0.26-0.92)
First 8	331 (54)	336 (42)		254.5	0.506	0.10 (-0.49-0.69)
Last 8	329 (40)	343 (57)		255.0	0.513	0.30 (-0.29-0.89)
1st - last 8	1 (49)	-7 (48)		273.5	0.774	-0.16 (-0.75-0.43)

	Controls (n=36)	Abnormal BD sleepers (n=27)	t (df)	Mann Whitney U	p	Hedges g (95% CI)
Mean RT	325 (32)	373 (49)	-4.798 (61)		**<0.001**	**1.18 (0.64-1.72)**
Median RT	312 (27)	355 (47)		209.0	**<0.001**	**1.15 (0.61-1.69)**
Lapses	1.8 (2.8)	6.6 (7.3)		202.0	**<0.001**	**0.91 (0.39-1.43)**
Fastest 8	262 (20)	283 (30)		274.5	**0.003**	**0.84 (0.32-1.36)**
Slowest 8	453 (108)	559 (118)	-3.716 (61)		**<0.001**	**0.93 (0.41-1.46)**
First 8	331 (54)	367 (68)		306.0	**0.012**	**0.59 (0.08-1.10)**
Last 8	329 (40)	393 (65)		168.0	**<0.001**	**1.21 (0.67-1.75)**
1st - last 8	1 (49)	-26 (53)		342.5	**0.046**	-0.53 (-1.03-0.02)
	Controls (n=36)	**Euthymic abnormal BD sleepers (n=11)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**
Mean RT	325 (32)	374 (55)	-3.619 (45)		**0.001**	**1.26 (0.54-1.98)**
Median RT	312 (27)	356 (57)		93.0	**0.008**	**1.20 (0.49-1.92)**
Lapses	1.8 (2.8)	6.9 (8.8)		90.0	**0.005**	**1.04 (0.33-1.75)**
Fastest 8	262 (20)	283 (35)		123.0	0.059	**0.85 (0.16-1.55)**
Slowest 8	453 (108)	569 (134)	-2.946 (45)		**0.005**	**1.00 (0.29-1.70)**
First 8	331 (54)	373 (55)		103.0	**0.017**	**0.76 (0.07-1.45)**
Last 8	329 (40)	401 (87)		84.0	**0.004**	**1.31 (0.58-2.03)**
1st - last 8	1 (49)	-27 (62)		160.0	0.351	-0.53 (-1.21-0.16)
	Euthymic normal BD sleepers (n=14)	**Euthymic abnormal BD sleepers (n=11)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**
Mean RT	337 (52)	374 (55)	-1.701 (23)		0.102	0.67 (-0.14-1.48)
Median RT	320 (40)	356 (57)		45.0	0.080	0.72 (-0.09-1.54)
Lapses	2.7 (4.1)	6.9 (8.8)		45.5	0.079	0.62 (-0.19-1.43)
Fastest 8	269 (28)	283 (35)	-1.107 (23)		0.280	0.43 (-0.37-1.23)
Slowest 8	498 (185)	569 (134)		47.0	0.101	0.42 (-0.38-1.21)
First 8	336 (45)	373 (55)	-1.899 (23)		0.070	0.72 (-0.09-1.54)
Last 8	342 (60)	401 (87)		39.0	**0.037**	0.78 (-0.04-1.60)
1st - last 8	-7 (51)	-27 (62)		64.0	0.477	0.35 (-0.45-1.14)

All data are means and standard deviation (SD).

Table 3-21 PVT variables in controls and BD sleep phenotypes

	Controls (n=36)	BD long sleepers (n=13)	t (df)	Mann Whitney U	p	Hedges g (95% CI)
Mean RT	325 (32)	384 (47)	-5.064 (47)		**<0.001**	**1.59 (0.89-2.30)**
Median RT	312 (27)	367 (43)		63.5	**0.001**	**1.70 (0.98-2.42)**
Lapses	1.8 (2.8)	7.9 (8.5)		97.5	**0.001**	**1.22 (0.54-1.90)**
Fastest 8	262 (20)	288 (24)	-3.678 (47)		**0.001**	**1.21 (0.53-1.89)**
Slowest 8	453 (108)	569 (122)		90.0	**0.001**	**1.02 (0.36-1.69)**
First 8	331 (54)	366 (58)		128.0	**0.016**	0.63 (-0.02-1.27)
Last 8	329 (40)	403 (58)		53.0	**<0.001**	**1.61 (0.90-2.32)**
1st - last 8	1 (49)	-37 (49)		139.5	**0.032**	**-0.76 (-1.41 to-0.11)**
	Controls (n=36)	**BD CRSD (n=12)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**
Mean RT	325 (32)	373 (40)	-4.227 (46)		**<0.001**	**1.39 (0.69-2.09)**
Median RT	312 (27)	358 (44)		78.5	**0.001**	**1.42 (0.71-2.13)**
Lapses	1.8 (2.8)	5.0 (3.9)		95.5	**0.003**	**1.02 (0.33-1.70)**
Fastest 8	262 (20)	289 (31)		101.5	**0.006**	**1.15 (0.46-1.84)**
Slowest 8	453 (108)	530 (66)	-2.336 (46)		**0.024**	**0.76 (0.09-1.43)**
First 8	331 (54)	376 (58)		108.0	**0.010**	**0.81 (0.13-1.48)**
Last 8	329 (40)	381 (49)		80.5	**0.001**	**1.21 (0.51-1.90)**
1st - last 8	1 (49)	-5 (30)		206.0	0.812	-0.13 (-0.78-0.52)
	Controls (n=36)	**BD OSA (n=12)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**
Mean RT	325 (32)	376 (42)	-4.316 (46)		**<0.001**	**1.45 (0.73-2.16)**
Median RT	312 (27)	357 (37)		66.0	**<0.001**	**1.49 (0.77-2.21)**
Lapses	1.8 (2.8)	6.6 (7.1)		92.0	**0.002**	**1.11 (0.42-1.80)**
Fastest 8	262 (20)	282 (29)		110.5	**0.012**	**0.87 (0.20-1.55)**
Slowest 8	453 (108)	561 (120)	-3.148 (46)		**0.003**	**0.96 (0.28-1.64)**
First 8	331 (54)	387 (74)		99.5	**0.006**	**0.93 (0.25-1.61)**
Last 8	329 (40)	408 (68)		52.5	**<0.001**	**1.61 (0.88-2.34)**
1st - last 8	1 (49)	-21 (55)		157.0	0.160	-0.43 (-1.09-0.23)

All data are means and standard deviation (SD)

performance on the PVT had no effect on the statistical significance of the findings. There were no statistically significant differences in PVT performance between BD patients prescribed antipsychotics, antidepressants, mood stabilisers or hypnotics and those not taking these medications.

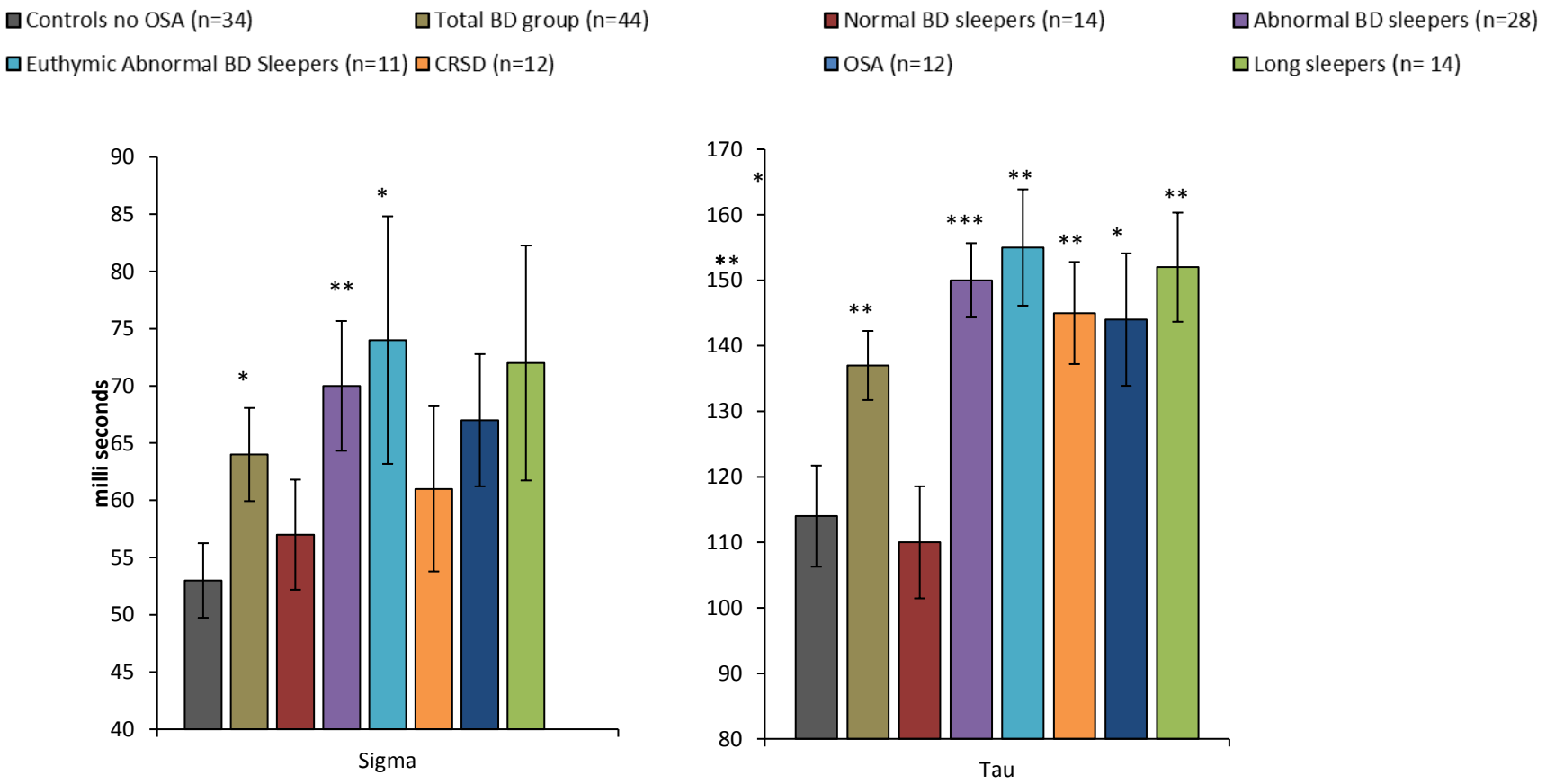
3.13.3 Variability in RT on the ANT and PVT

BD and sleep deprivation/restriction (SD/SR) have all been associated with increased intra-individual variability in attentional performance. The association of sleep abnormalities with intra-individual variability of attentional performance within BD participants was explored with ex-Gaussian analysis of RTs on the ANT and PVT. The variability data (σ and τ) for the ANT can be found in Table 3-22, Figure 3.16 and Figure 3.17 and for the PVT in Table 3-23, Figure 3.18 and Figure 3.19. A similar pattern of results was found for the ANT and PVT. ANCOVA performed where age or NART-IQ were associated with the outcomes had no effect on the statistical significance of the findings. Intra-individual variability in RT was greater in BD patients than controls with moderate effect sizes as demonstrated by greater σ and τ. There was also numerically greater intra-individual variability in RT in euthymic BD patients although effect sizes were reduced and only the difference in σ for the ANT RT was statistically significant. However, findings differed with respect to normal and abnormal BD sleepers. There was no evidence of greater intra-individual variability in RT in normal BD sleepers but abnormal BD sleepers including those in euthymia had significantly greater intra-individual variability in RT than controls with moderate to large effect sizes. The finding of greater intra-individual variability in RT was consistent for each of the 3 main BD sleep

Table 3-22 Ex-Gaussian analysis of intra-individual variability in mean ANT RT

	Controls (n=34)	Total BD group (n=44)	T test (df)	p	Hedges g (95%CI)
ANT RT sigma	53 (19	64 (27)	-2.079 (76)	**0.041**	**0.46 (0.00-0.91)**
ANT RT tau	114 (45)	137 (35)	-2.975 (76)	**0.004**	**0.57 (0.12-1.03)**
	Controls (n=34)	**Euthymic BD (n=25)**	**T test (df)**	**p**	**Hedges g (95% CI)**
ANT RT sigma	53 (19)	65 (29)	-2.033 (57)	**0.047**	0.50 (-0.03-1.02)
ANT RT tau	114 (45)	129 (39)	-1.619 (57)	0.111	0.35 (-0.17-0.87)
	Controls (n=34)	**Normal BD sleepers (n=14)**	**T test (df)**	**p**	**Hedges g (95% CI)**
ANT RT sigma	53 (19)	57 (18)	-0.728 (46)	0.470	0.21 (-0.41-0.83)
ANT RT tau	114 (45)	110 (32)	0.219 (46)	0.828	-0.09 (-0.72-0.53)
	Controls (n=34)	**Abnormal BD sleepers (n=28)**	**T test (df)**	**p**	**Hedges g (95% CI)**
ANT RT sigma	53 (19)	70 (30)	-2.734 (60)	**0.008**	**0.68 (0.17-1.20)**
ANT RT tau	114 (45)	150 (30)	-4.478 (60)	**<0.001**	**0.91 (0.39-1.44)**
	Controls (n=34)	**Euthymic abnormal BD sleepers (n=11)**	**T test (df)**	**p**	**Hedges g (95% CI)**
ANT RT sigma	53 (19)	74 (39)	-2.400 (43)	**0.021**	**0.82 (0.12-1.52)**
ANT RT tau	114 (45)	155 (32)	-3.401 (43)	**0.001**	**0.95 (0.24-1.66)**
	Euthymic normal BD sleepers (n=13)	**Euthymic abnormal BD sleepers (n=11)**	**T test (df)**	**p**	**Hedges g (95% CI)**
ANT RT sigma	60 (16)	74 (39)	-1.122 (22)	0.274	0.47 (-0.34-1.28)
ANT RT tau	107 (32)	155 (32)	-3.633 (22)	**0.001**	**1.45 (0.55-2.35)**

All data are mean and SD in milli seconds.



*p<0.05 vs. controls,**p<0.01 vs controls, ***p<0.001 vs controls.

Figure 3.16 Ex-Gaussian analysis of intra-individual variability in mean ANT RT in controls and BD normal and abnormal sleepers

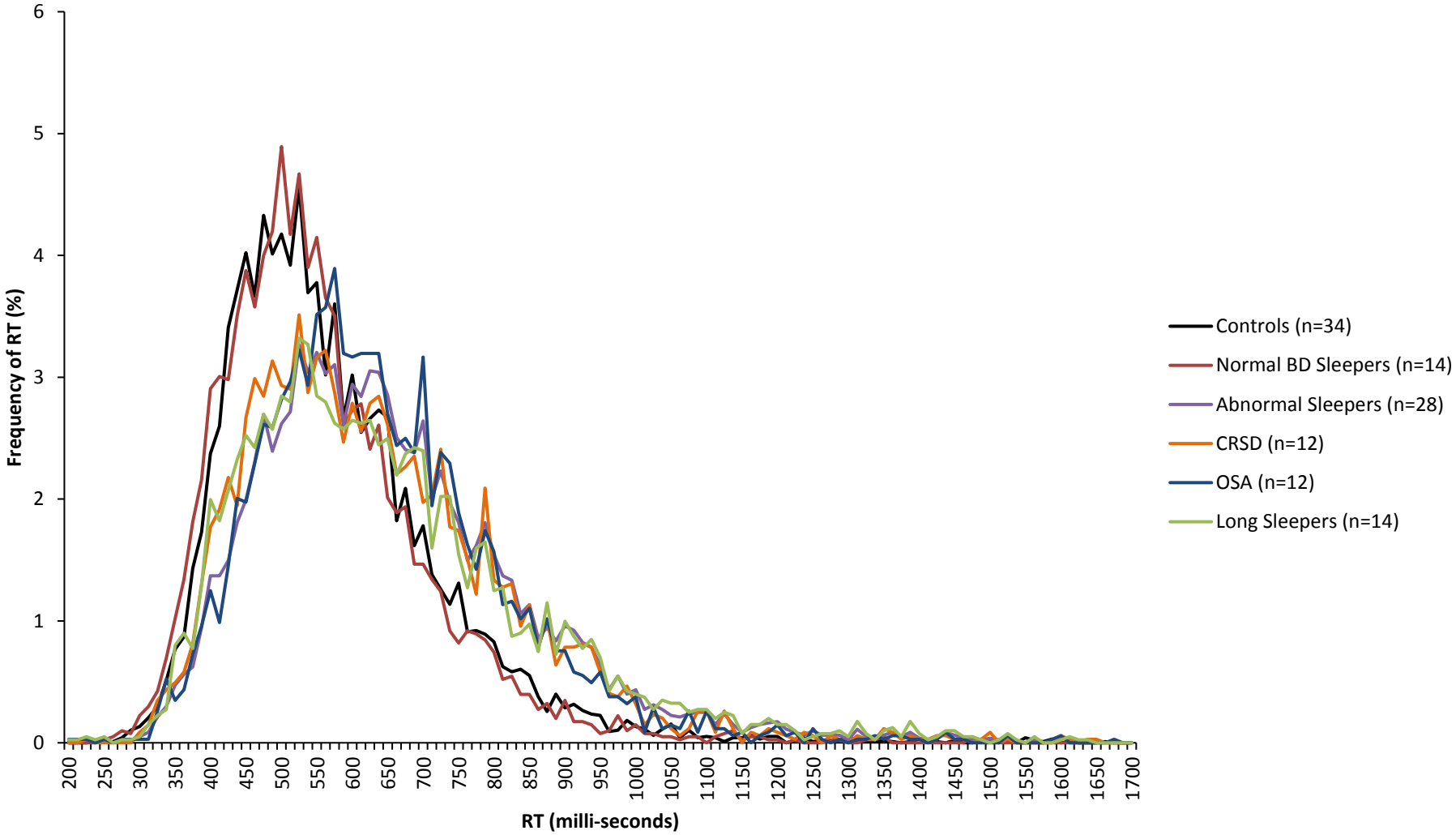
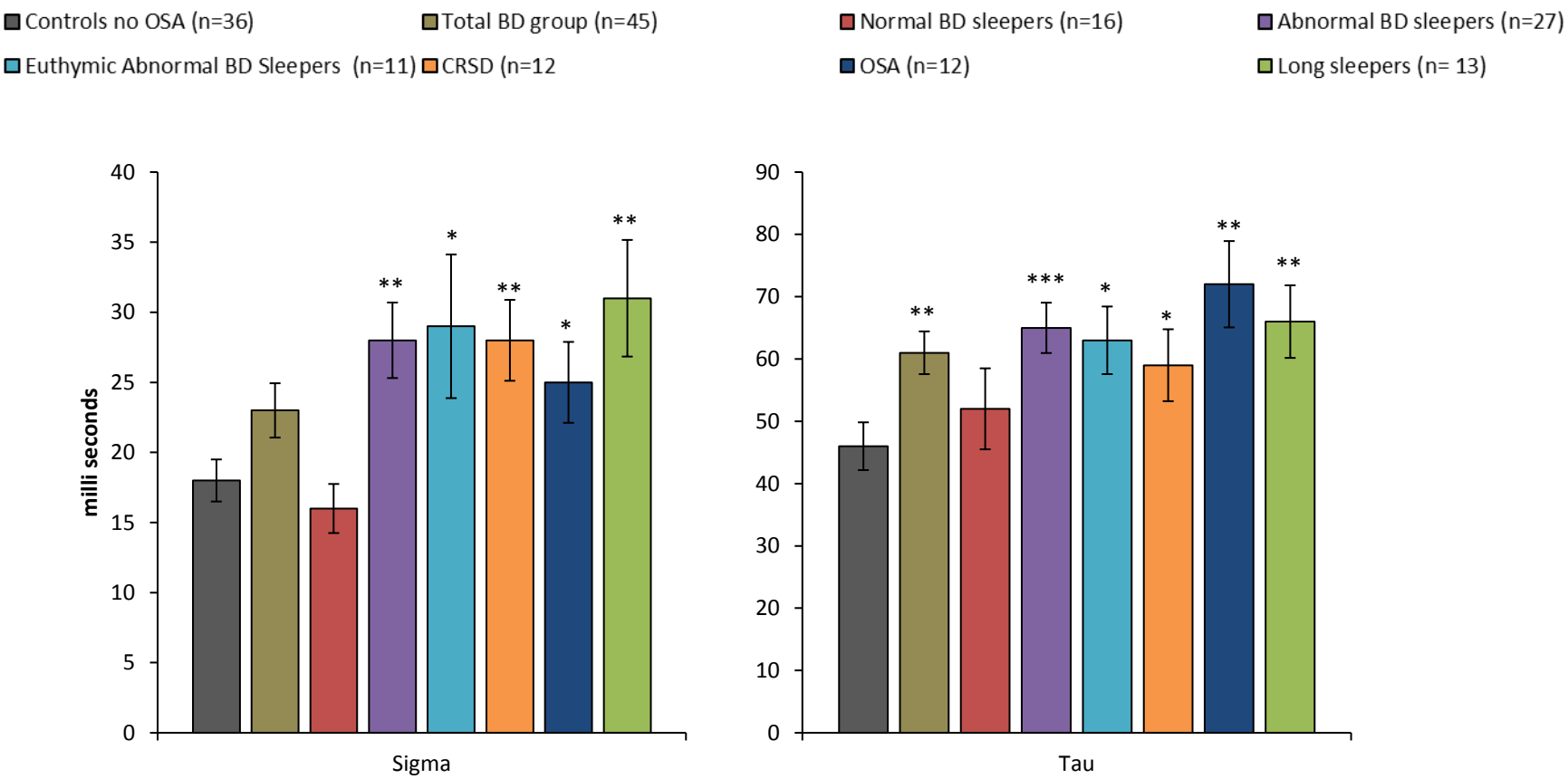


Figure 3.17 Ex-Gaussian distribution of ANT RT's in controls and normal and abnormal BD sleepers

Table 3-23 Ex-Gaussian analysis of intra-individual variability in mean PVT RT

	Controls (n=36)	Total BD group (n=45)	t (df)	p	Hedges g (95% CI)
PVT RT sigma	18 (9)	23 (13)	-1.907 (79)	0.060	0.43 (-0.01-0.88)
PVT RT tau	46 (23)	61 (23)	-3.093 (79)	**0.003**	**0.65 (0.20-1.10)**
	Controls (n=36)	**Euthymic BD group (n=26)**	**t (df)**	**p**	**Hedges g (95% CI)**
PVT RT sigma	18 (9)	21 (14)	-0.923 (60)	0.360	0.26 (-0.25-0.77)
PVT RT tau	46 (23)	56 (24)	-1.722 (60)	0.081	0.42 (-0.09-0.93)
	Controls (n=36)	**BD normal sleepers (n=16)**	**t (df)**	**p**	**Hedges g (95% CI)**
PVT RT sigma	18 (9)	16 (7)	0.755 (50)	0.454	-0.23 (-0.82-0.36)
PVT RT tau	46 (23)	52 (26)	-0.710 (50)	0.481	0.25 (-0.34-0.84)
	Controls (n=36)	**Abnormal BD sleepers (n=27)**	**t (df)**	**p**	**Hedges g (95% CI)**
PVT RT sigma	18 (9)	28 (14)	-3.236 (61)	**0.002**	**0.87 (0.34-1.39)**
PVT RT tau	46 (23)	65 (21)	-4.146 (61)	**<0.001**	**0.85 (0.33-1.37)**
	Controls (n=36)	**Euthymic abnormal BD sleepers (n=11)**	**t (df)**	**p**	**Hedges g (95% CI)**
PVT RT sigma	18 (9)	29 (17)	-2.415 (45)	**0.020**	**0.96 (0.26-1.66)**
PVT RT tau	46 (23)	63 (18)	-2.517 (45)	**0.015**	**0.76 (0.07-1.45)**
	Euthymic normal BD sleepers (n=14)	**Euthymic abnormal BD sleepers (n=11)**	**t (df)**	**p**	**Hedges g (95% CI)**
PVT RT sigma	16 (8)	29 (17)	-2.501 (23)	**0.020**	**0.99 (0.15-1.82)**
PVT RT tau	51 (27)	63 (18)	-1.196 (23)	0.244	0.49 (-0.31-1.29)

All data are means and standard deviation SD in milli-seconds



*p<0.05 vs. controls, **p<0.01 vs. controls ***p<0.001 vs. controls.

Figure 3.18 Ex-Gaussian analysis of intra-individual variability in mean PVT RT in controls and BD normal and abnormal sleepers

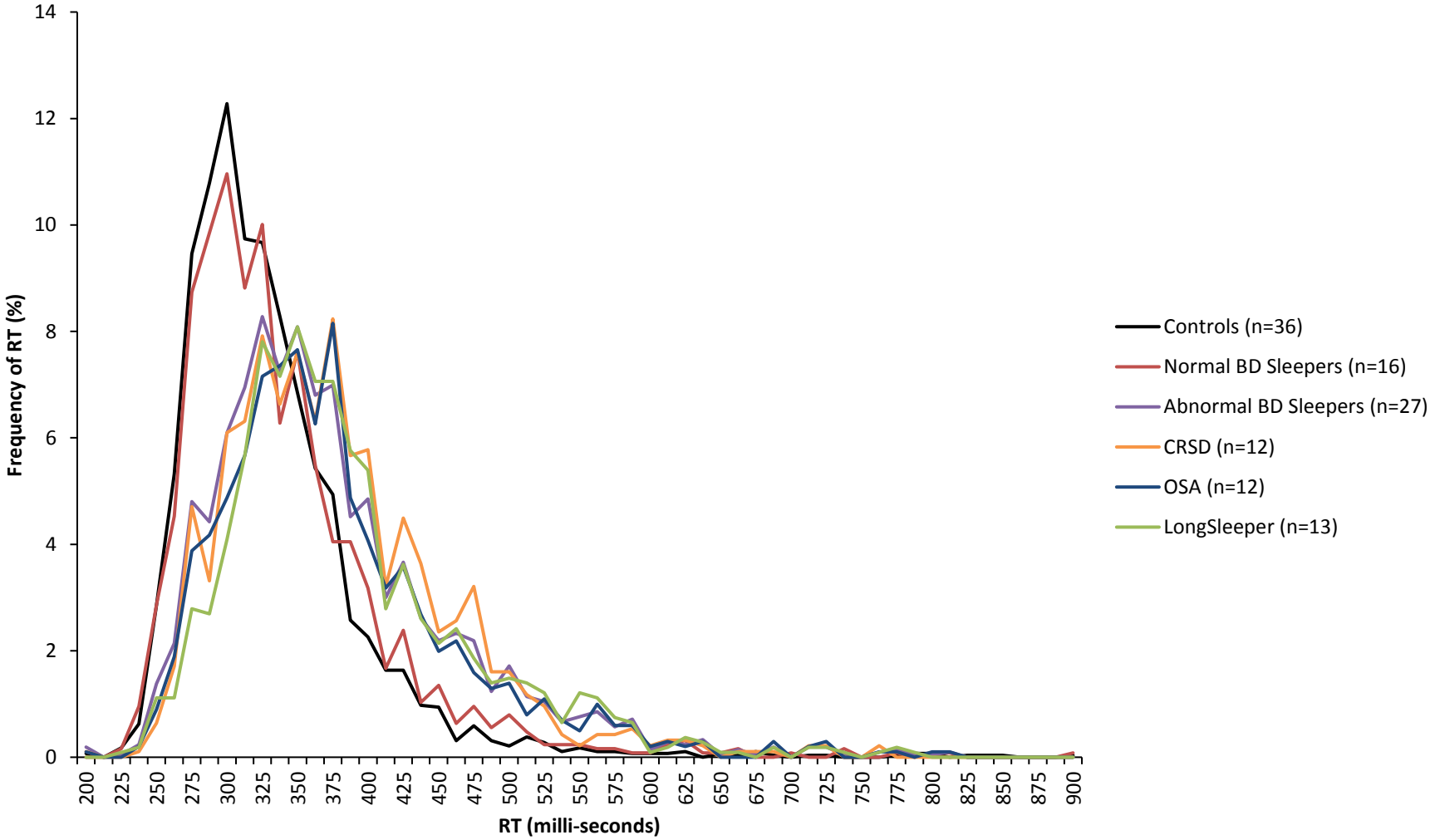


Figure 3.19 Ex-Gaussian analysis of intra-individual variability in mean PVT RT in controls and normal and abnormal BD sleepers

Table 3-24Ex-Gaussian analysis of intra-individual variability of mean ANT RT in controls and BD sleep phenotypes

	Controls (n=34)	**BD long sleepers (n=14)**	**T test (df)**	**p**	**Hedges g (95% CI)**
ANT RT sigma	53 (19)	72 (37)	-2.289 (46)	**0.027**	**0.74 (0.10-1.37)**
ANT RT tau	114 (45)	152 (30)	-3.601 (46)	**0.001**	**0.90 (0.26-1.55)**
	Controls (n=34)	**BD CRSD (n=12)**	**T test (df)**	**p**	**Hedges g (95% CI)**
ANT RT sigma	53 (19)	61 (25)	-1.004 (44)	0.321	0.38 (-0.28-1.04)
ANT RT tau	114 (45)	145 (27)	-2.971 (44)	**0.005**	**0.74 (0.06-1.41)**
	Controls (n=34)	**BD OSA (n=12)**	**T test (df)**	**p**	**Hedges g (95% CI)**
ANT RT sigma	53 (19)	67 (20)	-2.313 (44)	**0.025**	**0.71 (0.04-1.39)**
ANT RT tau	114 (45)	144 (35)	-2.585 (44)	**0.013**	**0.69 (0.02-1.36)**

All data are mean and standard deviation (SD) in milli-seconds (ms)

Table 3-25 Ex-Gaussian analysis of intra-individual variability in PVT RT in controls and BD sleep phenotypes

	Controls (no OSA) (n=36)	**BD long sleepers (n=13)**	**t (df)**	**p**	**Hedges g (95% CI)**
PVT RT sigma	18 (9)	31 (15)	-3.366 (47)	**0.002**	**1.18 (0.50-1.85)**
PVT RT tau	46 (23)	66 (21)	-3.015 (47)	**0.004**	**0.87 (0.22-1.53)**
	Controls (no OSA) (n=36)	**BD CRSD (n=12)**	**t (df)**	**p**	**Hedges g (95% CI)**
PVT RT sigma	18 (9)	28 (10)	-3.139 (46)	**0.003**	**1.06 (0.38-1.75)**
PVT RT tau	46 (23)	59 (20)	-2.059 (46)	**0.045**	0.57 (-0.09-1.24)
	Controls (no OSA) (n=36)	**BD OSA (n=12)**	**t (df)**	**p**	**Hedges g (95% CI)**
PVT RT sigma	18 (9)	25 (10)	-2.380 (46)	**0.022**	**0.74 (0.07-1.41)**
PVT RT tau	46 (23)	72 (24)	-3.510 (46)	**0.001**	**1.10 (0.41-1.79)**

All data are mean and standard deviation (SD)

phenotypes (Figure 3.17, Figure 3.19, Table 3-24 and Table 3-25). Euthymic abnormal BD sleepers had greater intra-individual ANT RT variability than euthymic normal BD sleepers indicated by a significantly greater τ with a large effect size but on the PVT only σ was significantly greater in euthymic abnormal sleepers than normal sleepers also with a large effect size. There were no statistically significant differences in ANT or PVT variability between BD patients prescribed antipsychotics, antidepressants, mood stabilisers or hypnotics and those not taking these medications.

3.13.4 Examination of the association of executive control with lapses in attention

Unsworth et al. (2010) have demonstrated that longer RTs or "lapses" are associated with a breakdown in executive control. Longer RTs are quantified in the τ statistic from the ex-Gaussian analysis of RTs and executive control is directly assessed with the conflict RT from the ANT. Therefore, the association between executive control and excessively long RT's can be assessed using ANT conflict RT and a measure of excessively long RT's such as PVT RT τ. If conflict RT could predict the difference in PVT RT τ between BD and control groups it would suggest that the increase in τ i.e. increase in excessively long RTs, in the BD groups was due to a breakdown in executive control. This can be assessed with hierarchical regression analysis using group (control or BD) and conflict RT in a model to predict PVT RT τ. We already know group predicts PVT RT τ as PVT RT τ is greater in BD patients. If adding conflict RT into the model before group significantly reduces or eliminates the ability of group to predict PVT RT τ it would suggest that ANT conflict RT, i.e. executive control, is the factor driving the increase in PVT RT τ.

Firstly, scatter plots were drawn to assess the relationship between conflict RT with PVT RT τ, in the control and BD groups. The scatter plots revealed one significant outlier for conflict RT in the BD group and this data point was Winsorised in order to reduce its influence on the correlation whilst still preserving the rank order. The Pearson's correlation between PVT RT τ and Winsorised ANT conflict RT was $r_{(34)} = 0.562$, p=0.001 in controls and $r_{(43)} = 0.510$, p<0.001 in BD patients. The results of the regression model using ANT conflict RT to predict PVT RT τ can be found in Table 3-26. Group, (controls vs. total BD), predicted 8.5% of the variance in PVT RT τ. Adding conflict RT into the model before group reduced the amount of variance in PVT RT τ predicted by group to <1% which rendered group an insignificant predictor of PVT RT τ. Group, (controls vs. abnormal BD sleepers), predicted 15.3% of the variance in PVT RT τ. Adding conflict RT into the model before group reduced the amount of variance in PVT RT τ predicted by group to 1.4%, rendering group an insignificant predictor on PVT τ. Finally group , (controls vs. euthymic abnormal BD sleepers), predicted 9.2% of the variance in PVT RT τ. Adding conflict RT into the model before group reduced the amount of variance predicted by group to <1% rendering group an insignificant predictor of PVT RT τ. These data suggest that the majority of the between group differences in PVT RT τ is related to performance on conflict RT or executive control of attention.

Table 3-26 Hierarchical regression models using ANT conflict RT and group to predict PVT tau.

Dependant variable	predictor	r^2	r^2 change	F for r^2 change	p
PVT τ	group[a]	0.085	0.085	7.137	**0.009**
PVT τ	conflict RT	0.3	0.3	32.142	**<0.001**
	group[a]	0.309	0.009	0.995	0.322
PVT τ	group[b]	0.153	0.153	10.674	**0.002**
PVT τ	conflict RT	0.280	0.280	22.99	**<0.001**
	group[b]	0.295	0.014	1.178	0.282
PVT τ	group[c]	0.092	0.092	4.346	**0.043**
PVT τ	conflict RT	0.285	0.285	17.107	**<0.001**
	group[c]	0.288	0.004	0.227	0.636

[a]controls vs. total BD group, [b]controls vs. abnormal BD sleepers, [c]controls vs. euthymic abnormal sleepers

3.13.5 Performance on the digit symbol substitution test

Participants completed two DSST's one at the beginning and end of the cognitive testing session. One BD normal sleeper did not complete DSST 2. Both controls and BD patients improved performance in DSST 2 compared to DSST 1 demonstrating a practice effect and no evidence of fatigue at the end of the protocol. The pattern of results comparing controls and BD patients was identical for DSST 1 and DSST 2 and only the results from DSST 1 are shown Table 3-27 and Figure 3.20. BD patients including those in euthymia scored significantly lower on DSST 1 than controls with moderate effect sizes. However, only abnormal BD sleepers including those in euthymia differed from controls with large effect sizes and normal BD sleepers did not differ from controls. Results were consistent for each BD sleep phenotype as all scored significantly lower on DSST 1 than controls with moderate to large effect sizes (Table 3-28). Euthymic BD abnormal sleepers had lower scores on DSST 1 than euthymic normal BD sleepers with a large effect size. There was however a significant correlation of age and DSST performance and after controlling for age with ANCOVA the

Table 3-27 Results of the DSST in controls and BD patients.

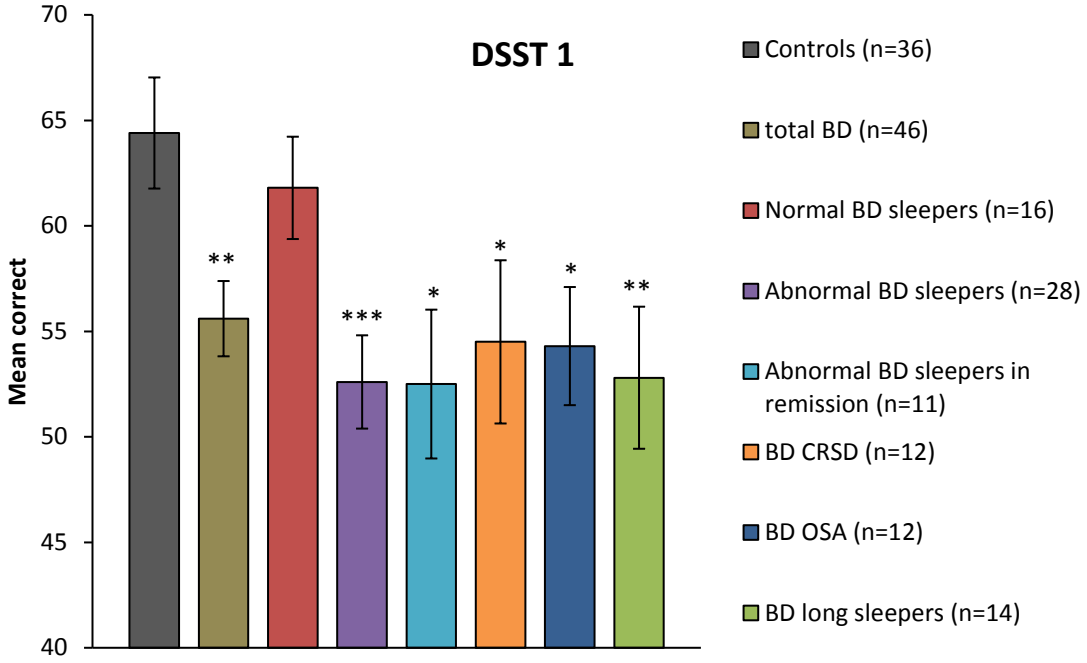
	Controls (n=36)	**Total BD group (n=46)**	**T test (df)**	**p**	**Hedges g (95% CI)**	**ANCOVA**
DSST 1	66.4 (15.8)	55.6 (12.1)	3.517 (80)	**0.001**	**-0.77 (-1.22 to -0.32)**	
	Controls (n=36)	**Euthymic BD (n=26)**	**T test (df)**	**p**	**Hedges g (95% CI)**	**ANCOVA**
DSST 1	66.4 (15.8)	57.9 (11.2)	2.351 (60)	**0.022**	**-0.60 (-1.11 to -0.08)**	
	Controls (n=36)	**BD normal sleepers (n=16)**	**T test (df)**	**p**	**Hedges g (95% CI)**	**ANCOVA**
DSST 1	66.4 (15.8)	61.8 (9.7)	1.288 (50)	0.204	-0.33 (-0.84 to 0.17)	
	Controls (n=36)	**BD abnormal sleepers (n=28)**	**T test (df)**	**p**	**Hedges g (95% CI)**	**ANCOVA**
DSST 1	66.4 (15.8)	52.6 (11.7)	3.884 (62)	**<0.001**	**-0.98 (-1.48 to -0.44)**	
	Controls (n=36)	**Euthymic BD abnormal sleepers (n=11)**	**T test (df)**	**p**	**Hedges g (95% CI)**	**ANCOVA**
DSST 1	66.4 (15.8)	52.5 (11.7)	2.707 (45)	**0.010**	**-0.91 (-1.61 to -0.21)**	
	Euthymic normal BD sleepers (n=14)	**Euthymic abnormal BD sleepers (n=11)**	**T test (df)**	**p**	**Hedges g (95% CI)**	**ANCOVA**
DSST 1	61.8 (9.5)	52.5 (11.7)	2.205 (23)	**0.038**	**-0.86 (-1.68 to -0.03)**	$F_{(1,22)} = 3.425$, $p=0.078^{a,}$

Data are mean and standard deviation (SD). a = age used as a covariant in the model.

Table 3-28 DSST 1 in controls and BD sleep phenotypes

	Controls (n=36)	**BD long sleepers (n=14)**	**T test (df)**	**p**	**Hedges g (95% CI)**	**ANCOVA**
DSST 1	66.4 (15.8)	52.8 (12.6)	2.890 (48)	**0.006**	**-0.89 (-1.53 to -0.25)**	**$F_{(1,47)}$ = 8.878, p=0.005[a]**
	Controls (n=36)	**BD CRSD (n=12)**	**T test (df)**	**p**	**Hedges g (95% CI)**	**ANCOVA**
DSST 1	66.4 (15.8)	54.5 (13.4)	2.346 (46)	**0.023**	**-0.77 (-1.44 to -0.10)**	**$F_{(1,45)}$ = 6.487, p=0.014[a]**
	Controls (n=36)	**BD OSA (n=12)**	**T test (df)**	**p**	**Hedges g (95% CI)**	**ANCOVA**
DSST 1	66.4 (15.8)	54.3 (9.7)	2.508 (46)	**0.016**	**-0.82 (-1.49 to -0.14)**	$F_{(1,45)}$ = 1.418, p=0.240[a]

Data are mean and standard deviation (SD) a = age used as a covariate in the model.



* p<0.05 vs controls, ** p<0.01 vs. controls, *** p<0.001 vs. controls

Figure 3.20 DSST 1 performance in controls and BD patients

difference only trended towards significance (p=0.078). There were no statistically significant differences in DSST performance between BD patients prescribed antipsychotics, antidepressants, mood stabilisers or hypnotics and those not taking these medications.

3.13.6 Performance on the trail making test

One control participant was not included in this analysis as their TRAILS B-A score was greater than 3 times the interquartile range and was therefore deemed an extreme outlier. There were no significant differences between controls and BD patients in performance on the TRAILS A or B even when examining for the

effects of potential co-variates so no further analyses were performed (Table 3-29).

Table 3-29 Results of the trail making test in controls and BD patients

	Controls (n=35)	Total BD group (n=46)	Test Statistic		
	Mean (SD)	Mean (SD)	t (df)	Mann Whitney U	p
TRAILS A	27 (11)	27 (9)	0.031 (79)		0.975
TRAILS B	53 (22)	58 (24)		755.5	0.637
TRAILS B-A	26 (14)	31 (20)	-1.081 (79)		0.283

Values are time taken to complete the task in seconds. Participant ASC052 (control) was omitted as their B-A time was greater than 3 times the interquartile mean and therefore an extreme outlier.

3.13.7 Performance on the digit span test

There were no significant differences between controls and BD patients in performance on the digit span forwards or backwards (Table 3-30). Correlation analysis found significant Pearson's correlations between NART-IQ and digit span forwards and backwards but age and BDI score did not correlate with any of the digit span scores. After controlling for NART-IQ the total BD group performed significantly worse on digit span forwards with a trend towards worse performance in digit span backwards. Euthymic BD patients trended towards a worse performance on digit span forwards, and normal BD sleepers performed worse on digit span forwards. Abnormal BD sleepers trended towards a worse performance on digit span backwards but euthymic abnormal BD sleepers did not differ from controls.

Table 3-30 Performance on the digit span in controls and BD patients

	Controls (n=36)	Total BD (n=46)	Test Statistic		ANCOVA[1]
	Mean (SD)	Mean (SD)	t (df)	p	
Digit Span forwards	9.6 (2.3)	9.2 (2.1)	0.700 (80)	0.486	**$F_{(1,78)} = 4.803$, p=0.031**
Digit Span Backwards	8.2 (2.6)	7.8 (2.5)	0.726 (80)	0.470	$F_{(1,78)} = 3.372$, p=0.07
	Controls (n=36)	**Euthymic BD (n=26)**			**ANCOVA[1]**
Digit Span forwards	9.6 (2.3)	9.4 (1.7)	0.323 (60)	0.748	$F_{(1,58)} = 3.569$, p=0.064
Digit Span Backwards	8.2 (2.6)	7.9 (2.6)	0.425 (60)	0.673	$F_{(1,58)} = 2.236$, p=0.140
	Controls (n=36)	**Normal BD sleepers (n=18)**			**ANCOVA[1]**
Digit Span forwards	9.6 (2.3)	9.1 (2.2)	0.778 (52)	0.440	**$F_{(1,50)} = 4.362$, p=0.042**
Digit Span Backwards	8.2 (2.6)	8.1 (2.7)	0.147 (52)	0.884	$F_{(1,50)} = 1.246$, p=0.270
	Controls (n=36)	**Abnormal BD sleepers (n=28)**			**ANCOVA[1]**
Digit Span forwards	9.6 (2.3)	9.3 (2.1)	0.425 (62)	0.673	$F_{(1,60)} = 2.830$, p=0.098
Digit Span Backwards	8.2 (2.6)	7.6 (2.3)	0.957 (62)	0.342	$F_{(1,60)} = 3.735$, p=0.058
	Controls (n=36)	**Euthymic abnormal BD sleepers (n=11)**			**ANCOVA[1]**
Digit Span forwards	9.6 (2.3)	9.6 (1.5)	0.014 (45)	0.989	$F_{(1,43)} = 0.929$, p=0.340
Digit Span Backwards	8.2 (2.6)	7.5 (2.4)	0.815 (45)	0.420	$F_{(1,43)} = 2.387$, p=0.130

[1]NART-IQ was used as the covariate in the ANCOVA

3.13.8 Performance on the Newcastle Spatial Working Memory Test

BD patients committed significantly more between search errors on the NSWM test than controls at levels 10, 12 and the total number of errors with a moderate effect size (Table 3-31). There was however a moderate correlation between age and total between search errors in controls and a weak correlation in BD patients. The differences between controls and BD patients were reduced to trend level after controlling for age with ANCOVA. There was a trend towards significantly more within search errors committed by BD patients on level 12 but no significant differences between groups in retouch errors. As there were no significant differences found between controls and the total group of BD patients after controlling for age no further analysis was performed.

3.13.9 Performance on the verbal learning test

BD patients recalled significantly fewer words on the immediate recall of the verbal learning test with a moderate effect size but the difference in delayed recall only trended towards statistical significance (Table 3-32). NART-IQ had significant correlations with immediate recall and delayed error total scores in BD patients and controls. Following ANCOVA using NART-IQ as the covariate, the differences in delayed error total between BD patients and controls and immediate recall between euthymic patients and controls were also statistically significantly different. The difference in delayed error total between controls and euthymic abnormal sleepers trended towards statistical significance ($p=0.061$). There were no significant differences between euthymic normal and abnormal BD sleepers on either variable. There were no statistically significant differences in verbal learning performance between BD patients prescribed antipsychotics, antidepressants, mood stabilisers or hypnotics and those not taking these

Table 3-31 Performance on the Newcastle Spatial Working Memory Test in controls and BD patients

	Controls (n=33)	Total BD (n=43)	T test (df)	Mann Whitney U		Hedges g	ANCOVA
Between search errors							
L8	14.3 (13.1)	19.2 (14.8)		574.0	0.155	0.34 (-0.11-0.80)	
L10	42.5 (23.2)	56.0 (29.7)	-2.156 (74)		**0.034**	**0.49 (0.03-0.95)**	$F_{(1,73)}$ = 2.465, p=0.121[a,1]
L12	76.2 (34.2)	95.4 (39.2)	-2.230 (74)		**0.029**	**0.51 (0.05-0.97)**	$F_{(1,73)}$ = 2.994, p=0.088[a,1]
Total	137.9 (67.0)	178.6 (81.6)	-2.323 (74)		**0.023**	**0.53 (0.07-0.99)**	$F_{(1,73)}$ = 3.111, p=0.082[a,1]
Within search errors							
L8	1.3 (2.7)	0.9 (1.6)		709.5	1.000	-0.18 (-0.64-0.27)	
L10	3.8 (3.3)	4.4 (3.9)		656.5	0.576	0.16 (-0.29-0.62)	
L12	7.2 (6.6)	11.4 (9.8)		527.0	0.055	**0.49 (0.03-0.95)**	
Total	12.6 (7.9)	17.2 (13.0)		580.5	0.176	0.41 (-0.05-0.87)	
Retouch							
L8	1.1 (1.7)	1.0 (1.6)		649.5	0.493	-0.06 (-0.51-0.39)	
L10	2.3 (2.9)	2.8 (4.4)		683.0	0.774	0.13 (-0.32-0.58)	
L12	2.6 (2.4)	4.3 (6.1)		585.0	0.186	0.35 (-0.11-0.80)	
Total	6.6 (7.0)	8.9 (10.2)		64.5	0.371	0.25 (-0.20-0.71)	

Controls excluded ASC094 (extreme outlier on within searches), ASC004 & ASC095 (extreme outliers on retouch). BD excluded ASC033, ASC040, ASC069 (extreme outliers on retouch). a= age used as covariate, 1 = significant interaction between age and group.

Table 3-32 Performance on the verbal learning test in controls and BD patients

	Controls (n=36)	**Total BD (n=46)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**	**ANCOVA[1]**
Immediate recall total	12.1 (3.6)	9.5 (4.4)	3.224 (80)		**0.002**	**-0.60 (-1.05 to -0.16)**	**$F_{(1,78)}$ = 13.999, p<0.001**
Delayed error total	8.4 (3.6)	11.6 (7.2)	-1.752 (80)		0.084	**0.54 (0.09-0.98)**	**$F_{(1,78)}$ = 10.975, p=0.001[a,b]**
	Controls (=36)	**Euthymic BD (n=26)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**	**ANCOVA[1]**
Immediate recall total	12.1 (3.6)	10.6 (4.7)	1.311 (60)		0.195	-0.33 (-0.84-0.17)	**$F_{(1,58)}$ = 4.551, p=0.037**
Delayed error total	8.4 (3.6)	10.2 (5.4)		373.5	0.176	0.40 (-0.11-0.91)	$F_{(1,58)}$ = 3.232, p=0.077[a,]
	Controls (n=36)	**Normal BD sleepers (n=16)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**	**ANCOVA[1]**
Immediate recall total	12.1 (3.6)	10.8 (4.2)	1.165 (50)		0.250	-0.31 (-0.90-0.29)	$F_{(1,48)}$ = 3.681, p=0.061
Delayed error total	8.4 (3.6)	9.1 (5.4)	-0.559 (50)		0.579	0.16 (-0.43-0.75)	$F_{(1,48)}$ = 1.121, p=0.295
	Controls (n=36)	**Abnormal BD sleepers (n=28)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**	**ANCOVA[1]**
Immediate recall total	12.1 (3.6)	9.1 (4.4)	3.432 (62)		**0.001**	**-0.71 (-1.22 to -0.20)**	**$F_{(1,60)}$ = 12.806, p=0.001**
Delayed error total	8.4 (3.6)	11.6 (5.8)		331.0	**0.019**	**0.67 (0.17-1.18)**	**$F_{(1,60)}$ = 11.499, p=0.001**
	Controls (n=36)	**Euthymic abnormal BD sleepers (n=11)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**	**ANCOVA[1]**
Immediate recall total	12.1 (3.6)	10.6 (5.3)	1.332 (45)		0.193	-0.33 (-1.01-0.34)	$F_{(1,43)}$ = 1.982, p=0.166
Delayed error total	8.4 (3.6)	10.6 (4.4)	-1.709 (45)		0.094	0.57 (-0.11-1.26)	$F_{(1,43)}$ = 3.707, p=0.061
	Euthymic normal BD sleepers (n=14)	**Euthymic abnormal BD sleepers (n=11)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**	**ANCOVA[1]**
Immediate recall total	10.9 (4.2)	10.6 (5.3)	0.384 (23)		0.731	-0.06 (-0.83-0.71)	$F_{(1,22)}$ = 0.008, p=0.932
Delayed error total	8.8 (4.4)	10.6 (4.4)	-1.051 (23)		0.304	0.40 (-0.39-1.17)	$F_{(1,22)}$ = 0.907, p=0.351

[1]NART used as covariate. [a]= Levene's test of equality of error variances is significant, [b] = significant interaction between group and covariate

Table 3-33 Performance on the verbal learning test in controls and BD sleep phenotypes

	Controls (n=36)	BD long sleepers (n=14)	t (df)	Mann Whitney U	p	Hedges g (95% CI)	ANCOVA
Immediate recall total	12.0 (3.7)	8.9 (4.1)	2.592 (48)		**0.013**	**-0.80 (-1.44 to -0.16)**	**$F_{(1,61)}$ = 5.640, p=0.022**[1]
Delayed error total	8.4 (3.6)	10.4 (5.9)	-0.965		0.340	0.45 (-0.17-1.08)	
	Controls (n=36)	**BD CRSD (n=12)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**	**ANCOVA**
Immediate recall total	12.0 (3.7)	10.5 (5.6)	1.041 (46)		0.303	-0.35 (-1.01-0.31)	
Delayed error total	8.4 (3.6)	11.1 (5.6)	-1.924 (46)		0.061	0.64 (-0.03-1.30)	$F_{(1,45)}$ = 3.215, p=0.080[1]
	Controls (n=36)	**BD OSA (n=12)**	**t (df)**	**Mann Whitney U**	**p**	**Hedges g (95% CI)**	**ANCOVA**
Immediate recall total	12.0 (3.7)	9.8 (5.6)	1.514 (46)		0.137	-0.51 (-1.17-0.15)	
Delayed error total	8.4 (3.6)	11.3 (5.4)	-2.079 (46)		**0.043**	**0.70 (0.03-1.36)**	$F_{(1,45)}$ = 1.754, p=0.192[1]

[1]**NART used as covariate.**

medications. Comparisons between controls and individual sleep phenotypes can be found in Table 3-33. Long sleepers had a deficit in immediate recall and those with OSA committed more delayed recall errors than controls.

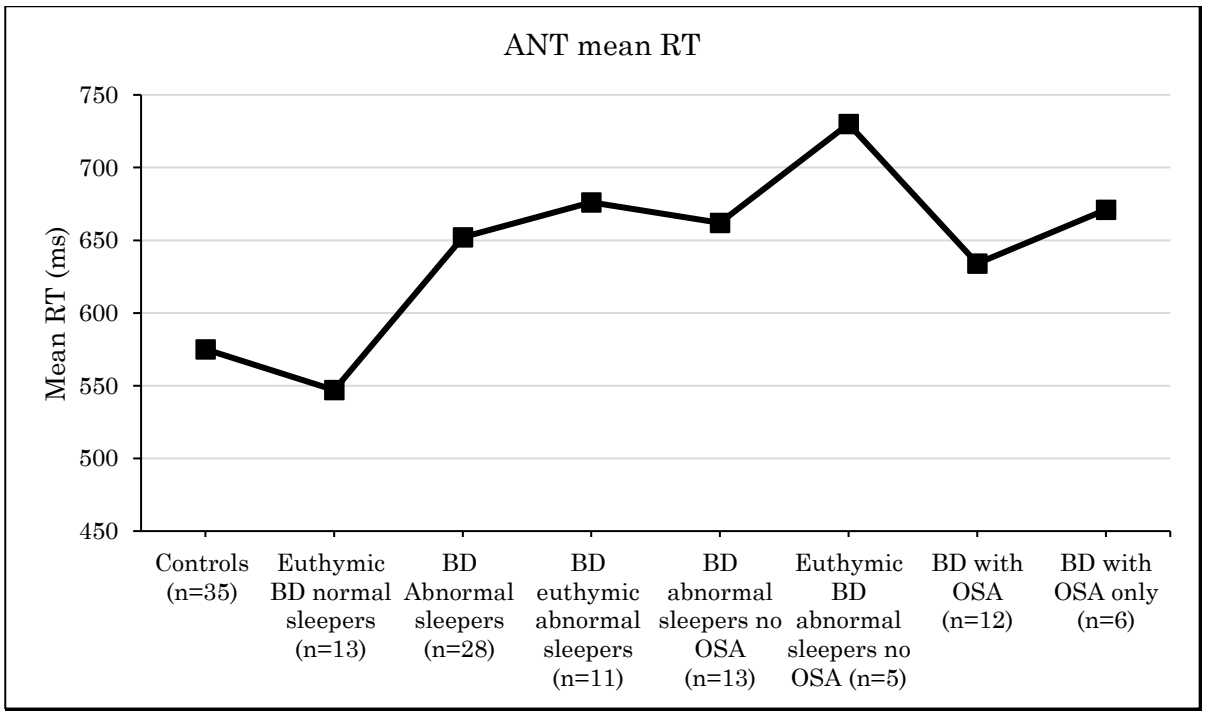
3.13.10 Cognitive performance on tasks of attention and psychomotor speed in patients with and without OSA.

As OSA has been demonstrated to be associated with cognitive deficits and the aetiology of cognitive deficits in people with OSA may be different to that from other sleep abnormalities the data for the main outcomes that demonstrated an association with sleep abnormalities were examined in normal and abnormal sleepers with and without OSA. The mean and SD of the main RT data from the ANT and PVT and the number of correct responses on the DSST can be found in Table 3-34. Figure 3.21, Figure 3.22 and Figure 3.23 show the data for these variables plotted on line graphs to aid visual comparison of performance between BD normal and abnormal sleepers with and without OSA. Due to the small sample sizes no statistical analysis was performed. The performance in mean ANT RT, mean ANT conflict RT, mean PVT RT and the number of PVT lapses across all abnormal BD sleepers and was not influenced by the presence or absence of OSA. This was also true of ANT mean tau. For PVT tau performance was also similar across abnormal sleepers with and without OSA with the exception of euthymic abnormal sleepers without OSA who has a mean PVT tau similar in magnitude to controls and normal BD sleepers. However as there were only five BD euthymic abnormal sleepers without OSA no firm conclusions can be drawn about the influence of OSA on PVT tau. It is possible given the consistency of the other RTs that this may be a chance finding due to the small sample size. A larger sample size is required to confirm or reject this finding. As BD patients

Table 3-34 Performance on the ANT, PVT and DSST in abnormal BD sleepers with and without OSA.

	Controls (n=35 for ANT, n=36 for PVT,DSST)	Euthymic BD normal sleepers (n = 13 for ANT, n=14 for PVT, DSST)	BD Abnormal sleepers (n=28 for ANT, DSST, n=27 for PVT)	BD euthymic abnormal sleepers (n=11)	BD abnormal sleepers no OSA (n=13)	Euthymic BD abnormal sleepers no OSA (n=5)	BD with OSA (n=12)	BD with OSA only (n=6)
ANT mean RT	575 (101)	547 (69)	652 (102)	676 (128)	662 (128)	730 (149)	634 (74)	671 (22)
ANT Tau	117 (48)	107 (32)	150 (30)	155 (32)	153 (28)	160 (30)	144 (35)	148 (40)
ANT Conflict RT	128 (35)	111 (27)	169 952)	172 (74)	172 (56)	177 (90)	162 (47)	176 (50)
PVT mean RT	325 (32)	337 (52)	373 (49)	374 (55)	369 (56)	389 (75)	376 (42)	380 (51)
PVT Lapses	1.8 (2.8)	2.7 (4.1)	6.6 (7.3)	6.9 (8.8)	6.5 (8.1)	9.6 (12.8)	6.6 (7.1)	7 (8.5)
PVT Tau	45.9 (22.9)	51 (27)	65 (21)	63 (18)	58.9 (17.1)	48.5 (15.0)	71.8 (24.0)	76 (25)
DSST 1	66.4 (15.8)	61.8 (9.5)	52.6 (11.7)	52.5 (11.7)	53.3 (13.1)	44.8 (7.9)	54.3 (9.7)	52 (7.9)

BD patients with OSA only had normal sleep patterns but an AHI $\geq$ 5. All data for ANT and PVT are mean and standard deviation (SD) in milli seconds. Data for the DSST is the number of correct responses. ANT = Attention Network Test, PVT = Psychomotor Vigilance test, DSST = Digit Symbol Substitution Test



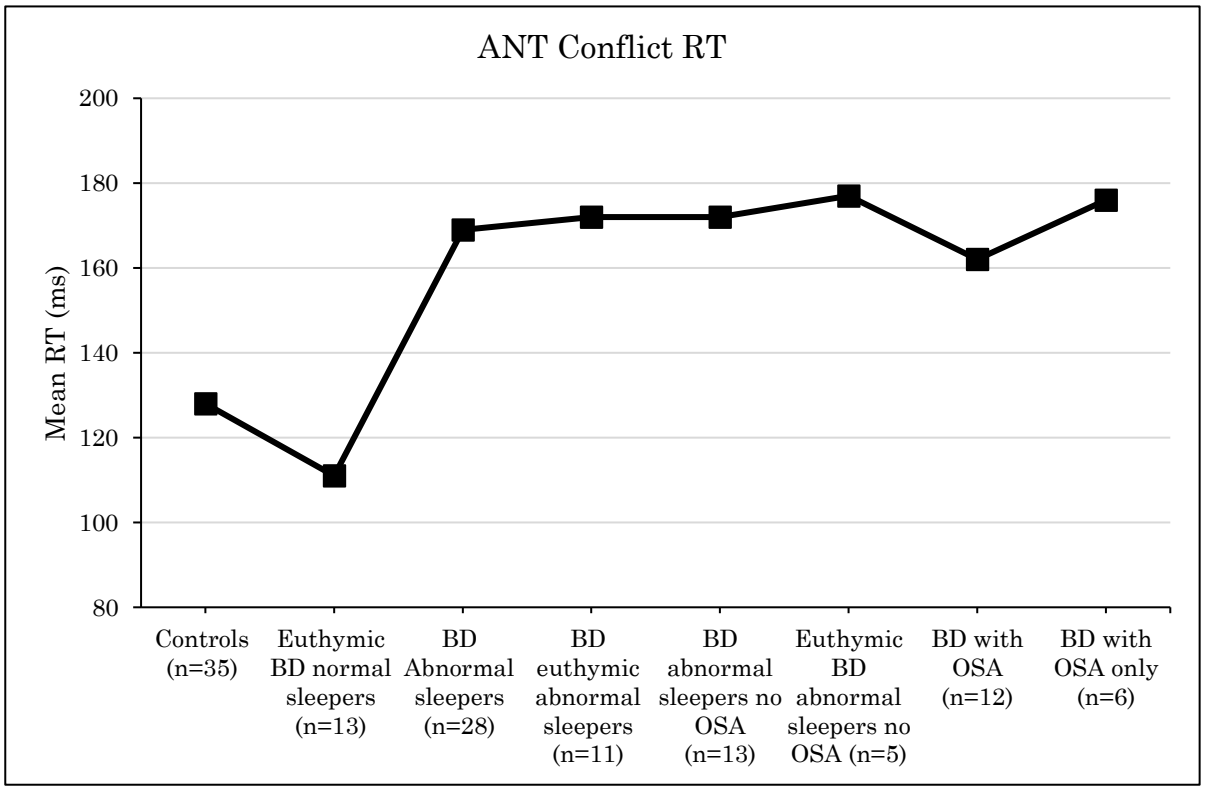
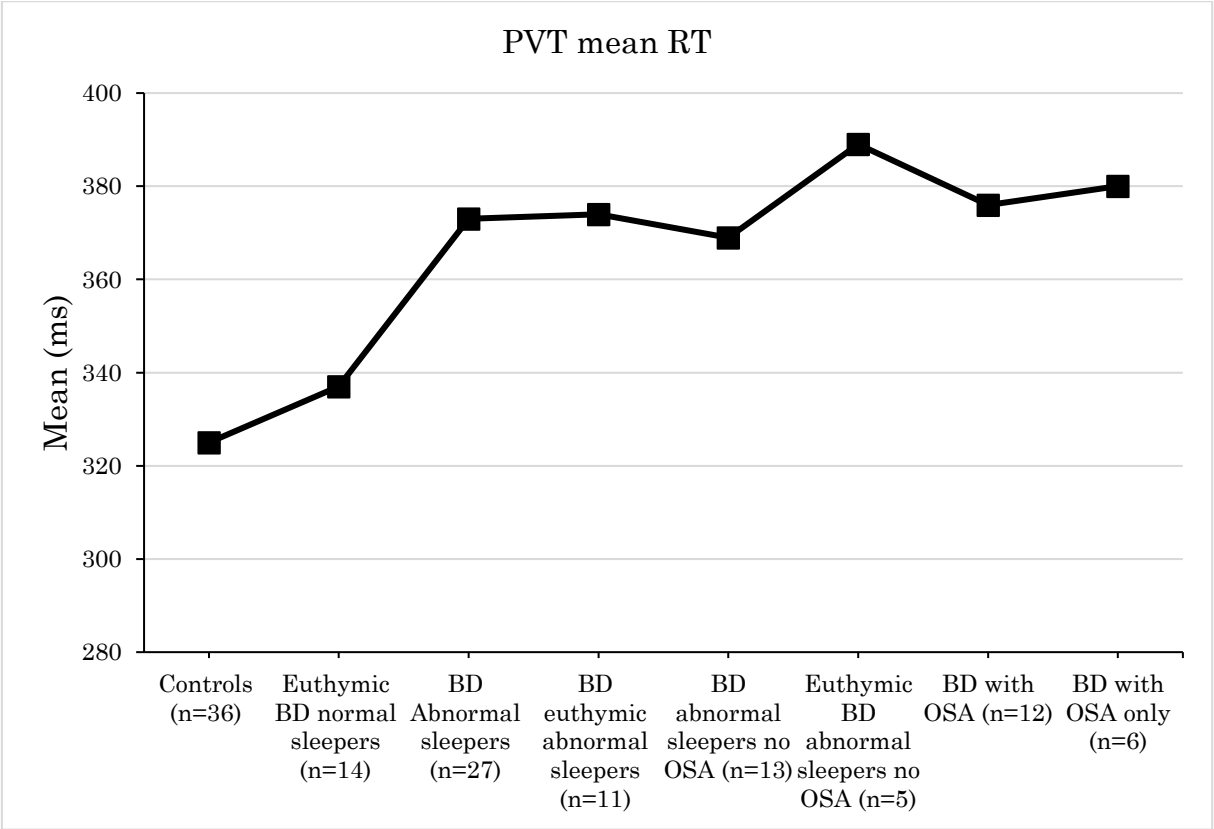


Figure 3.21 Mean RT and conflict RT on the ANT in abnormal sleepers with and without OSA



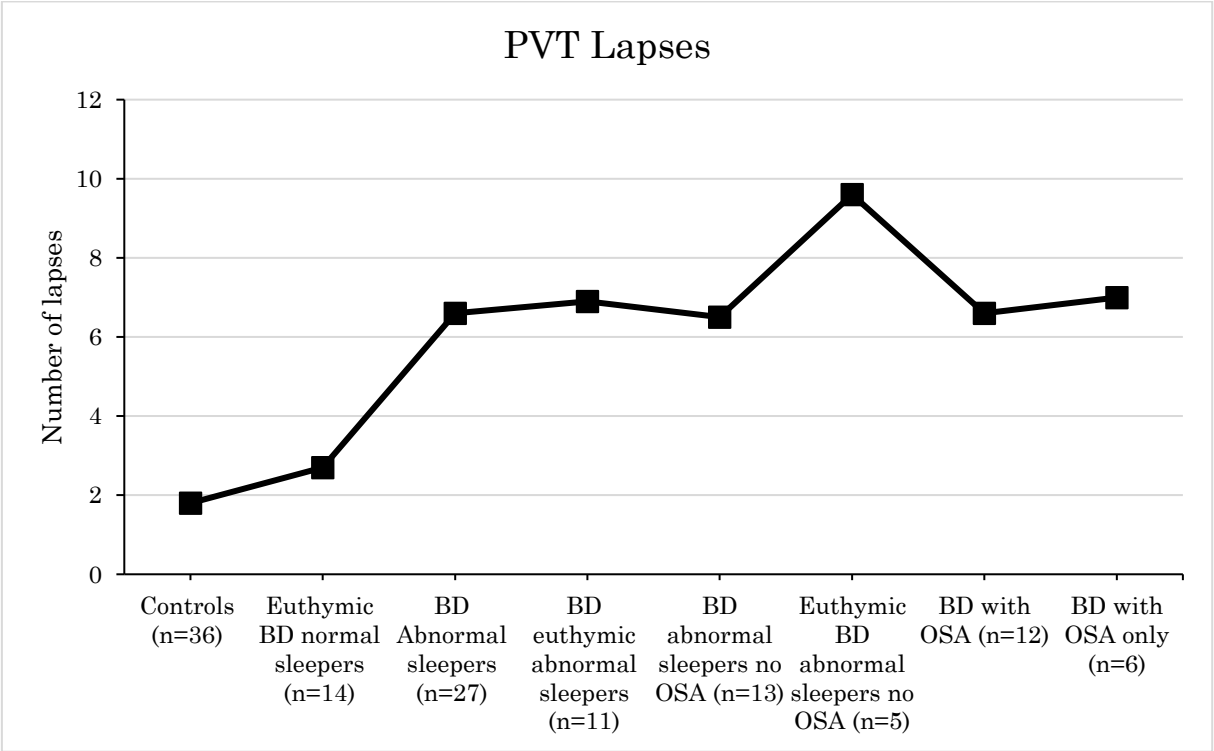
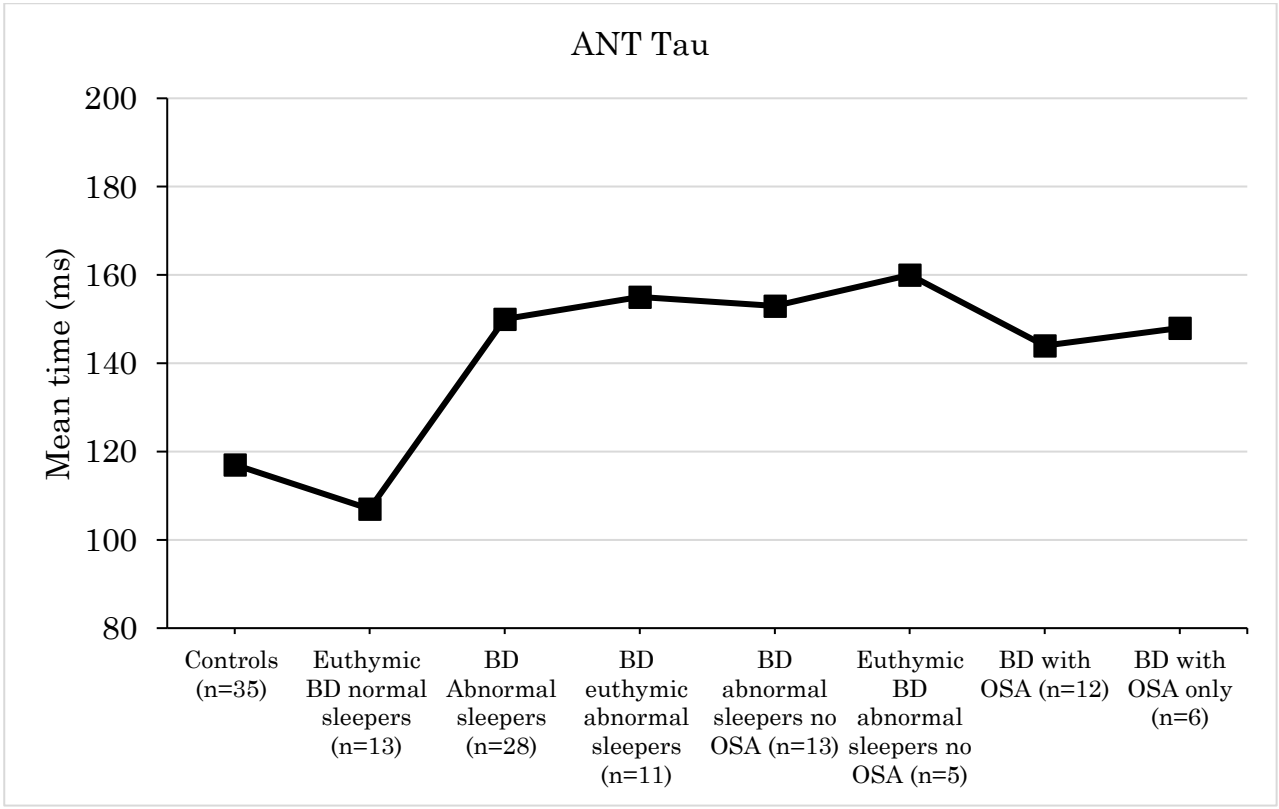


Figure 3.22 Mean PVT RT and number of lapses in abnormal BD sleepers with and without OSA



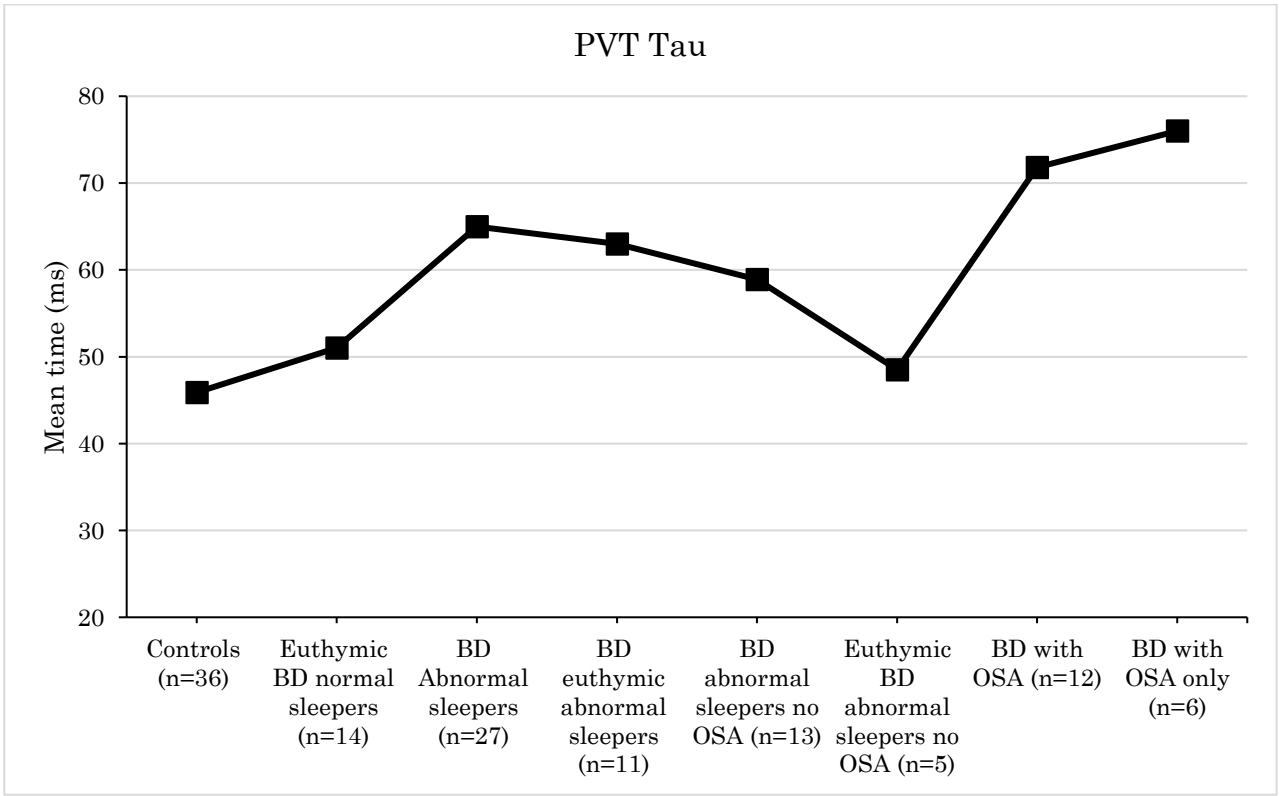


Figure 3.23 ANT and PVT tau in abnormal BD sleepers with and without OSA

with OSA but otherwise normal sleep, (the BD with OSA only group) had similar performance to the total BD group with OSA 50% of whom had additional sleep abnormalities there was no evidence of an additive effect of OSA + other sleep abnormalities on cognitive function. Performance on the DSST was also consistent in all abnormal BD sleepers and did not appear to be influenced by the presence or absence of OSA (Figure 3.24).

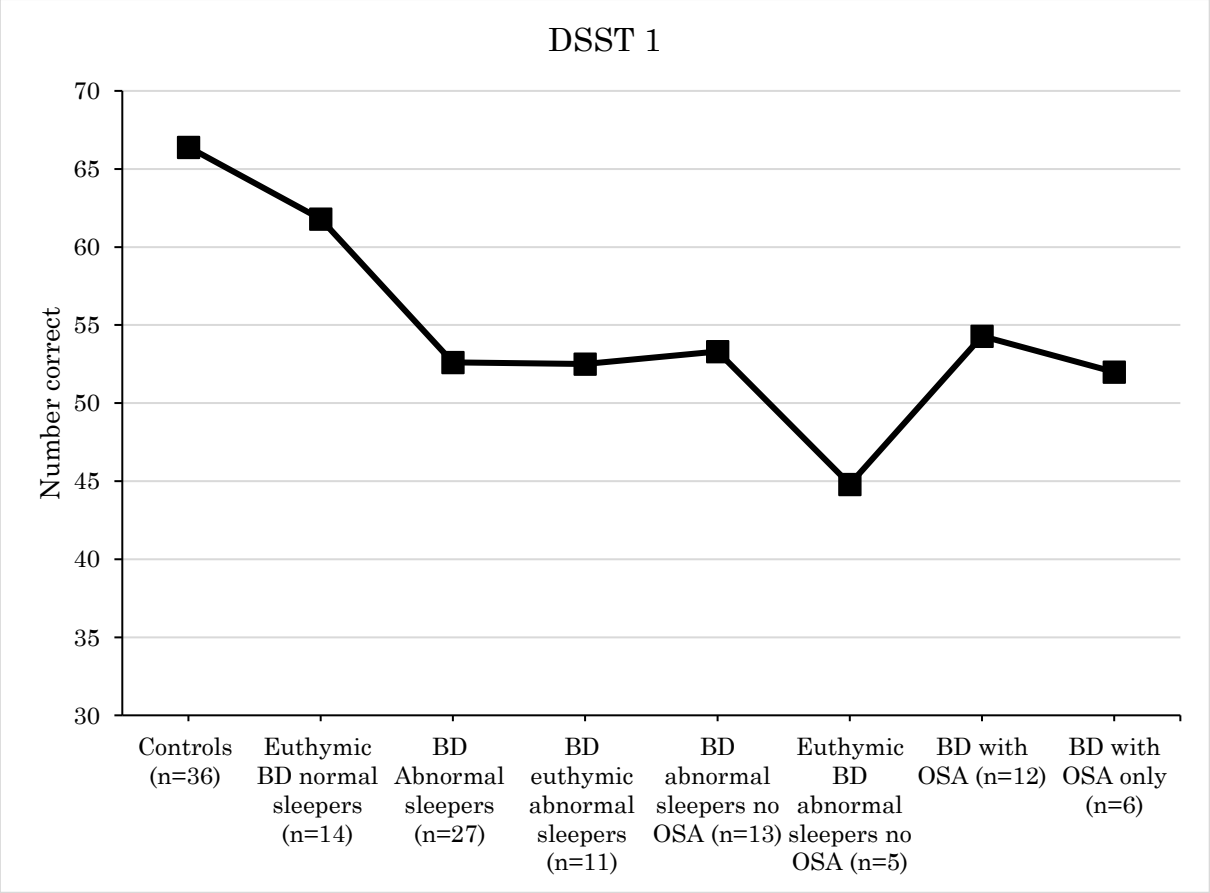


Figure 3.24 DSST performance in BD abnormal sleepers with and without OSA

3.13.11 Cognitive performance in objectively and subjectively defined abnormal sleepers.

In order to test the hypothesis that objectively defined abnormal sleepers would have worse cognitive performance than those with only subjectively defined sleep

abnormalities a comparison was made between objective normal/subjective abnormal and all objective abnormal BD sleepers in performance on the three cognitive tests most impaired in the BD subgroups the DSST, ANT and PVT. For the ANT and PVT only the mean RT, and mean RT tau were compared and additionally for the ANT conflict RT. The results of these comparisons can be found in Table 3-35. Objectively defined abnormal sleepers performed numerically worse on all variables assessed but the difference only reached statistical significance for the PVT and ANT mean RT and ANT RT τ. After controlling for age only the difference in ANT τ remained statistically significant but the differences in mean ANT and PVT trended towards significance.

Table 3-35 Performance on the DSST, ANT and PVT in objectively and subjectively defined abnormal BD sleepers

Data are means and SD	Objective normal/Subjective abnormal (n=10)	All objective abnormal (n=28)	t(df)	p	ANCOVA
DSST 1	58 (13)	53 (12)	-1.165 (36)	0.252	
DSST 2	60 (16)	54 (14)	-1.194 (36)	0.240	
PVT Mean RT	333 (40)	373 (49)	2.360 (36)	**0.024**	$F_{(1,34)} = 3.142$, p=0.085
PVT RT Tau	55 (29)	65 (21)	1.214 (36)	0.233	
ANT Mean RT	547 (75)	652 (102)	2.834 (35)	**0.008**	$F_{(1,34)} = 3.048$, p=0.09
ANT RT Tau	110 (34)	150 (30)	3.427 (35)	**0.002**	**$F_{(1,34)} = 6.843$, p=0.013**
ANT Conflict RT	133 (41)	169 (52)	1.917 (35)	0.063	

3.13.12 Correlations between accelerometry sleep variables and cognitive performance

As a further exploratory assessment of the association between sleep and cognitive function correlation analyses were performed to assess the relationship between the accelerometry variables and mean RT on the PVT in BD patients. Mean PVT RT was chosen as vigilant attention has been demonstrated to be the most sensitive cognition to the effects of sleep disruption, and mean RT was significantly slower in this study in abnormal sleepers. The Pearson's

correlations can be found in Table 3-36. Significant but weak correlations were found for PVT mean RT and nocturnal sleep + SIBD, SIBD and IV-SIBD. Although there was also a significant correlation with IV-sleep offset, on examination of the scatter plot this was influenced by a few outliers. Scatter plots of the significant correlations with mean PVT RT are shown in Figure 3.25.

Table 3-36 Correlation between PVT and ANT RT and accelerometry sleep variables

		TIB	IV-TIB	Noc sleep	IV-Noc sleep	Noc sleep + SIBD	SIBD	IV-SIBD	SE	IV-SE	IV-Sleep onset	IV-Sleep offset
PVT RT	$r_{(45)}$ p	.155 0.310	.114 0.457	.102 0.504	.179 0.240	.331 0.026	.377 0.011	.323 0.031	-.178 0.242	.183 0.229	.190 0.211	.356 0.017

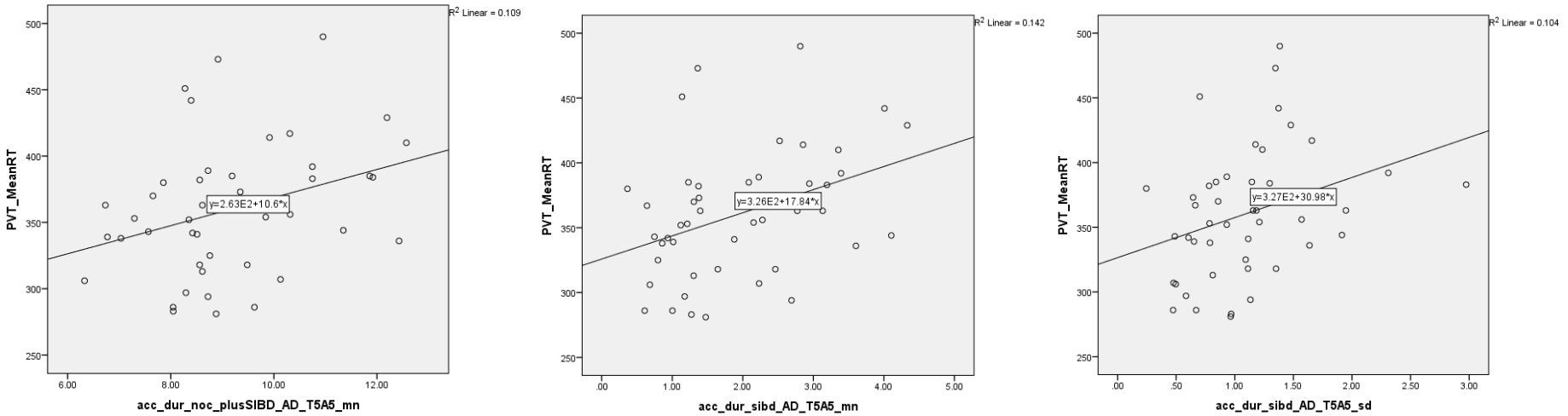


Figure 3.25 Scatter plots of significant correlations between PVT mean RT and accelerometry sleep variables

4. Chapter 4 - Discussion

4.1 Overview

In this study psychosocial function, QoL, biological/circadian rhythm and sleep function of 46 controls and 47 BD patients was assessed over 21 days. At the end of the sleep assessment period cognitive function was measured and associations between cognitive performance and sleep were explored. Firstly a summary of the main findings is presented followed by a discussion of the individual findings, how they relate to the existing literature and the implications for people with BD. The strengths and limitations of this study will then be discussed along with suggestions for future research. It should be noted that the control group consisted of participants without any sleep abnormalities and therefore comparisons between BD patients and controls should be interpreted in this context. The control group may therefore not be representative of the general population where sleep abnormalities are common. It is possible that these participants may also differ on additional unmeasured characteristics from the general population.

4.2 Summary of the main findings

4.2.1 Subjective sleep, biological rhythm, function and QoL assessments

Depressed and euthymic BD patients reported worse subjective sleep quality than controls with depressed patients reporting worse sleep than euthymic patients. Approximately one third of the BD patients reported clinically significant symptoms of insomnia. BD patients also reported greater a disturbance in subjectively assessed biological rhythm, function and QoL than controls with depressed BD patients having the worst outcomes in this respect. Psychosocial function was independently predicted by depressed mood and sleep quality. QoL was independently predicted by depressed mood, function and sleep

quality. These findings suggest that poor subjective sleep quality may play an important role in addition to that of depressed mood in poor function and QoL in BD.

4.2.2 Objectively assessed sleep and physical activity

BD patients had significantly greater accelerometry estimated length and variability in TIB, nocturnal sleep time, sustained daytime inactivity and lower SE than controls. BD patients had greater variability in sleep offset time. Depressed BD patients differed from controls on all variables except SE. Euthymic BD patients only differed from controls with a significantly lower SE. Depressed BD patients had a significantly longer nocturnal sleep duration than euthymic BD patients but did not differ significantly on any other variables. Both depressed and euthymic BD patients had lower levels of physical activity than controls.

A significantly greater proportion of BD patients (29%) than controls (9%) had an AHI > 5 indicating OSA. Accelerometry indicated 30.4% of BD patients were long sleepers, 26.1% had a CRD and 8.7% were short sleepers. A proportion of patients had multiple sleep abnormalities with several long and short sleepers also displaying characteristics of a CRD with or without OSA.

4.2.3 Mood, biological rhythm, function and QoL in objectively assessed normal and abnormal BD sleepers

Objectively defined normal and abnormal BD sleepers including those in euthymia had lower mood, worse sleep quality, psychosocial function and QoL and more disturbed biological rhythms than controls. Objectively defined

euthymic abnormal sleepers had greater biological rhythm disturbance and lower function and QoL than euthymic normal sleepers.

4.2.4 Cognitive function and its association with sleep

Abnormal BD sleepers including those in euthymia performed worse on tasks of attention than controls and euthymic normal sleepers. There was also greater intra-individual variability in RT in abnormal BD sleepers than controls and normal BD sleepers. A similar pattern of results was found for performance on the DSST which assesses processing speed. No evidence was found for an association between sleep abnormalities and performance on tests of task switching (TMT), working memory (digit span and NSWM). Deficits were found in BD patients compared to controls in short-term memory performance but there was little difference in performance between euthymic normal and abnormal BD sleepers.

4.2.4.1 Correlations between accelerometry sleep variables and cognitive performance

There were few statistically significant correlations between accelerometry sleep variables and cognitive performance in the BD group. Only nocturnal sleep + SIBD, mean SIBD and IV-SIBD had significant correlations with performance on PVT mean RT.

4.3 Discussion of subjective sleep quality, biological rhythm, psychosocial function and QoL.

I hypothesised that BD patients would have worse subjective sleep quality, psychosocial function and QoL and greater disruption in biological rhythm than controls. I also hypothesised that sleep quality and biological rhythm would be associated with psychosocial function and QoL. The results from this study support these hypotheses.

4.3.1 Subjective sleep

The finding of worse sleep quality in euthymic BD patients than controls is consistent with previous studies using the PSQI where between 40 and 83% of euthymic patients reported poor sleep quality (PSQI > 5) compared to 50% in this study (Harvey et al., 2005; Rocha et al., 2013; Geoffroy et al., 2014a; Karthick et al., 2015; Cretu et al., 2016). However, it should be noted that the BD sample in this study was not selected at random from the BD population and therefore may not be representative of the total BD population. As this is a sleep study it may have preferentially attracted BD patients who had sleep and circadian disturbances and inflated the numbers of participants with sleep complaints. In this study there was a strong correlation between sleep and mood and depressed BD patients had worse subjective sleep quality than euthymic patients. Significant symptoms of insomnia were also more commonly reported on the HAMD sleep items in depressed (48%) than euthymic (21%) patients. It should be noted though that the HAMD sleep items are neither a diagnostic, or validated tool for insomnia although they do provide an indicator of the prevalence of subjective insomnia complaints in the BD group. Previous studies found rates of insomnia meeting diagnostic criteria in euthymic BD patients of 14% (St-Amand

et al., 2013) and 55% (Harvey et al., 2005) and of 37% scoring above 7 on the ISI indicative of clinically significant insomnia symptoms (Gershon et al., 2012). Therefore the frequency of patients with significant insomnia symptoms in this study is within the previously reported range in euthymic patients. Several authors have proposed that there is a complex interplay between sleep and emotional regulation where night time sleep effects daytime mood and emotional reactivity and that daytime experiences, emotions and mood affect sleep (Harvey, 2008; Harvey et al., 2011; Gruber and Cassoff, 2014). This has led to a view that sleep disturbances may be a mechanism contributing to the onset and maintenance of mood disorders (Harvey, 2011). Although in this study there was a clear relationship between sleep and mood, due to its cross sectional nature it is unknown if the sleep problems proceeded the mood disturbance and had a causal role in mood changes or visa-versa. A longitudinal study where the temporal relationship between sleep and mood is assessed would provide further information on the relationship between sleep and mood and whether changes in sleep can predict changes in mood. One longitudinal study has demonstrated that large sleep and bed rest changes (> 3 hour change in sleep/bedrest) proceeded changes in mood by approximately one day (Bauer et al., 2006). This finding however does not demonstrate a causal role as the sleep changes could have just been prodromal symptoms of an upcoming mood change. To demonstrate a causal role for sleep disturbances in mood changes an interventional study would be required where sleep is manipulated and the effects on mood are then assessed. This could be through the inducement of sleep disturbances or SD in stable good sleeping BD patients and to assess any following changes in mood. This approach may however be difficult to justify for ethical reasons. An alternative

approach would be to examine the effects of treating sleep problems in a population of BD patients with significant sleep disturbances and then to assess the immediate effects on mood and longitudinally the number of future relapses. A group of BD patients with sleep problems who received no interventions to improve sleep would be a suitable control group.

4.3.2 Biological rhythm assessed on the BRIAN

This study provided evidence of greater disturbances of the biological rhythm in depressed and euthymic BD patients than in controls. Greater BRIAN scores in depressed and euthymic BD patients have been reported previously (Giglio et al., 2009b; Giglio et al., 2010; Duarte Faria et al., 2015; Pinho et al., 2015; Cudney et al., 2016; Iyer and Palaniappan, 2017; Mondin et al., 2017). BRIAN scores had strong correlations with depressed mood indicating that disturbed biological rhythms may be a causal factor in precipitating or maintaining mood episodes or a consequence of lowered mood in BD but longitudinal studies would be required to confirm this. That biological rhythm disturbance remains in euthymic patients however suggests that it may be a trait in BD patients and this study adds further evidence to support the view that biological rhythm disturbance is an integral part of BD (Harvey, 2008; Harvey, 2011). In addition, Duarte Faria et al. (2015) found that BD patients had higher BRIAN scores than patients with MDD even after adjusting for mood. Euthymic BD patients, but not remitted MDD patients also had greater BRAIN scores than controls. This suggests that BD patients have additional causes of biological rhythm disturbance in addition to mood disturbance and are different from unipolar patients.

4.3.3 Psychosocial function

The finding of reduced psychosocial function compared to controls in euthymic and depressed BD patients is consistent with previous studies utilising the FAST and supports the view that even during euthymia many BD patients do not return to full functional capacity (Rosa et al., 2010b; Rosa et al., 2010a; Pinho et al., 2015). The regression analysis found only depressed mood and sleep quality remained independent predictors of function demonstrating that sleep may be an important treatment target when trying to improve function in BD. This view is supported by the fact that euthymic objective abnormal sleepers had lower psychosocial function than controls and euthymic normal BD sleepers. A previous review found impaired function in euthymic BD was mainly related to subsyndromal symptoms and cognitive impairment (Tohen et al., 2003) but that review did not consider sleep as a potential influencer of function. Rosa et al (2009) found that older age, depressive symptoms, number of previous mixed episodes and previous hospitalisations independently predicted variance in FAST score in euthymic BD patients but they did not assess the effects of sleep or biological rhythm. Giglio et al. (2010) found that BRIAN score, depressive symptoms and age but not PSQI were independent predictors of FAST score in euthymic BD and a recent study that did not utilise the PSQI found BRIAN score and depressed mood were independent predictors of FAST in a mix of euthymic and symptomatic patients (Pinho et al., 2015). The regression analysis in the current study was performed in a mixed population of euthymic and depressed BD patients. The differences in findings from the Giglio et al. study maybe due to the fact their analysis was limited to euthymic BD patients and sleep disturbances may have been minimal (they do not report the mean PSQI score).

Pinho et al did not include PSQI assessed sleep in their regression model and without using PSQI score in the regression model the current study found a similar result. In the current study BRIAN score was only dropped from the regression model predicting FAST after the addition of both PSQI and BDI scores probably because of shared variance of BRIAN with both of these factors.

4.3.4 Quality of life

The lower QoL in euthymic and depressed BD patients in this study is consistent with the findings of a comprehensive review of QoL in BD (Michalak et al., 2005). In the current study QoL was significantly lower in depressed than euthymic patients and there was a strong correlation between depressed mood/anxiety, sleep quality, biological rhythms and QoL demonstrating that a multitude of factors may influence QoL. The regression model to predict QoL found that BDI, FAST and PSQI scores were independent predictors of QoL. This demonstrates an important role of sleep quality in QoL in BD and is supported by the fact that euthymic abnormal BD sleepers had lower QoL than both controls and euthymic normal BD sleepers. Sleep has also been associated with QoL in the general and non-psychiatric populations. For example excessively long sleep duration (> 9 hours) in adults had a negative association with QoL (Groeger et al., 2004) and sleep disordered breathing (SDB) has been associated with significant impairment across broad domains of QoL (Baldwin et al., 2001) Insomnia also severely impacts QoL across broad domains affecting both physical and psychological wellbeing (Ishak et al., 2012a). Few studies have examined the association between sleep and QoL in BD. In the STEP-BD study the Quality of Life Enjoyment and Satisfaction-Short Form (Q-LES-Q) was used to assess QoL in short (<6hours per night), long (>9hours per night) and normal (6.5-8.5 hours

per night) sleepers (Gruber et al., 2009). Short and long sleepers had poorer life satisfaction compared to normal sleepers, as indicated by both the overall satisfaction and total scores on the Q-LES-Q. One recent study examined the effect of depressed mood, BRIAN and PSQI scores on QoL in both depressed and euthymic BD patients (Cudney et al., 2016). Regression analysis found only BRIAN and depressed mood were independent predictors of QoL. PSQI was not an independent predictor of QoL in this study possibly because the sleep items on the BRIAN may account for the role of sleep disturbance in QoL. The results in the present study were therefore similar to this as in the present study BRIAN was only dropped from the regression model to predict QoL when FAST was added. FAST was not included in the Cudney et al. study.

4.4 Discussion of the objective sleep and physical activity assessments

4.4.1 Obstructive sleep apnoea

I hypothesised that BD patients would have a higher prevalence of OSA than controls and the results of this study support that hypothesis. Although only controls with no reported sleep problems were recruited four of those (9.1%) had an AHI > 5 including two with an AHI > 15 (moderate OSA) demonstrating that not all people who have OSA are aware they have this condition. The prevalence of OSA in the BD group was however 3 times that in controls (28.6%) although only 9.8% of the BD population had moderate OSA and none severe. A strength of this finding is that OSA was identified objectively with overnight respiratory sleep studies and a previous study in BD demonstrated the importance of objective testing as they found a poor positive and negative predictive value of screening with OSA questionnaires (Soreca et al., 2015). However, as the BD

sample in this study was not selected at random from the BD population it is possible that more patients with sleep problems enrolled for the study who may therefore have biased the sample increasing the prevalence of OSA in this study. The prevalence of OSA found in this study is however comparable to previous studies in BD which used objective screening, 21% (Kelly et al., 2013) and 39% (Soreca et al., 2015) and a recent meta-analysis reported a prevalence of 24% in BD (Stubbs et al., 2016). The finding of an increased prevalence of OSA in BD patients is important as OSA is associated with consequences such as daytime fatigue, sleepiness, impaired cognitive function, social interaction and QoL and increased risk of metabolic syndrome and cardiovascular disease. These consequences are common in people with BD and it is possible that OSA plays a direct role in their development in BD populations. In this study BD patients with OSA had significantly worse psychosocial function than those without OSA. This demonstrates that even mild OSA as seen in this population there are important clinical consequences. The reduced function may have been related to a number of factors. In this study nearly 50% of BD patients with OSA were objectively rated as long sleepers which may have been related to fragmented night time sleep resulting in daytime fatigue and sleepiness and prolonged daytime rest. Indeed, there was a significant correlation between AHI and ESS which supports this hypothesis. The ESS was also significantly greater in the BD patients with OSA although it was still below 10 so considered in the normal range. That it was still in the normal range mage be related to the fact the majority of BD patients only had mild OSA. In addition, it is possible that undiagnosed OSA may lead to misdiagnosis of other sleep disorders such as insomnia and inappropriate prescription of hypnotics. Three of the OSA patients

in this study were prescribed hypnotics and these patients had a longer mean nocturnal sleep duration (8.9 v. 7.7 h) and 24-h sleep duration (11.3 v. 9.7 h) than those not prescribed hypnotics which may therefore have contributed to the longer sleep durations. Another important observation in this study was that a greater proportion of patients with OSA had a history of suicide attempt. There is a greater prevalence of depression in OSA populations which has been linked to hypoxaemia and increased inflammatory cytokines found in people with OSA (Harris et al., 2009). It is possible that the BD patients with OSA in this study have experienced more severe depressive episodes than those without OSA due to these factors which may have led to a greater risk of suicide. There was no significant difference in the depressive symptoms between BD patients with and without OSA in this study. However as this study only measured mood at the time of the study it is not possible to say if those with OSA suffer a greater severity of depressive symptoms when they relapse. Increased suicidal ideation and suicide attempts has been reported in patients from the general population with OSA. Choi et al. (2015) found a prevalence of suicidal ideation in a cohort of 117 consecutively untreated OSA patients in a sleep disorder clinic of 20.5% with 42% of these having attempted suicide. Mean BDI scores in this sample were 9.7 (SD 8.4). The severity of insomnia symptoms, lower mood and dysfunctional beliefs about sleep were associated with suicidal ideation and the relationship between suicidal ideation and insomnia symptoms remained significant after controlling for mood symptoms. In the present study the mean score on the HAMD sleep items was 1.42 (SD 1.7) which is not especially high but as this study is cross sectional it can only report insomnia symptoms at the time of the study. It is possible that insomnia symptoms fluctuate longitudinally and may

contribute to suicidal ideation during periods when they are worse. A recent study has also found a strong association between OSA and suicidal ideation in post-traumatic stress disorder (PTSD) (Gupta and Jarosz, 2018). In this study the severity of OSA was directly associated with suicidal ideation and mood was found to be a mediator. Hypoxaemia was only found to be related to suicidal ideation in those with severe OSA. In patients with moderate or mild OSA only depressive symptoms were related to suicidal ideation. The association of OSA with depressive symptoms and suicidal ideation suggests that this should be an important treatment target in BD patients. Currently however studies show variable outcomes on depressive symptoms when treating OSA with CPAP with some showing improvements in depression whilst others do not (Harris et al., 2009).

In this study there was a weak association between AHI and BMI in BD patients ($r=0.332$) but although mean BMI or the proportion with a BMI $\geq$ 30 kg/m^2 were greater they did not differ significantly between those with and without OSA. Increased obesity is a recognised risk factor for OSA in the general population (Young et al., 2004) and psychiatric patients (Stubbs et al., 2016) and it is possible that the increased rates of obesity in the BD population may have been one cause of the increased prevalence of OSA. There is also likely a role of medication in the increased prevalence of OSA in psychiatric patients. Psychotropic medications such as benzodiazepines may worsen OSA through respiratory depression and oropharyngeal muscle relaxation and antipsychotics may increase the risk of developing OSA through weight gain and their effects on the serotonin system which is important in the regulation of central respiratory drive airway diameter and resistance (Shirani et al., 2011). Indeed both obesity

and long term neuroleptic use have previously been found to be independent risk factors for OSA in psychiatric patients (Winkelman, 2001; Khazaie et al., 2017). In this study there did not appear to be an association between medication use and OSA as there was no excess of any particular medication group in the BD patients with OSA. However as this study is cross sectional an association cannot be ruled out as previous medication use may have led to weight gain and the development of OSA in this group.

4.4.2 Accelerometry variables

I hypothesised that BD patients would have longer TST (nocturnal sleep), lower SE and more variable sleep than controls when assessed with accelerometry and the results of this study partially support this hypothesis. The results of the overall BD group and depressed BD population are in keeping with the hypothesis but not that for the euthymic BD patients who did not differ from controls in TST or sleep variability.

4.4.2.1 Accelerometry variables in euthymic BD

The lack of differences between euthymic BD patients and controls in this study is not consistent with the three meta-analyses of accelerometry studies in euthymic BD patients which all found a longer TST with SMDs ranging 0.57 to 0.65 (Geoffroy et al., 2014b; Ng et al., 2015; De Crescenzo et al., 2017). There was however moderate heterogeneity in the findings of individual studies included in the meta-analyses (e.g. $I^2 = 44\%$ in Geoffroy et al., 2014) and several of the individual studies also found no significant differences in TST so the finding here is not an isolated finding. In the present study the differences between euthymic BD patients and controls were in the same direction as the meta-analyses and it

could be that this study was underpowered to demonstrate statistically significant differences between euthymic patients and controls. In addition, although these meta-analyses are reported to be in euthymic BD patients some of the included studies with the largest SMDs in TST between BD and controls did not used strict methods for defining euthymia. In one study patients were classed as euthymic based on clinician opinion rather than rating scales, (Millar et al.,2004), and others used higher than conventional scores for HAMD defined remission (Salvator et al., 2008; Ritter et al., (2012). Therefore further studies in more strictly defined euthymic patients are required before firm conclusions can be drawn about sleep in euthymic BD. A further reason to be cautious about the conclusions from the meta-analyses is that presently there are relatively few accelerometry studies in euthymic BD patients and current studies are small in sample size. For example in the meta-analysis reported by Geoffroy et al. (2014b) only 9 studies with a median sample size of 40 participants (range 27-68) including 202 euthymic BD patients and 210 controls were analysed meaning that the reported estimates are likely imprecise.

The finding of lower SE in euthymic patients in this study is consistent with two of the meta-analyses (Geoffroy et al., 2014c; De Crescenzo et al., 2017) but not with that reported by Ng et al. (2015) who reported no difference in SE. This analysis however included an additional study than the other analyses with a significantly greater SE in the BD group compared to controls.

The present study did not find evidence of increased variability in sleep in euthymic BD patients which is not consistent with the only meta-analysis that reported this variable (Ng et al., 2015). However in two, (Millar et al., 2004;

Jones et al., 2005), of the three studies used to calculate variability in the meta-analysis euthymia was not strictly defined so this finding needs confirming in more strictly defined euthymic patients.

Several other accelerometry related factors may explain differences in findings between studies. The present study is the first study in BD to utilise the GENEActiv accelerometer and the GGIR algorithm with the majority of the other studies using Actiwatch devices and algorithms. Differences in sleep estimates between devices may have contributed to the different findings. Although this could be seen as a weakness of this study when comparing to previous studies the GENEActiv device was chosen with future studies in mind for the reasons previously described including recording in SI units that can be more readily compared between different devices. It is hoped that studies such as this one will encourage future researchers to utilise devices recording in SI units and then future data sets can be pooled into a single analysis which may produce more accurate estimates of sleep variables. A further factor that may influence study findings are the differing lengths of recording periods of included studies. As sleep is variable in BD longer recording periods may give a more accurate estimate of sleep variables. There is a wide variance of recording length in currently available studies ranging from 3 to 54 days which likely contributes to between study outcomes. A strength of the current study is that it used 21 days of recording which is longer than all but 2 of the studies included in the meta-analyses.

Other factors that may account for variability between studies include gender, age, the proportion of BDI and BDII participants and medication use in the

populations studied. Sleep characteristics vary across age groups in the general population (Hirshkowitz et al., 2015) and may in BD. The mean age of BD patients in the studies included in the meta-analyses ranged from 33 to 54 years so could count for some of the variability between study findings. Geoffroy et al. (2014b) reported larger standard mean differences (SMD) in sleep variables between BD and controls in studies with a larger age difference. The current studies also include different proportions of participants with BD I and BDII. The present study differed from others as it had a greater proportion of BDII than BDI patients whereas previous studies either only included BDI participants or a majority of BD I participants. There may be differences in the sleep of BDI and BDII patients which could account for different findings between studies. Differences in medication use e.g. hypnotics, between BD populations may have contributed to between study variance. In BD many patients take combination treatments and variable dosing schedules so it is difficult to evaluate the role of medication in sleep and none of the meta-analyses were able to explore the effects of medication use. Hypnotic use varied between 0% and 78% in studies and in the present study was 19.1% so there was a large variability. Finally there may be other unmeasured confounders of sleep in the BD populations such as length of illness, number of previous episodes and other AXIS I co-morbidities.

4.4.2.2 Accelerometry variables in depressed patients

In depressed BD patients the results from this study demonstrated several differences from controls including significantly longer TIB and TST and greater variability in TIB, TST, sleep onset and offset times and SE. In addition, TST was significantly longer than in euthymic BD patients. In the only other accelerometry study in depressed BD patients I am aware of Robillard et al.

(2013a) reported similar findings to this study of longer TIB and TST over 7 nights of accelerometry although the mean age of BD participants was 23 years compared with 46 years in this study. There are several reasons why depressed patients may have increased TIB and TST. During depressive episodes patients may experience a lack of energy, increased fatigue and decreased motivation and therefore choose to spend more TIB and sleep for longer. Poorer sleep quality and higher rates of insomnia and OSA in depressed patients as in this study may increase tiredness resulting in longer TIB and increased opportunity to sleep. In the present study depressed BD patients reported higher ESS scores indicating greater daytime sleepiness although they were still within the normal range. An alternative explanation for longer TST in depressed BD patients is that it is overestimated by accelerometry due to the difficulty in distinguishing between actual sleep and restful wakefulness. It is possible that depressed patients simply rested more without actually taking more sleep. Another possible explanation for longer TIB and TST time is that fewer of the depressed BD patients were in current employment than controls. This may simply mean unemployed patients without a need to rise at a specific time for work simply had more time to spend in bed, sleeping or resting.

Increased variability in all accelerometry sleep variables compared to controls was also a feature of sleep in the depressed BD patients. Increased variability in the sleep wake cycle was not assessed in all the previous accelerometry studies but in those that assessed variability, greater variability was generally reported (Millar et al., 2004; Jones et al., 2005; Gershon et al., 2012). The increased variability of the sleep wake cycle suggests instability of circadian rhythms. This view is supported by the fact that BRIAN scores increased incrementally from

controls, to euthymic and depressed BD patients and that BRIAN scores correlated with the variability in accelerometry assessed wake times (Spearman's $r_{(46)} = 0.343$ ($p=0.019$)), TIB ($r_{(46)} = 0.427$ ($p=0.003$)), TST ($r_{(46)} = 0.410$ ($p=0.005$)) and SE ($r_{(46)} = 0.376$ ($p=0.01$)) in BD patients. There are several possible reasons for increased variability in sleep in BD patients. Normally the sleep wake cycle is driven by and coupled to the circadian clock which is entrained by environmental zeitgebers. However the timing of the circadian system is driven by regular exposure to environmental zeitgebers and the regularity of exposures may change in BD patients particularly when they experience a mood episode. For example, the strongest zeitgeber is light and dark exposure. BD patients may have a different pattern of light exposure than healthy controls perhaps due to spending longer TIB or a result of unemployment and related changes in social behaviour. This could then influence the circadian clock resulting is less stability in the rhythm and further behavioural changes which then result in less regular exposure to other zeitgebers such as eating patterns and physical activity. Collectively these behavioural changes may self-perpetuate and contribute to and maintain a weakened or variable biological circadian rhythm. Finally, a further reason for greater variability in the sleep wake cycle may simply be due to measurement error. As the sleep of BD patients is more disrupted than in controls it is possible that accelerometry is less accurate in assessing the transition between sleep and wake periods than it is in controls and this results in greater variability in the estimates.

4.4.2.3 Accelerometry estimated physical activity

I hypothesised that BD patients would have lower levels of physical activity than controls and this study found that both depressed and euthymic BD patients had

lower physical activity levels than controls supporting this hypothesis. Several previous accelerometry studies also found lower levels of physical activity in euthymic BD patients than controls (Harvey et al., 2005; Jones et al., 2005; Salvatore et al., 2008; St-Amand et al., 2013; Janney et al., 2014) but not McGlinchey et al. (2014). There are several possible explanations for lower physical activity in BD. Depressive symptoms, poor sleep quality and primary sleep disorders such as OSA may induce fatigue and lack of motivation to exercise. A review has also found evidence that lower physical activity in BD is associated with social isolation, lower educational achievement and medical comorbidities (Vancampfort et al., 2013). Sylvia et al. (2013) reported that less frequent weekly activity was associated with greater severity of and more time with depressed mood in BD and a systematic review found that increased physical activity was associated with less depression and better function and QoL (Melo et al., 2016). However, in the present study physical activity levels were similar in depressed and euthymic BD patients suggesting low physical activity levels are more of a trait rather than related to levels of depression. It is possible that physical activity levels drop during depressive episodes and never recover to premorbid levels despite recovery from depression. Several lines of evidence demonstrate that sleep abnormalities including insomnia and SDB in adults are associated with lower levels of physical activity (Kline, 2014). In euthymic BD patients an accelerometry study found that for each standard deviation increase in sleep disturbance, (total wake time), there was a 3% decrease in next day physical activity and that increased activity led to sleep improvements in BD patients with the worst sleep disturbances (McGlinchey et al., 2014). On examination of the data in the present study, physical activity levels were

numerically lower in objectively identified abnormal sleepers than normal sleepers, so supportive of a role of poor sleep, but none of the differences reached conventional levels of statistical significance. It is possible that the association between sleep and physical activity is bidirectional with poor sleep leading to less physical activity which in turn reinforces poor sleep habits and quality. A longitudinal study is required to test this hypothesis. Finally sedative medications may reduce physical activity levels. One study reported that adolescents treated with antipsychotics performed less physical activity than mentally ill antipsychotic naïve adolescents (Vancampfort et al., 2016). However in the present study BD patients prescribed antipsychotics actually performed significantly more physical activity than those not prescribed antipsychotics so this finding does not support a role of antipsychotic medication in lower levels of physical activity. There were no differences in physical activity levels in those taking hypnotics or not.

Sleep and exercise are proposed to have a bidirectional relationship with poor sleep reducing a person's capacity for exercise and physical activity being associated with better sleep quality (Kline, 2014; Chennaoui et al., 2015).This suggests that increasing exercise and physical activity may be a potential intervention to improve sleep performance in BD. A meta-analysis has demonstrated that acute and chronic exercise can increase SWS and reduce SOL, WASO and REM sleep in the general population (Kubitz et al., 1996). There is also evidence that moderate aerobic exercise may improve some aspects of insomnia. For example Reid et al (2010) found that moderate aerobic physical activity along with sleep hygiene education improved sleep quality assessed with the PSQI, SOL, TST, daytime dysfunction and SE in adults with chronic

insomnia. Interestingly there were also improvements in depressive symptoms, reductions in daytime sleepiness and improvements in vitality. Improvements in the severity of insomnia and reduced depression and anxiety have also been demonstrated in a group of insomnia patients who increased their activity levels to the minimum level in public health guidelines (Hartescu et al., 2015). Greater levels of physical activity are also associated with a decreased incidence of OSA (Awad et al., 2012). Moderate physical activity and resistance training for 150 minutes per week for a 12 week period has been demonstrated to significantly improve the AHI in sedentary overweight adults with OSA independently of its effects on BMI (Kline et al., 2011). Given both insomnia and OSA are common in BD these data are encouraging and suggest that increasing physical activity levels may be beneficial in BD. One study in BD patients demonstrated that increased physical activity was associated with improved sleep by decreasing TWT for patients with moderately disturbed sleep (McGlinchey et al., 2014). However further work is required to assess the practicality of increasing and sustaining physical activity in clinical BD populations and the longer term effects on sleep performance.

4.4.2.4 Accelerometry defined sleep phenotypes

I hypothesised there would be a greater number of BD patients with abnormal sleep phenotypes including long sleepers, short sleepers and those with a CRD than in the control group. The results of this study partially support that view in that there were greater numbers of long and CRD sleepers but not short sleepers. The finding that approximately 50% of the BD group were abnormal sleepers should not however be taken as an estimate of the prevalence of sleep abnormalities since the BD population in this study was not selected at random

from the wider BD population. The differences with controls should also be interpreted in the context that controls with known sleep problems were excluded from the study. Therefore these findings should be viewed as providing an indication of the types of sleep abnormalities that are present in this BD population. Regarding a potential role of medication in sleep abnormalities more abnormal sleepers were prescribed non-lithium mood stabilisers than normal sleepers. However, as this study is cross sectional it is not possible to know if sleep abnormalities developed following mood stabiliser initiation or if mood stabilisers were prescribed as part of the treatment of sleep abnormalities. However mood stabilisers have not been reported to cause significant sleep disturbances so it is unlikely they were a cause of the sleep abnormalities. The abnormal sleepers had lower mood and function and greater biological rhythm disturbance than normal sleepers and it is possible that the greater degree of mood stabiliser prescribing in this group simply reflects an attempt to treat these patients more aggressively.

4.4.2.4.1 Long sleepers

Long sleepers in this study were defined as having a mean of > 10 hours sleep per 24 hours over the assessment period which includes both nocturnal and daytime sleep periods i.e. nocturnal sleep + SIBD and 30.4% of the BD patients compared to 4.8% of controls met this criteria. However considering accelerometry has poor specificity for correctly identifying daytime sleep from periods of quiet restfulness this group should be viewed conservatively as having a mean of > 10 hours of sustained inactivity of similar characteristics to sleep as some of this time could just be restful wake periods. A question arises as to if this group represent patients with hypersomnia and as discussed in the literature review Kaplan and

Harvey (2009) proposed that psychiatric hypersomnia may be better defined as long TIB rather than long TST. The data in this study conform to that view as only 3/14 of the long sleepers had nocturnal sleep periods > 9 hours, but 14/14 spent > 10 hours TIB + SIBD and 9/14 spent > 12 hours TIB + SIBD. Although as previously stated this is not a prevalence study the 30% of BD patients identified with long sleep is within the reported range of 17 to 78% of depressed BD patients with reported hypersomnia (Kaplan and Harvey, 2009) and similar to the 25% reported in euthymic BD patients (Kaplan et al., 2011). One possible reason for long sleep in this study was that nearly 50% of the long sleepers had an AHI > 5. OSA fragments sleep leading to daytime sleepiness and sedentary behaviour and may have led to long sleep defined in this study. Indeed 3/5 of the long sleepers with OSA reported a baseline ESS $\geq$ 10. A role of medication in this group also cannot be discounted as the long sleepers were significantly more likely to be prescribed hypnotics than those without long sleep. As this study is cross sectional it is not possible to tell if hypnotic use had a direct rule in inducing long sleep but it would seem counter intuitive to prescribe a hypnotic to a patient with pre-existing long sleep. It is possible that hypnotics may have increased both night-time sleep and daytime drowsiness resulting in long sleep by the definition used in this study. The long sleepers in this study actually had numerically greater HAMD sleep scores than non-long sleepers (2.7 vs. 1.9) and it is possible that hypnotics were prescribed more frequently in an attempt to treat insomnia symptoms. Two of the long sleeping patients prescribed hypnotics also had OSA. It is possible that these patients with OSA reported sleep disturbances and the hypnotics were prescribed in an attempt to alleviate the sleep disturbances without the physician knowing the patient suffered from OSA.

This highlights the need to diagnose OSA in BD patients as hypnotic prescription in OSA is inappropriate and may worsen the disorder.

4.4.2.4.2 Circadian rhythm disorders

Twenty-six percent of BD patients met criteria for a CRD in contrast to 9.5% of controls. Similar numbers of BD patients and controls had advanced (2.1 vs. 2.3%) or delayed sleep phase (6.5% vs. 7.1%) but non 24-hour sleep wake rhythm and irregular sleep/wake rhythms only occurred in the BD group. In previous BD studies higher rates of delayed sleep phase have been reported. Robillard et al. (2013a) reported a prevalence of 62 %, (accelerometry confirmed sleep onset > 1.30am), in young depressed BD patients; Steinan et al. (2016) reported a prevalence of 10% in BD patients with current sleep problems defined using clinical interview and symptom rating scales and Takaesu et al.(2016) diagnosed 26% of euthymic BD patients presenting consecutively at an outpatients clinic with delayed sleep phase based on a clinical interview and sleep logs according to the ICSD-3. However, the mean age in the Robillard et al study was just 23.2 years and the other two studies both found an association of delayed sleep phase with younger age. The lower prevalence in the present study maybe therefore be due to the older age group studied as only five BD participants were aged under 30 years. The mean age of those with delayed sleep phase in this study was 44 years, (range 37-49). It is possible that delayed sleep phase is more common in younger BD patients and that it persists in some patients as they age. Some evidence also suggests that delayed sleep phase may proceed the development of non-24-hour sleep wake rhythms (Uchiyama and Lockley, 2015). Four BD patients met these criteria in this study but as it is cross sectional it is unknown if they previously had a delayed sleep phase.

Regarding the other CRD's in Takaesu et al's (2016) cohort 6% were diagnosed with a non-24-hour sleep wake disorder and 2% irregular sleep/wake rhythm disorder both phenotypes identified in the present study. I am not aware of any other studies that have assessed the prevalence of CRDs in BD patients.

4.4.2.4.3 Short sleepers

Only four BD patients in this study met the criteria for short sleep, (compared to two controls) and two of these also had a CRD. Short sleep may represent a normal sleep phenotype if it is not accompanied by complaints of sleep difficulties or daytime dysfunction (American Academy of Sleep Medicine, 2014) but 3/4 patients had a PSQI score $\geq$ 5 indicating they had subjective poor sleep quality. Short sleep is associated with insomnia (American Academy of Sleep Medicine, 2014), but only one of the BD short sleepers scored >3 on the HAMD sleep items indicating significant insomnia symptoms. Overall 25% of the BD patients scored > 3 on the HAMD sleep items indicating clinically significant insomnia symptoms indicating that in this cohort insomnia symptoms are not associated with the short sleep definition. There are two possible explanations for this. It is possible that despite suffering from insomnia symptoms BD patients may have been be able to sleep > 6 hours per night by prolonging TIB. It is also possible that accelerometry overestimated the TST in this patient group due to the difficulty in detecting transitions between sleep and wake and sleep from restful wakefulness. I am not aware of any other study reporting the numbers of objectively identified short sleepers within BD populations however the literature review found that previous studies reported rates of insomnia ranging 14-55% of subjects although none of these used objective measures to confirm these diagnoses.

4.4.2.4.4 The presence of multiple sleep abnormalities

It is worthy of note that some patients met criteria for a number of sleep phenotypes (Figure 3.8). It is possible that having one sleep abnormality may lead to the development of another. For example, the presence of OSA resulting in poor sleep quality and daytime sleepiness may lead to long 24-hour sleep as patients try and catch up on sleep by spending more TIB or taking daytime naps. This in turn could lead to behavioural changes, perhaps expressed as increased biological rhythm disturbance which then alters exposure to zeitgebers and consequently leads to a CRD. This hypothesis could explain the fact that significant numbers of patients had overlapping sleep abnormalities but would require to be tested in longitudinal studies from first BD onset or even the BD prodrome to observe how the sleep phenotype merges over time.

4.5 Discussion of the relationship between objective and subjective sleep assessment

The results of this study demonstrated that the majority of patients with objective sleep abnormalities also subjectively rated their sleep as of poor quality (PSQI > 5). However there was also some disagreement between subjective and objective evidence of sleep abnormalities (Figure 3.10). There are several possible explanations for this. As accelerometry is a poor discriminator of transitions between sleep and wake and correctly identifying periods of wake from restful wakefulness it may have underestimated sleep disruption and periods of wake during the night, incorrectly classifying them as sleep. Alternatively patients with sleep disorders such as insomnia and patients with BD have been demonstrated to misconceive their sleep. They often overestimate the length of SOL and number of night time awakenings (Harvey et al., 2005) and so may

subjectively rate their sleep worse than the objective measures demonstrate. Finally, medications or medical co-morbidities that cause daytime sleepiness and fatigue may lead people to inappropriately believe that those symptoms were down to poor sleep and so subjectively rate their sleep worse than it actually is.

Conversely some patients, (n=8), with objective evidence of sleep abnormalities subjectively rated their sleep as normal (PSQI < 5). This may be due to the definitions of sleep abnormalities used in this study. As there is natural variation in sleep length and timing in the general population some patients with for example long/short/delayed/advanced sleep may still have experienced and rated their sleep as of good quality. In this study, three of those with abnormal objective but normal subjective sleep were short sleepers, two long sleepers and one phase advance sleeper and may have regarded their sleep as of sufficient quality. Three subjects with objective abnormalities, one irregular CRD sleeper, one CRD NOS and one with OSA (AHI 14.2) may have been expected to rate their sleep quality as poor. That they did not demonstrates the differences in how people subjectively rate their sleep. These differences demonstrate that it is important to use both objective and subjective assessments of sleep as they provide different information about sleep function.

4.6 Discussion of the relationship between objective sleep abnormalities, mood, function and QoL.

An important finding in this study was that euthymic BD patients with objective sleep abnormalities had worse function and QoL and greater biological rhythm disturbance than controls and euthymic normal BD sleepers. The effect size compared to controls was large. Subjective sleep quality was not different

between euthymic normal and abnormal sleepers and therefore this demonstrates that objective sleep abnormalities are associated with poor clinical outcomes independently of mood and subjective sleep quality. To my knowledge this is the first study to demonstrate an association between objectively defined sleep abnormalities, function and QoL independently from mood. This finding suggests that objective sleep abnormalities are an important treatment target as it is possible that normalising objective sleep abnormalities may improve clinical outcomes in BD. Further evidence to support this view comes from the fact that function and QoL were numerically lowest in BD patients that had three objective sleep abnormalities (long + CRD + OSA). This suggests there may be an additive negative effect of multiple sleep abnormalities. However, this conclusion must be taken with extreme caution given the very small numbers in each group and studies with larger sample sizes will be needed to confirm this.

In addition to the fact that objective sleep abnormalities had an independent association with clinical outcomes the data also suggested that there is an additive effect of having both objective and subjective sleep abnormalities on clinical outcomes. BD patients with both objectively and subjectively rated sleep abnormalities had significantly lower function and greater biological rhythm disturbance than patients with only either objective or subjectively assessed abnormal sleep. These differences also remained significant after controlling for BDI score. This suggests that the subjective feeling of poor sleep does still carry additional clinical burden.

4.7 Discussion of cognitive function and its association with sleep abnormalities.

4.7.1 Discussion of performance on attentional tasks and the evidence of an association of sleep abnormalities

I hypothesised that patients with BD would perform worse in tests assessing attentional function than controls and that the worst performing BD patients would be those with the greatest sleep disturbances. The results of this study from the ANT and PVT support that hypothesis. However when interpreting these results it is important to remember that attention is not a single construct and the results from this study show deficits in various aspects of the attention network. At the basic level attention comprises the ability to achieve and maintain an alert state (Fernandez-Duque and Posner, 2001) and attend to the task in hand blocking out competing and distracting stimuli (Sturm and Willmes, 2001; Pilcher et al., 2007; Lim and Dinges, 2008). This aspect of attention is often termed simple or vigilant attention. The ability to sustain vigilant attention is crucial to all other aspects of cognitive function as without being able to maintain vigilance and prevent oneself becoming distracted performance on all other tasks would suffer. Vigilant attention is often assessed with simple RT tasks such as continuous performance tasks and the PVT. Two other networks make up the attention system, the orienting and the executive control networks (Posner and Petersen, 1990). The orienting network allows the selection of specific sensory information from multiple sensory inputs and can be reactive e.g. when something attracts your attention, or voluntary, e.g. when a subject searches for a target to attend to. The executive control network enables the ability to control behaviours in order to achieve intended goals, resolving conflict among

alternative responses and inputs from different brain areas e.g. impulse inhibition (Fan et al., 2009). The orienting and executive networks can both be assessed with the ANT whilst the PVT assesses vigilant attention and executive control. The brain networks involved in these different aspects of attention have been identified in fMRI studies (Lawrence et al., 2003; Fan et al., 2005) and may be differentially vulnerable to the effects of sleep abnormalities.

4.7.1.1 Vigilant attention and the association with sleep abnormalities

A deficit in vigilant attention was demonstrated in BD patients as mean RT was significantly slower in BD patients than controls on both the ANT and PVT suggesting patients were less able to sustain attention on the task. In the euthymic patients the difference in mean RT was only statistically significant on the PVT but it is likely that the lack of statistically significant difference on the ANT was down to a lack of statistical power as the mean RT in euthymic patients was similar to the overall BD group. This data is consistent with meta analyses that demonstrate a slowing of RT in euthymic BD patients compared to controls on the continuous performance test (CPT) (Robinson et al., 2006; Torres et al., 2007), and in a previous study utilising the ANT (Marotta et al., 2015). I am unaware of any previous studies utilising the PVT in BD. There is good evidence that the longer RT was associated with abnormal sleep in BD. Firstly only abnormal sleepers had longer RTs and normal sleepers did not differ from controls. As mean RT was also longer in euthymic abnormal sleepers this effect was independent of mood. In the case of the ANT, mean RT was also longer in euthymic abnormal BD sleepers compared to euthymic normal BD sleepers. The effect was robust as demonstrated by the large effect sizes. The lack of significant difference in mean PVT RT between euthymic normal and abnormal BD sleepers

may have been due to a lack of statistical power as the mean difference was a similar size to the total normal and abnormal BD sleeper groups where this difference was significant. Secondly as in studies of RT following SD in healthy populations, (Lim and Dinges, 2008), the euthymic abnormal BD sleepers also experienced a general slowing of RTs (a time on task effect), and an increase in the intra-individual variability of RTs. The increased intra-individual variability was demonstrated by differences between euthymic abnormal sleepers, (but not normal sleepers) and controls on σ and τ from the ex-Gaussian analysis, and the increased number of PVT lapses. The general slowing of RTs is demonstrated by the fact that euthymic abnormal sleepers, (but not normal sleepers), had slower fastest eight and slowest eight RTs than controls on the PVT. The time on task effect was demonstrated by the fact that in abnormal BD sleepers, the last eight RTs were significantly slower than the first eight RTs, an effect not present in the control group or normal BD sleepers. In euthymic abnormal sleepers the difference with controls was not statistically significant but this was likely due to a lack of power as numerically the difference was similar as that in the total abnormal sleeper group. These findings of a general slowing of RT, time on task effect and increased PVT lapses are consistent with studies assessing the effects of experimentally induced SD on RT using the PVT in healthy participants (Lim and Dinges, 2008; Dorrian et al., 2004; Belenky et al., 2003; Van Dongen et al., 2003). In addition, a general slowing in ANT RT has been demonstrated in healthy men following 24 hours of SD (Martella et al., 2011) and in patients with primary insomnia (Liu et al., 2014; Perrier et al., 2015). Collectively as this similar pattern of results to that seen in healthy controls following SD was only found in abnormal BD sleepers this suggests that sleep abnormalities may have

been driving these observations. These differences did not appear to be driven by differences in psychotropic medication use since there were no statistically significant differences in ANT or PVT performance in BD patients taking any particular type of medication or not.

4.7.1.2 Executive control of attention and the association with sleep abnormalities

This study also provides evidence for impairment in the attentional executive control network in abnormal BD sleepers. A break down in the executive control of attention and hence ability to sustain attention on the task is proposed to be responsible for the increase number of lapses seen on the PVT following SD (Unsworth et al., 2010). The greater number of lapses on the PVT and greater τ on both the PVT and ANT demonstrate an increase in slower RTs as these only occurred at greater frequency to controls in abnormal BD sleepers including those in euthymia. This demonstrates that impairment in the executive control system was only present in those with abnormal sleep and this effect was independent of mood. I am unaware of any previous studies assessing lapses on the PVT in BD patients but a previous study has demonstrated an increase in τ using ex-Gaussian analysis of RTs on a continuous performance task in BD patients (Gallagher et al., 2015). In this study a longer τ was found in both euthymic and depressed BD patients but τ was greatest in depressed BD patients. Based on the evidence in this study it is likely that significant sleep abnormalities were present in a greater proportion of the depressed than euthymic BD patients which may account for the greater τ in that group. Euthymic BD patients also had a greater τ than controls which was a different finding to this study. This difference may be accounted for by the different tasks utilised in the studies or differences in the characteristics between euthymic

patients between the studies such as proportion with BD I (higher in Gallagher et al.), differences in illness severity or in sleep abnormalities. In addition, the present study may have lacked statistical power to demonstrate a greater τ in euthymic patients as it was numerically greater on both the ANT and PVT and trended towards significance on the PVT. Further evidence for a deficit in executive control in abnormal BD sleepers comes from their significantly longer conflict RTs than controls and normal BD sleepers on the ANT regardless of mood state. The conflict RT directly assesses executive control of attention (Fan et al., 2002). The finding of longer ANT conflict RT following sleep disturbances is consistent with the results of a study in healthy men following 24 hours of SD (Martella et al., 2011) and in two studies in people with primary insomnia (Liu et al., 2014; Perrier et al., 2015) which demonstrate the ANT is sensitive to sleep abnormalities. Marotta et al. (2015) found a deficit in conflict RT on the ANT in euthymic BD patients compared to controls which is not consistent with this study where no deficit was found in euthymic patients. This may be due to a lack of statistical power in the present study as conflict RT was longer in euthymic BD patients than in controls by 17ms.

4.7.1.3 The orienting network and the association with sleep abnormalities

The present study also found evidence of impairment in the orienting network in BD patients. That the orienting RT was slower in this study demonstrated that BD patients were less able to speed up their RTs by making use of the spatial information than controls. The subgroup analyses however found that the orienting deficit was only present in the euthymic and normal sleeping BD groups and not in the abnormal sleeping groups. In context of the findings relating to vigilance and executive control where the deficits were only present in

the abnormal sleeping BD patients this finding is perhaps surprising. It is possible that the null finding in abnormal sleepers compared to controls was due to limited statistical power as the orienting RT was numerically longer than in controls and not significantly different than that in normal BD sleepers but the data does not suggest that the orienting network was more greatly impaired by sleep abnormalities. It is also possible that the impairment in the orienting network found in this study was not related to sleep abnormalities but other factors that were not accounted for in this study. It should however be considered that this finding may be the result of a type I error due to the multiple comparisons between groups as the p values were only just at conventional levels of statistical significance (0.042 and 0.05). The evidence from previous studies that the orienting network is vulnerable to sleep abnormalities is not conclusive. Casagrande et al. (2006) found that 24 hours of prolonged wakefulness resulted in vigilance impairment but not in orienting on a covert orienting task, a finding similar to this study. In contrast, Martella et al. (2011) found 24 hours of prolonged wakefulness resulted in decrements in the orienting network assessed by the ANT. Martella et al. suggested the differences in findings may be due to task differences and that orienting may only be effected by SD in tasks that involve involuntary or bottom up mechanisms of attention such as the ANT. This idea however is not supported by the results of the present study since no deficit on orienting RT was found in abnormal sleepers. Two previous studies did not find evidence of a deficit in the orienting network in euthymic BD patients using the Covert Orienting of Visuospatial Attention Task (Barekatain et al., 2008) or the ANT (Marotta et al., 2015). Collectively the data in BD on orienting function is inconsistent and suggests that the orienting network may only be impaired in

a subset of BD patients. This study does not provide evidence that there is an association of orienting function with sleep abnormalities.

4.7.1.4 The alerting network and the association with sleep abnormalities

This study found no evidence of a deficit in the alerting network in BD patients on the ANT which is consistent with the finding by Marotta et al. (2015). This finding demonstrates that BD patients including the abnormal sleeping group could speed their responses following an alerting cue to a similar degree to controls during the ANT. Martella et al. (2011) found no impairment on the alerting network during the ANT following 24 hours of SD. They suggested this may be due to the fact that the alerting effect of the visual stimulus during the ANT is quite small. RT decreased by only around 35 milli seconds in their study and approximately 40 milli seconds in the present study following an alerting cue. They suggested that a task where the alerting effect had a larger influence on RT may have found a clearer effect on the alerting network. Martella et al. did actually find a deficit in alerting RT following SD on RTs involving incongruent flankers demonstrating an interaction between the alerting and executive control networks but that interaction was not assessed in the present study so a comparison of results is not possible.

4.7.1.5 Are the increased number of excessively long RTs in BD related to a break down in executive control of attention?

Unsworth et al (2010) have demonstrated that excessively long RTs on the PVT are related to a break down in executive control. The executive control network enables an individual to block conflicting stimuli and remain focussed on the task. The ANT provided an opportunity to test this hypothesis in the present

study as it assesses executive control and ex-Gaussian analysis can quantify excessively long RTs through the τ statistic. The regression analysis demonstrated that conflict RT was able to predict the difference in PVT RT τ between BD patients and controls including the abnormal sleeping subgroups. Adding conflict RT into the regression model before group rendered group an insignificant predictor of PVT τ. This finding is in agreement with those of Unsworth et al. (2010) and demonstrates that the increased frequency of excessively long RTs on the PVT in BD patients including those with sleep abnormalities is associated with a breakdown in executive control. Long RTs or lapses in non-sleep deprived individuals are thought to arise from transient disruptions of the top down cognitive control processes that rely on the frontal lobes and it has been demonstrated that neural correlates of lapses following SD differed from those that occur after normal sleep (Chee et al., 2008). Specifically, during lapses after SD, including those of similar magnitude to those occurring after normal sleep, Chee et al. found reduced activation of the fronto-parietal regions, visual cortex activation and in the thalamus that contrasts with the elevated thalamic activation during non-lapse periods. It was hypothesised that in the SD state, there is a reduction in the number of neurons and/or the amount of time that fronto-parietal neurons can be recruited to compensate for attentional lapses. Since this brain region has suboptimal functioning in BD patients regardless of mood state (Chen et al., 2011) it is possible that BD patients are more vulnerable to the effects of SD than healthy controls and therefore clinical sleep abnormalities are of sufficient severity to increase RT variability and attentional lapses. An alternative explanation for increased numbers of excessively long RTs in BD patients has been proposed by Gallagher

et al. (2015) who point out that increased variability has been associated with aging and mild dementia and may be a marker of reduced white matter integrity (Walhovd and Fjell, 2007; Fjell et al., 2011). Given the evidence for decreased white matter integrity in BD (Macritchie et al., 2010; Sarrazin et al., 2014; Wise et al., 2016), Gallagher et al. hypothesised that this could contribute to the increased RT variability found in BD patients. Considering this hypothesis further and of specific relevance to this study is the fact that cognitive decline in older adults is not only associated with decreased WMI but also with increased sleep abnormalities (Lo et al., 2016). Therefore both decreased white matter integrity and sleep abnormalities may be influencing executive control of attention and these two factors may be related. Bellesi et al. (2013) demonstrated that transcription of genes involved in the promotion of oligodendrocyte precursor cell proliferation, (cells that produce myelin), phospholipid synthesis and myelination occurs mainly during sleep. Genes implicated in apoptosis, cellular stress response, and oligodendrocyte differentiation were activated during wake. This suggests that disruption or lack of sleep may result in lower myelination of neurons resulting in reduced WMI. Support for this relationship has been demonstrated in several studies. A day of wake in healthy individuals was demonstrated to result in a reduction in WMI which was further exacerbated when followed by 9 hours of sleep deprivation (Elvsashagen et al., 2015). Impaired WMI has also been demonstrated in people with OSA (Chen et al., 2015; Tummala et al., 2016), insomnia (Li et al., 2016) and in adolescents with significant sleep variability (Telzer et al., 2015). In addition both short (Yaffe et al., 2016) and long (Ramos et al., 2014) sleep duration in healthy adults has been associated with reduced white matter integrity. This evidence therefore supports

the possibility that the relationship between sleep and reduced white matter integrity may underlie cognitive deficits associated with sleep loss. Indeed Zhu et al (2017) have recently demonstrated that cognitive instability evidenced by a greater number of lapses on the PVT is significantly associated with worse WMI following SD. Specifically, individual differences in cognitive stability after SD were associated with the integrity of the white matter tract connecting fronto-parietal attention networks and the white matter tract connecting the two hemispheres. Another study has also demonstrated that greater WMI in the axonal pathway connecting the frontal and parietal brain regions, (the superior longitudinal fasciculus), was associated with better resistance to a decline in working memory performance following SD (Cui et al., 2015). These findings suggest the possibility that BD patients who have worse WMI may be more susceptible to the effects of sleep abnormalities on cognitive performance as sleep abnormalities may have an additive effect on already compromised WMI. Two studies have examined the association of sleep and WMI in BD. Verkooijen et al. (2017a) examined the association of sleep disruptions and irregular physical activity estimated with accelerometry and WMI. In controls more effective sleep was associated, as expected, with increased WMI but in BD patients the opposite relationship was observed with more effective sleep associated with reduced white matter integrity. This unexpected relationship was thought to be related to the confounding effects of antipsychotics on white matter in the BD patients. Benedetti et al. (2017) however found that accelerometry estimated greater time asleep was positively associated with increased WMI in a cohort of depressed BD I patients. Collectively this evidence suggests there is a possibility that the association of cognitive impairment with sleep abnormalities in BD could be

driven by underlying effects of sleep abnormalities on WMI. This possibility should be explored by studies assessing sleep function, WMI and cognitive function in patients with BD.

4.7.1.6 Potential mechanisms for the association of sleep abnormalities and attentional function

As discussed previously one mechanism hypothesised to explain the association of sleep with attentional function is that sleep has been demonstrated to be essential for the maintenance of normal brain function and that a loss of sleep is associated with functional brain abnormalities (McKenna and Eyler, 2012). fMRI studies have demonstrated that the attentional networks consist of distinct anatomical brain areas with the alerting network associated with increased activation in the fronto-parietal areas and thalamus, the orienting stimuli with left and right superior parietal lobe activation and conflict flankers with anterior cingulate, left and right frontal areas and left and right fusiform gyrus (Fan et al., 2005). These networks although overlapping to some extent could also could be differentially vulnerable to sleep abnormalities resulting in different effects of sleep abnormalities on the individual attentional networks. In addition studies have also demonstrated that during cognitive tasks the brain can compensate for poor performance by recruiting additional brain areas to maintain performance following sleep loss (Portas et al., 1998; Drummond et al., 2004; Tomasi et al., 2009). This may be an explanation why findings between studies about specific deficits are variable and task dependent.

Attention may be a particularly vulnerable cognition to sleep abnormalities since the frontal brain areas that make up the attentional networks have been

demonstrated to be vulnerable to sleep loss. SD reduces activation in frontal brain areas, the medial frontal gyrus and ACC, areas that are part of the executive control network (Ma et al., 2015). fMRI studies in BD patients have demonstrated that the most consistent area of the brain that has lower activity than controls in BD patients is the inferior-frontal gyrus (IFG), an important part of the attention networks and that this area is also consistently underactive in BD patients during both cognitive and emotional processing (Chen et al., 2011). It is therefore possible that sleep abnormalities interact with an innate brain dysfunction in frontal areas in BD patients resulting in greater decreases in attentional function (McKenna and Eyler, 2012). This hypothesis would need to be tested utilising fMRI studies of brain function during the cognitive testing.

As obstructive sleep apnoea has been associated with deficits in attentional function (Beebe et al., 2003), the attentional data was also examined in patients with and without OSA. It has been hypothesised that cognitive deficits associated with OSA may be the result of sleep fragmentation and intermittent hypoxia (Cross et al., 2017) and therefore this may result in a different pattern or severity of cognitive dysfunction compared to that associated with other sleep disorders such as insomnia or circadian rhythm disorders. The results however in this study did not demonstrate any differences in attentional function between the BD abnormal sleepers with and without OSA. This was true for mean ANT and PVT RTs and for the tau statistics that demonstrated increased variability in mean RT. That the group of all BD patients with OSA, 50% of whom also had other concomitant sleep abnormalities did not have worse cognitive function than the those who's only sleep abnormality was OSA suggests that in this study there was not an additive effect of OSA on cognitive function. It may have been

expected that the presence of OSA would further worsen attentional performance. In this study however although patients with OSA did have greater levels of daytime sleepiness than those without OSA the mean scores on the ESS were still within the normal range so there was no evidence of excessive daytime sleepiness in the OSA group. In addition, two thirds of the BD patients with OSA only had mild OSA and the others moderate OSA. The mean oxygen desaturation index of 4.3 was also in the mild range. It is therefore possible that the severity of OSA was not great enough to further impact on the cognitive deficits present in this group. It is also possible that there is a ceiling effect of sleep abnormalities on cognitive function and that the levels of cognitive deficit reached could not deteriorate any further with additional sleep abnormalities. This could be due to adaptive mechanisms in the brain protecting against further loss of cognitive function or that the mechanism by which sleep abnormalities impair cognitive function had reached their maximum.

4.7.2 Discussion of the association of performance in the DSST and sleep abnormalities

I hypothesised that BD patients would have deficits in processing speed which will be most pronounced in patients with sleep abnormalities. The results of this study support this hypothesis as the total BD and euthymic BD group performed significantly worse than controls on the DSST a task which assesses processing speed. This finding is consistent with meta-analyses that found deficits in DSST performance in euthymic BD patients with effect sizes (Cohen's d) ranging from approximately -0.6 to -0.8 (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009; Kurtz and Gerraty, 2009; Mann-Wrobel et al., 2011). The effect size for the deficit in DSST performance in euthymic BD patients in the

present study was -0.57 to -0.60 (Hedges' g) so at the lower end of the range in the meta-analyses. Subgroup analysis found that normal BD sleepers did not differ from controls whilst abnormal BD sleepers including those in euthymia performed worse than controls. In the euthymic abnormal BD sleepers the effect sizes of -0.98 and -1.01 (Hedges' g) were larger than those reported in the meta-analyses possibly due to the 100% presence of abnormal sleepers. In Lim and Dinges (2010) meta-analysis effect sizes (Hedges' g) for deficits in processing speed following SD were small (-0.25 for accuracy and -0.3 for RT) and the two studies that assessed DSST speed found no effect of SD on performance. However, two studies not included in the meta-analysis have found a deficit in performance on the DSST following both SD and SR (Van Dongen et al., 2003; Banks et al., 2010) which does demonstrate the test is sensitive to the effects of sleep. When interpreting these results it must be considered that the DSST is not a pure processing speed task and performance is also dependant on graphomotor speed, perceptual speed, visual scanning efficiency, memory and executive control (Joy et al., 2003; Cepeda et al., 2013). Cepeda et al. demonstrated that the dependence of the DSST on executive control was only apparent in children and older adults and they hypothesised this was due to the fact that demands of processing speed tasks on executive control are age dependent. As tasks of processing speed require executive control people without fully developed executive control networks (children) or those with cognitive decline of the executive control network (older adults) may perform less well on processing speed tasks than those with fully developed and intact executive control networks e.g. younger adults. It is therefore possible that the deficit in performance in the DSST in abnormal BD sleepers was due to the effects of sleep

abnormalities on the executive control network rather than purely processing speed.

The analysis of DSST performance in BD patients with and without OSA did not find any evidence for a differential or additive effect of OSA on the DSST performance. As discussed above this may be due to several reasons such as the presence of generally mild OSA in this population and the possibility that a ceiling effect of the influence of sleep abnormalities on cognitive function had already been reached.

4.7.3 Discussion of performance on the trail making test and the association with sleep abnormalities

The TMT assess a number of cognitive functions including speed of visual search (TMT-A), working memory and task switching ability (TMT-B) while TMT B-A reduces the speed of visual search and working memory demands therefore assessing primarily the cost of task switching, an executive function (Sanchez-Cubillo et al., 2009). In this study there were no significant differences in TMT-A, TMT-B or TMT B-A between BD and controls suggesting no differences in the cognitive functions assessed. This finding is not consistent with meta-analyses that found a deficit in euthymic BD patients on TMT-A & B with moderate to large effect sizes (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009; Kurtz and Gerraty, 2009; Mann-Wrobel et al., 2011). The individual patient meta-analysis found a moderate deficit in TMT-A & B compared to controls (Bourne et al., 2013). One possible reason for the lack of performance deficit in the current study is that the patients included in the meta-analyses were mainly BD I whereas in this study the majority of patients (66%) were

diagnosed with BD II disorder. A systematic review identified five studies comparing BD II patients (not all in euthymia) with controls on the TMT of which three studies found no performance difference, one found no performance difference compared with normative TMT data and one found a significant deficit in BD II patients (Sole et al., 2011). A meta-analysis comparing cognitive performance in BDI and BD II patients found that BDII patients did perform better than BD I patients on TMT-B but that difference was not statistically significant (Bora et al., 2011). It is therefore possible that BD II patients differ from BD I patients in performance on the TMT and may account for the lack of deficit found in the current study. With regard to performance following SD three studies utilising the TMT were included in the meta-analysis with two finding a deficit in speed of small to moderate effect size and one finding no effect of SD (Lim and Dinges, 2010). Task switching was also only found to account for around 30% of the variance in TMT B-A performance in the analysis by Sanchez-Cubillo et al. (2009). It may be that the combination of a high proportion of BD II patients who have less vulnerability to a deficit on this task than BD I patients and the exposure to clinical sleep abnormalities rather than total SD contributed to the lack of difference with controls. It is also possible that as the time to complete this task is very short, the BD patients were able to focus attention on the task for sufficient time to complete it without a significant performance decrement. Therefore, this study provided no evidence of an association between sleep abnormalities and performance on the TMT, a task that requires visual searching, working memory and task switching capabilities.

4.7.4 Discussion of performance on the digit span test and the association with sleep abnormalities

The digit span is a task assessing working memory, an executive function and no difference was found in performance on the digit span in BD patients compared with controls. However, after controlling for NART-IQ with ANCOVA BD patients performed significantly worse on digit span forwards with a trend towards worse performance on the backwards component. This data is therefore in support my hypothesis that BD patients would have a deficit in executive functions, in this case working memory. Meta-analyses of previous studies found deficits of small effect size in digit span forwards (Mann-Wrobel et al., 2011) and moderate to large effect sizes for digit span backwards in euthymic BD patients (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009; Mann-Wrobel et al., 2011). The individual patient meta-analysis found a small deficit in digit span forwards and moderate in digit span backward (Bourne et al., 2013). In the euthymic subgroup in the present study there was a trend towards a deficit in the forwards component. Although I was unable to calculate effect sizes due to the differences only becoming apparent after controlling for NART score it is likely the effect sizes were small. It is possible that the small deficit found in the present study compared to those in the meta-analyses was due to the greater number of BD II patients in this study. However the meta analysis found no differences in digit span forwards or backwards between BD I and BD II patients (Bora et al., 2011) and a systematic review found working memory was impaired in six out of nine studies in BD II patients compared to controls (Sole et al., 2011) so that is unlikely to be a factor. After controlling for the differences in NART-IQ abnormal BD sleepers trended to worse performance on digit span

backwards but in euthymic abnormal sleepers there were no apparent differences between BD patients and controls. This data then does not provide support for an association with sleep abnormalities and lower working memory performance. The meta-analysis of SD and cognitive function found working memory accuracy was found to be impaired by SD with a moderate effect size -0.55 (Lim and Dinges, 2010). However, studies specifically using the digit span task as a measure of working memory found little evidence of effect of SD on performance with five out of seven studies finding no performance decrement following SD and two with small deficits of effect sizes of 0.2 suggesting that this particular task is not vulnerable to the effects of SD. This may explain why unlike in the tasks of attention there was no obvious decrement in performance in abnormal BD sleepers.

4.7.5 Discussion of performance on the Newcastle Spatial Working Memory Test and the association with sleep abnormalities.

After co-varying for age there were no differences in performance between BD patients and controls on the Newcastle Spatial Working Memory Test so this finding does not support the hypothesis that BD patients have deficits in spatial working memory. As it was pre specified that no further analysis would be performed on tests that did not differ at the total group level an analysis of any potential relationship with abnormal sleep was not performed. The meta-analyses do not specifically report effect sizes for performance on tasks of spatial working memory but a previous study using a similar spatial working memory task in depressed BD patients also found no significant performance decrement in BD patients compared to controls (Gallagher et al., 2014).

4.7.6 Discussion of performance on the verbal learning test and the association with sleep abnormalities

I hypothesised BD patients would have a deficit in short term memory compared to controls and the results from the verbal learning test support this hypothesis as the total BD group performed worse than controls in both immediate and delayed recall after co-varying for NART-IQ with moderate effect sizes. Euthymic BD patients performed worse than controls on the immediate recall but there was only a trend towards a deficit in delayed recall with small effect sizes. Meta-analysis of previous studies found deficits of moderate to large effect size in BD for immediate and delayed recall in verbal learning tests (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009; Mann-Wrobel et al., 2011; Bourne et al., 2013). However meta-analysis has demonstrated that BD I patients perform worse than BD II patients on verbal learning tasks (Bora et al., 2011) and a narrative review of the BD II literature only found a deficit in verbal learning compared to controls in 4/9 studies (Sole et al., 2011). The high proportion of BD II patients in the present study may therefore have limited the deficit and effect size. The tests used in the present study also differs slightly from the studies used in the meta-analyses as they used the California Verbal learning test (CVLT) and this may also partially account for the differences in outcomes. The results of this study do not support a strong association between short term memory and sleep abnormalities. The normal BD sleepers did not differ from controls on either measure, although there was a trend to worse immediate recall after controlling for NART-IQ. The abnormal sleepers performed significantly worse on immediate and delayed recall with moderate effect sizes but euthymic abnormal sleepers only trended towards a statistically

significant difference in delayed recall errors with controls. The numerical differences between normal sleepers and euthymic abnormal sleepers were small being only 0.2 words for immediate recall and 1.5 words for delayed recall errors. This suggests that the larger effect for the total abnormal sleeper group compared to controls was largely related to lower mood scores in this group. The meta-analysis of short term SD and cognitive function found short term memory was vulnerable to SD but only with a small effect size (d = -0.38) (Lim and Dinges, 2010). It is however also possible that as the euthymic abnormal sleepers did have worse numerical performance on this task, that the small sample size of euthymic abnormal sleepers in the present study was underpowered to detect a difference of small effect size with controls.

4.7.7 Discussion of cognitive function in subjectively and objectively defined abnormal sleepers

I hypothesised that BD patients with objectively defined sleep abnormalities would perform worse on cognitive tasks than those without objectively defined sleep abnormalities but who subjectively rate their sleep as of poor quality. The results of this analysis partially support this hypothesis. Objective abnormal sleepers performed numerically worse on all measures assessed although only the differences in ANT and PVT mean RT and ANT τ were statistically significantly different. After co-varying for age only ANT τ differed significantly but ANT and PVT mean RT trended towards being significantly longer. It is likely that this analysis was under powered as there were only 10 participants with abnormal subjective but normal objective sleep. These results add strength to the finding in this study that it is objective sleep abnormalities that are associated with objectively assessed cognitive function and subjectively rated

poor sleep quality in the absence of objective sleep abnormalities has a lesser effect on cognition. In fact those with only subjective sleep abnormalities performed at a similar level to controls in terms of RT. For example mean ANT RT was 566ms in the control group and 547ms in the subjective abnormal sleepers and mean PVT was 325ms in the control group and 333ms in the subjective abnormal sleepers.

4.7.8 Discussion of correlation analyses between accelerometry sleep variables and cognitive function.

An exploratory analysis was performed to examine the relationship between accelerometry variables and mean PVT RT as assessments of attentional performance. There were significant positive linear relationships between 24-hour sleep, SIBD and its variability and mean PVT RT. This finding is supportive of the view that long sleep is associated with a decline in attentional performance because as 24-hour sleep and daytime inactivity increased mean PVT RT increased. This finding is consistent with studies that have demonstrated an association of long sleep with poor cognitive function (Lo et al., 2016) although those findings related to worse executive functions and verbal and working memory rather than in attention. Lo et al. found both short and long sleep were associated with worse cognitive function in an inverted U shaped relationship. There was a linear relationship in the present study but that is possibly because there were so few short sleepers and no participants had less than 6 hours 24-hour sleep. Lo et al. used a definition of < 5hours nocturnal sleep for short sleepers which is shorter than the definition of short nocturnal sleepers used in this study of < 6 hours. Only four BD patients met that criterion so there was little opportunity to find a relationship with short sleep. Of note, there was also a

significant relationship with SIBD demonstrating that sustained daytime inactivity may have a role to play in cognitive function. As previously discussed, due to the limitation of accelerometry it cannot be sure if SIBD is actually time spent asleep or just sustained inactivity, but greater amounts were associated with poorer performance on the PVT. It is possible that SIBD is greater in patients that have poor nocturnal sleep and they spend time resting or sleeping in the daytime in an attempt to catch up on sleep. However, time spent in SIBD did not correlate with either ESS or AHI so was unrelated to daytime sleepiness or the presence of OSA so these reasons are unlikely to be the cause of worse attentional performance in this study. The finding of this relationship between long sleep/sedentary daytime behaviour and PVT performance suggests that daytime sedentary behaviour may be a worthwhile treatment target in BD to improve cognitive performance.

4.7.9 Overall conclusions about the association of sleep and cognitive function.

This findings from this study have demonstrated a strong relationship between objective sleep abnormalities and cognitive performance in BD patients. The strongest evidence is for a relationship between sleep abnormalities and attentional performance including the executive control of attention with some evidence for an association with verbal learning. The study provided no evidence for an association between sleep abnormalities and working memory or set shifting, both executive functions. Attention is the function that has proven most vulnerable to SD and SR in experimental studies and the evidence from this study is consistent with that finding. This study provides new evidence that objectively defined clinical sleep abnormalities in a population of BD patients are also associated with attentional deficits and that this association appears to be

independent of potential confounders such as mood and age. The results also demonstrated that a variety of sleep abnormalities are associated with poor performance in that patients with long sleep, a CRD and/or OSA had a similar level of poor performance. There was no evidence for a differential effect of OSA on cognitive function compared to other sleep abnormalities. The data also suggests that patients with multiple sleep abnormalities may have the worst cognitive performance but this suggestion is preliminary and requires confirmation in larger samples.

When considering the findings from this study it is important to note that they only demonstrates an association between sleep abnormalities and cognitive deficits. This study does not provide any evidence of a direct causal relationship between sleep abnormalities and cognitive function. An interventional study where sleep is manipulated and its effects on cognitive function are assessed is required to demonstrate a causal relationship. It is possible that the sleep abnormalities and cognitive deficits are induced by the same brain lesion and therefore the associations found in this study simply reflect this. In addition, not all potential confounders of a relationship between sleep and cognitive function were measured in this study. For example, length of illness, the number of manic episodes and hospitalisations have both been associated with lower cognitive function (Robinson and Ferrier, 2006), and these variables were not assessed in this study. It is possible that it is these features that have a causal role in cognitive deficits and that patients with a more severe course of illness also have a greater degree of sleep abnormalities. The association of sleep abnormalities with cognitive deficits would simply be a reflection of the association of sleep abnormalities with a more severe illness course which resulted in greater

cognitive deficits. Future studies should also collect information on these potential confounders between the relationship between sleep and cognitive function so that their potential effects can be controlled.

4.7.10 Should the results of this study be considered as exploratory and hypothesis generating - the issue of multiple statistical comparisons?

A weakness of this study relates to the statistical analysis comparing cognitive function between subgroups of BD patients and controls. The analysis included multiple comparisons between controls and BD patients for each statistical test. Controls were compared to the following five BD populations; total BD group, euthymic BD group, normal BD sleepers, abnormal BD sleepers and abnormal BD sleepers in remission. Performing multiple comparisons increases the chance of a type I error. I.e. incorrectly rejecting the null hypothesis. In this study the only control employed to reduce the risk of type I error was that if there was no statistically significant difference between controls and the total BD group on a cognitive task then no further statistical analyses were performed on that task. This method is probably not adequate to protect against type I errors and for this reason and further reasons discussed below the results of this study should be considered as exploratory and hypothesis generating. The hypotheses generated are listed in the following section and the issue of multiple testing and correcting for multiple testing with a Bonferroni correction, a common method employed is discussed here in the context of this study and the results.

A more rigorous way of controlling for multiple comparisons and reducing the risk for type I error is to apply a Bonferroni correction (Bland and Altman, 1995). The Bonferroni correction adjusts for the increased risk of rejecting a null

hypothesis by increasing the level of alpha required in order to reject the null hypothesis. The alpha level required is calculated by dividing the level of alpha desired to denote statistical significance, usually 0.05, by the number of comparisons made (Bland & Altman, 1995). In this study an alpha level of 0.05 was used to denote a significant difference and five statistical comparisons were performed per test and so an alpha level of 0.05/5 = 0.01 would be required to denote a statistically significant difference between groups and therefore reject the null hypothesis. Using the same principal a corrected p value can also be calculated which is achieved by multiplying the actual p value obtained by the number of tests. In this study that would mean multiplying each p value obtained by five. If applying the Bonferroni correction to this study then the majority of the statistically significant differences between controls and abnormal BD sleepers and controls and controls and euthymic abnormal BD sleepers would remain. This is because p values of <0.01 were obtained for many of the subgroup analyses, (listed below), compared to controls in the pre-specified tests. These then can be considered as significantly different from controls at an alpha level of < 0.05 after Bonferroni correction.

- Differences in cognitive performance that remained statistically significantly different between controls and BD subgroups after Bonferroni correction. The corrected p values calculated by multiplying the actual p value by five (the number of comparisons) are shown in brackets.
    - Mean ANT RT – abnormal BD sleepers (0.005), euthymic abnormal BD sleepers (0.01).
    - ANT conflict RT – total BD group (0.025), abnormal BD sleepers (<0.005), euthymic abnormal BD sleepers (0.03).

- PVT mean RT - total BD group (<0.005), abnormal BD sleepers (<0.005), euthymic abnormal BD sleepers (0.005).
- PVT lapses - total BD group (0.005), abnormal BD sleepers (<0.005), euthymic abnormal BD sleepers (0.025).
- ANT RT tau – total BD group (0.02), abnormal BD sleepers (<0.005), euthymic abnormal BD sleepers (0.005).
- PVT RT tau – total BD group (0.015), abnormal BD sleepers (<0.005).
- DSST – total BD group (0.005), abnormal BD sleepers (<0.005), euthymic abnormal BD sleepers (0.05).
- Verbal learning immediate recall – total BD group, abnormal BD sleepers.
- Verbal learning delayed recall errors – total BD group (<0.005), abnormal BD sleepers (0.005).

Cognitive tests that were no longer statistically significantly different following Bonferrroni correction. The corrected p value is shown in brackets.

- Mean ANT RT – total BD group (0.14).
- ANT orientating RT – total BD group (0.2), euthymic BD (0.21), normal BD sleepers (0.25).
- PVT mean RT – euthymic BD (0.235),
- PVT lapses – euthymic BD (0.25),
- PVT RT tau – euthymic abnormal BD sleepers (0.075).
- Digit span forwards – total BD group (0.155).
- Newcastle spatial working memory, total between search errors – total BD group (0.115).

- Verbal learning immediate recall – euthymic BD patients (0.185).

Overall applying the Bonferroni correction only had a limited impact on the study findings demonstrating that the majority of results from this study were unlikely to be type I errors. In particular, the differences between BD abnormal sleepers and BD euthymic abnormal sleepers and controls remained significant in tests of attention and processing speed. Considering attention is the cognitive domain most strongly impacted by sleep disruption this finding is plausible and suggests it is correct to the reject the null hypothesis. Two further reasons also suggest why the findings are unlikely to be type I errors. Firstly the effect sizes of the deficits in performance in tests of attention and processing speed in the abnormal sleeping BD groups compared to controls fall were large in magnitude (Hedges g >0.9). It would seem unlikely that so many differences of large effect size would be found by chance. Secondly, there was consistency in the pattern of results between measures of the same cognitive domain. In both tests of attention, (PVT and ANT), the pattern of results was identical across BD subgroups with abnormal sleepers and euthymic abnormal sleepers having the worst performance (with large effect sizes). Normal sleepers on both tests did not differ from controls. This pattern of results was also found across the other cognitive domains where although the magnitude of the differences between groups were much smaller and rarely reached statistical difference, numerically they followed the same pattern of results. If these results were chance findings due to multiple testing it would be expected that the significant differences between groups would be more randomly spread throughout the BD subgroups and would not follow this consistent pattern. It should also be noted that Bonferroni correction

is considered a conservative method for controlling for multiple comparisons. It reduces statistical power thereby increasing the risk of type II errors and rejecting important differences between groups (Rothman, 1990; Perneger, 1998). It has been argued that it is appropriate when examining data to simply report what was done, why it was done and then discuss the plausibility and possible interpretations of the result. This should allow a researcher or reader to draw a reasonable conclusion without the need for Bonferroni corrections especially if it is clear that the results are biologically plausible and not the result of data dredging (Perneger, 1998). In this study the results are plausible given their consistency with prior evidence of an association of cognitive deficits, particularly in attention, with sleep disruption. In addition, the subgroups of BD patients selected for comparison with controls were identified a priori based on the evidence and were not found as a result of data dredging.

Despite the argument that the findings of deficits in attention and processing speed in BD abnormal sleepers do not appear to be due to chance or the performance of multiple comparisons it is still appropriate to view these results conservatively and view them as exploratory. Firstly, some of the findings were no longer significant after applying the Bonferroni correction as described above. In addition, the sample sizes for the BD subgroups were small and therefore there is less confidence in these results despite the statistical significance of the findings. These findings require confirmation in a larger study where the statistical power is greater and adjustments for multiple comparisons are pre-specified. In addition further studies are required that measure other potential confounders in any relationship between sleep and cognitive function such as length of illness and the number of mood episodes and hospitalisations. These

variables may not have been equally distributed between normal and abnormal sleepers and may therefore be present as unmeasured residual confounders.

4.7.11 Hypotheses generated by the study results

The following hypotheses are generated from the study findings.

1. Deficits in attention, executive control of attention, processing speed and verbal learning in BD are present only in patients with objectively defined sleep abnormalities including long 24-hour sleepers, CRD and OSA.
2. Sleep abnormalities have a causal role in deficits in attention, processing speed and verbal learning in BD patients mediated through impairment of brain functions involved in cognitive processing.
3. Deficits in attentional performance associated with sleep abnormalities underlie poorer performance in other cognitive domains.

4.8 Overall study conclusions, how they enhance our knowledge in this field and their relevance to clinical practice

4.8.1 Overall conclusions

This study has provided important new data on sleep and its association with psychosocial and cognitive function in patients with BD. The following can be concluded from the evidence presented.

- Subjective and objective sleep abnormalities and circadian rhythm disturbances were common in both euthymic and depressed BD patients in this cohort. These include short sleep, long 24-hour sleep, circadian

rhythm disturbances and OSA. Co-existing sleep abnormalities were common in this cohort.

- On average accelerometry indicated that BD patients have longer and more variable sleep patterns than controls although there were few differences in sleep variables between euthymic BD patients and controls.
- Euthymic and depressed BD patients performed significantly lower levels of physical activity than controls.
- Subjective and objective sleep abnormalities are both associated with lower psychosocial function and QoL independently from mood.
- Only objectively confirmed sleep abnormalities were associated with worse cognitive function and this was independent of mood.
- Consistent with previous research on sleep and cognitive function the cognitive domain most strongly associated with sleep abnormalities was attention and the executive control of attention. There was also an association with verbal learning and processing speed.
- Long 24-hour sleep, CRDs and OSA appeared to have similar associations with cognitive function but cognitive function may be worse in patients with multiple sleep abnormalities.

4.8.2 How do these findings enhance our knowledge about the mechanisms of the association between sleep and cognitive function

As identified in the literature review previous researchers have hypothesised that there is a role of sleep in cognitive function in BD (McKenna and Eyler, 2012; Boland and Alloy, 2013). McKenna and Eyler focussed on the potential mechanisms that may underlie an association between sleep and cognitive function. They hypothesised that sleep and circadian dysfunction may be

involved in the cognitive and emotional processing deficits seen in BD through overlapping neurobiological systems. They proposed that as sleep has been demonstrated to be important in maintaining the functional integrity of the PFC/limbic connectivity essential for normal emotional and cognitive processing sleep abnormalities may have a role in the development and maintenance of BD. Although the present study did not examine brain function there was a relationship between sleep abnormalities, mood and cognitive function which is consistent with this hypothesis.

Boland and Alloy, (2013) stated that theoretical support for the hypothesis that sleep disturbances contribute to sustained cognitive deficits in BD evidenced by the fact that SD and additionally clinical sleep disorders such as insomnia and OSA, which are prevalent in BD, are associated with cognitive deficits that overlap with those seen in BD in other populations. They proposed three possible models of sleep mediated deficits in psychosocial and cognitive function (Figure 1.11). The results of this study provide some support for model two where impaired psychosocial and occupational function are the result of sleep mediated cognitive deficits and mood disturbance. For example attentional deficits were present in the total group of euthymic BD patients that included some abnormal sleepers but were absent in normal BD sleepers. Attentional deficits were more prevalent and with a larger effect size in abnormal BD sleepers and were of similar magnitude in both depressed and euthymic abnormal sleepers which suggests the abnormal sleep rather than the decreased mood is the strongest factor in attentional function. The sleep abnormalities were also associated with increased depressive symptoms which also have a direct effect on psychosocial

and occupational function. It should however be noted that a causal effect of sleep abnormalities on mood cannot be concluded from this study.

In summary this study enhances our knowledge on the association between sleep and cognitive function by providing new evidence of associations using objective assessments of sleep and cognitive function. This evidence provides support to theoretical models based on neuropsychological models derived from sleep and BD research.

4.8.3 The clinical implications of the study findings

A number of findings from this study are relevant to the clinical management of people with BD. As sleep and circadian abnormalities were common and associated with worse clinical outcomes, they should become a target for rigorous assessment and treatment in BD. The finding that clinical sleep abnormalities are associated with attentional deficits in BD is important. Attentional deficits are thought to be a core cognitive deficit in BD and deficits in other cognitive domains may be at least in part secondary to the results of poor attention. Therefore, if sleep abnormalities are an underlying cause of attentional deficits it is possible that improving sleep may result in widespread improvements in cognitive function, however this possibility requires further study. This study has demonstrated it is practical to utilise instruments such as accelerometry and home based respiratory studies to assess sleep and circadian rhythm in psychiatric outpatients. The potential benefits of rigorously assessing sleep and circadian rhythms are that this may help identify the most effective and appropriate treatments. Patients who for example complain of poor sleep quality and resultant daytime sleepiness, without proper assessment may be

misdiagnosed as insomniacs when in fact they may have OSA. This may result in inappropriate treatment with hypnotics when a more appropriate treatment for patients with moderate to severe OSA would be continuous positive airways pressure (CPAP). CPAP has proven an effective treatment for OSA and also results in modest improvements in attentional function (Kylstra et al., 2013). In this study mild OSA was associated with cognitive deficits and appropriate treatment strategies should also be put in place for patients with mild OSA. Patients with circadian rhythm abnormalities may benefit from chronotherapy, social rhythm therapy. Chronotherapy has proven useful in the treatment of mood disorders (Coogan and Thome, 2011) and social rhythm therapy has previously proven effective in reducing relapse and improving psychosocial and work function in patients with BD (Frank et al., 2005; Frank et al., 2008; Inder et al., 2015). Patients with BD may also benefit from increased physical activity. AS well as the well documented improvements in physical health, increased physical activity may also improve sleep function in patients with BD which in turn may then lead to improvements in cognitive function.

4.9 Methodological strengths and limitations

4.9.1 Study strengths

This study had several strengths. Participants underwent comprehensive assessment of sleep and circadian function with both subjective and objective measures. Control participants with either subjective or objective sleep abnormalities were excluded from the study which ensured the BD group were compared to a control group with normal sleep function. Objective sleep assessment included accelerometry, which has been demonstrated as a satisfactory method for the assessment of sleep and circadian rhythms. The

accelerometry assessment lasted for 21 consecutive days providing adequate time to characterise the sleep wake cycle. The accelerometer utilised in this study recorded in SI units so the data from this study can be more easily compared and combined with future studies using SI devices and allows for combining data in meta-analyses. OSA was diagnosed using overnight respiratory studies with a validated device.

4.9.2 Study limitations

There are several limitations to this study. Firstly, control participants without sleep abnormalities were recruited to this study. These participants may not therefore be fully representative of the general population where sleep abnormalities are common. It is possible that these participants may also differ from the general population in other unmeasured characteristics that may effect their cognitive performance. Therefore, the differences between controls and BD participants found in this study should be interpreted as differences between good sleeping healthy controls and BD patients. Previous studies comparing cognitive function between controls and BD patients have not screened out controls with sleep abnormalities such as OSA. Therefore, this study may not be directly comparable to other studies assessing cognitive function in BD or the differences in sleep variables between controls and BD patients. The failure to recruit insomnia patients without a mental health disorder also prevented the examination of the association between sleep and cognitive function in a non-psychiatric population. Therefore, it was not possible to examine any differential relationship between sleep abnormalities and cognitive function in both a BD population and a non-psychiatric population.

Another limitation to this study was that controls and BD patients were not precisely matched for age, NART-IQ and employment status. The potential confounding effects of age and NART-IQ were examined and controlled with ANCOVA but it would have been desirable to have more evenly matched groups. Unemployment for example, rather than directly influencing cognitive function may influence circadian behaviour due to a lack of regular daily activities and may have influenced sleep wake patterns in the BD group. No adjustments were made for employment status. Participants were not drawn randomly from the BD population which may have resulted in selection bias. The population studied may not therefore be representative of the total BD population and may have included a greater number of patients with sleep abnormalities or help seeking behaviour. However, this study was not designed as a prevalence study and this should not have had an effect on the relationship between sleep and cognitive function. In addition some characteristics of the BD population were not measured such as those relating to the course and severity of BD. These characteristics may not have been equally distributed across subgroups of BD patients such as the normal and abnormal sleepers and may have therefore be un-controlled confounders of the relationship between sleep and cognitive function.

There are some statistical limitations in the methodology of this study. The study was underpowered to make comparisons between BD subgroups such as depressed and euthymic abnormal sleeping groups and those with different sleep phenotypes. This may have led to type two errors due to a lack of statistical power to detect true between group differences. This also meant that comparisons between different sleep phenotypes and between those with multiple

sleep abnormalities may be unreliable due to the small sample sizes and require replication in larger samples. A further statistical limitation was that certain characteristics such as mood and sleep abnormalities could not be treated as continuous variables and were treated as categorical variables, i.e. present or absent. Dichotomising data in this way leads to a loss of information and statistical power and there is also uncertainty in defining the cut point (Royston et al., 2006). However due to the fundamental differences in mood between BD patients and controls the BD group was divided into subgroups of euthymic patient and depressed patients to control for mood. The reason for this method was that mood symptoms were fundamentally different in controls and BD patients due to the inclusion criteria. Therefore, it was not appropriate to control for mood symptoms with ANCOVA when there is heterogeneity in regression lines between mood and cognitive function between groups. Euthymic BD patients who would have mood symptoms more similar to controls were therefore also compared to control for the effects of mood. A weakness in this method is that despite being classified as euthymic BD patients may still have residual mood symptoms that have not been controlled for. In the euthymic abnormal sleepers however the mean BDI score was 3.6 (SD 2.7) vs. 0.7 (SD 1.8) in controls so there were differences in mood score that may have been responsible for the differences in cognitive function although it is likely these were minimal. A further weakness is that type of relationship between mood and cognitive function could not be explored and whether this relationship was linear or had other properties. The same limitations apply to the analyses performed comparing normal and abnormal sleepers with controls. Sleepers were divided into those with and without objective sleep abnormalities based on sleep length

and pattern. These are arbitrary definitions based on perceived normal ranges of sleep length and timing in the general population. It would have been better to treat abnormal sleep as a continuous variable to more fully assess its relationship with cognitive function. However there was no simple continuous measure of sleep abnormality available as the nature of the sleep abnormalities were so variable. This approach also prevented assessment of the relationship of the severity of sleep abnormalities with cognitive function. However despite this approach this study identified differences between normal and abnormal sleepers and controls including those who were euthymic. The confounding effect of depressive symptoms was also likely not important in these comparisons as BDI scores were almost identical in euthymic normal and abnormal sleepers (3.8 (SD 2.7) vs. 3.6 (SD 1.9) respectively) and therefore the main difference between these groups was the sleep abnormalities. However as described above there may have been other un-measured differences between normal and abnormal sleepers in illness history and severity that may therefore be unmeasured confounders of this relationship.

A further limitation of this study is that there was little control for multiple comparisons in the study which may have increased the chances of type I errors. This limitation has already been extensively discussed in section 4.7.10.

Although a strength of this study was the objective sleep assessments there are also some limitations of the specific methods employed. Accelerometry has been validated against PSG but it lacks specificity in correctly identifying periods of restful wakefulness from sleep and transitions between wake and sleep. This is especially the case in people with disturbed sleep. Therefore the estimates of

sleep variables are likely not 100% accurate. In particular, accelerometry has difficulty in correctly identifying daytime sleep so 24-hour sleep time was not able to be calculated and the study used a measure of nocturnal sleep and daytime sedentary behaviour as an estimate of 24-hour sleep. There were also several limitations of the actual device and algorithm utilised in this study. Firstly, neither the device nor the algorithm have been validated with PSG specifically in BD patients. Secondly, the algorithm did not calculate two common variables reported in other accelerometry studies, sleep onset latency and WASO and these may have been useful in assessing the relationship between sleep and cognitive function. Although accelerometry was utilised for the detection of PLMS the algorithm that was in development was not available in time for analysis of the data collected. Therefore it is unknown if any patients had PLMS which may have been a cause of some of the sleep abnormalities.

A limitation of this study is its cross sectional design which means no conclusions could be drawn about direction of causality in the associations of sleep abnormalities, mood, psychosocial and cognitive function. An interventional study would be better suited to answer this question where sleep was manipulated and the consequences assessed.

A further limitation is that the majority of BD patients were prescribed psychotropic medications which may influence sleep/wake cycles, daytime alertness and cognition. However, medication use was not associated with any of the cognitive outcomes assessed in the study so it seems unlikely they had any influence on the primary objectives of this study. In addition, it is not ethical to

ask patients to stop medications and these patients are representative of the general BD population.

A final limitation of this study was noted after completion of the data analysis. Four of the control subjects with advanced or delayed sleep phases were actually included within the control cohort and therefore theoretically were not strictly defined normal sleepers. In the BD group those with phase advanced or delayed sleep were considered as abnormal sleepers, although several of these also had evidence of other sleep abnormalities so were true abnormal sleepers. The main analyses were performed again without the inclusion of these controls. The study findings and levels of statistical significance were identical to when they were included and so the results are reported in this thesis including those controls with delayed or advanced sleep phase.

4.10 Future research

As this study is the first to demonstrate an association of objective sleep abnormalities with cognitive function future research should firstly aim at replicating the findings in this study whilst addressing the limitations of this study described above. Future studies should utilise advances in the methods of assessment of the sleep wake cycle including better discrimination between sleep and restful wakefulness. This would give better information on daytime sleep, more accurate quantification of total 24-hour sleep and therefore enable discrimination between the roles of actual daytime sleep versus daytime sedentary behaviour in cognitive function. Better characterisation of sleep should also include formal diagnosis of sleep disorders in participants. Given the high rate of CRD in BD the assessment of participant exposure to light may also have

be beneficial. Light is the strongest zeitgeber for the circadian system and differences in light exposure may help in the understanding of the causes of CRDs. The accelerometer utilised in this study was able to assess light exposure but as participants could cover the light meter with clothing or bed clothing this data was not utilised. Having a device worn over clothing that recorded light exposure or additionally having a light meter in the bedroom may have been beneficial in understanding differences between patients and controls and those with and without CRDs. Future studies should continue to record accelerometer data in SI units and efforts should be made to pool data. This will allow increased sample sizes and statistical power for subgroup comparisons. It would also be useful to develop a standardised battery of cognitive assessments that have been demonstrated to be impaired in BD and additionally associated with sleep abnormalities. This would also allow cross study comparisons and the pooling of data.

Future research should include longitudinal studies than can also explore the effect of therapeutic interventions to improve sleep function in BD patients and assess their effects on psychosocial and cognitive function. For example future studies could include assessment of the efficacy of social rhythm therapy, melatonin, CBTi, and CPAP for improving sleep and potentially cognitive function in BD. Increased physical activity should also be explored as a potential treatment to improve sleep function in BD and if improved sleep achieved via greater physical activity also results in reductions in cognitive deficits. To further understand the mechanisms for the association of sleep and cognitive function PSG should be performed in different sleep phenotypes to more carefully characterise the nature of the sleep abnormalities and search for abnormalities

in the sleep EEG. EEG abnormalities could then also be examined for associations with impaired cognitions. In addition, fMRI should be utilised to study brain function in BD patients with clinical sleep abnormalities whilst performing cognitive tests in order that the brain areas most impacted by sleep abnormalities could be identified. fMRI studies should also be performed as an integral part of interventional studies. This would allow the exploration of the treatment of sleep abnormalities on brain function and how that is associated with any improvements in cognitive function. WMI and its association with sleep abnormalities and cognitive function should also be explored in BD as this may provide evidence of the aetiology of cognitive deficits in BD. Since attention is the cognitive domain most strongly associated with sleep abnormalities future studies should assess the effect of attentional deficits on other cognitive functions such as memory and executive functions. It is possible that deficits in attentional function underlie deficits in other cognitive functions and this possibility should be further explored. Future research should also more closely examine the relationship between sleep associated cognitive deficits and psychosocial function and how improvements in sleep and cognitive function are associated with psychosocial outcomes. Another important line of future research would be to closely examine the association between sleep abnormalities and mood. There was a clear association of sleep abnormalities with mood in this study but the nature of the relationship and direction of causality is unknown. A longitudinal interventional study assessing sleep, mood and cognitive function and the impact of interventions either improving or worsening sleep function will allow direction of causality to be assessed.

5. Appendix

Appendix A Healthy volunteer participant eligibility questionnaire

Northumberland, Tyne and Wear NHS
NHS Foundation Trust

Newcastle University

The Association between Sleep and Cognition in Bipolar Disorder and Insomnia.

(The ASCRIBE Study)

Participant Eligibility Questionnaire

Healthy volunteers

Date:

Rater's initials:

Study Code:

Date of Birth:	Age (18-60):	
Gender:	Ethnicity:	
	Inclusion	Exclusion
NART IQ : (required> 90)	Yes	No
Fluent in English	Yes	No
Personal or first degree relative of axis I psychiatric disorder (confirmed by MINI)	No	Yes
Grid HAMD17 score <7	Yes	No
YMRS score <5	Yes	No
Currently psychiatrically well confirmed by MINI interview	Yes	No
PSQI score < 5	Yes	No
ESS score < 10	Yes	No
Self reported sleep problems	No	Yes
Current alcohol or substance misuse (defined by DSM IV criteria)	No	Yes
Current shift work	No	Yes
Head injury with loss of consciousness	No	Yes
Major neurological disorder	No	Yes
Major medical disorder	No	Yes
Taking psychotropic medication	No	Yes
Consent form signed	Yes	No

National Adult Reading Test (NART)

Chord	Heir	Placebo
Ache	Radix	Abstemious
Depot	Assignate	Detente
Aisle	Hiatus	Idyll
Bouquet	Subtle	Puerperal
Psalm	Procreate	Aver
Capon	Gist	Gauche
Deny	Gouge	Topiary
Nausea	Superfluous	Levuiathan
Debt	Simile	Beatify
Courteous	Banal	Prelate
Rarefy	Quadruped	Sidereal
Equivocal	Cellist	Demesne
Naive	Facade	Syncope
Catacomb	Zealot	Labile
Gaoled	Drachm	Campanile
Thyme	Aeon	

Total NART Score_____ Predicted IQ_____

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSM-IV

	Modules	Time Frame	Meets Criteria	DSM-IV	ICD-10
A	Major depressive episode	Current (2 weeks) Recurrent	☐ ☐	296.20-296.26 single 296.30-296.36 Recurrent	F32.x F33.x
	MDE with melancholic features (optional)	Current (2 weeks)	☐	296.20-296.26 Single 296.30-296.36 Recurrent	F32.x F33.x
B	Dysthymia	Current (past 2 yrs)	☐	300.4	F34.1
C	Suicidality	Current (past month) Risk: low medium high	☐		
D	Manic Episode	Current Past	☐ ☐	296.00-296.06	F30.x-F31.9
	Hypomanic Episode	Current Past	☐ ☐	296.80-296.89	F31.8-F31.9/F34.0
E	Panic Disorder	Current (past month) Lifetime	☐ ☐	300.01/300.21	F40.01-F41.0
F	Agrophobia	Current	☐	300.22	F40.00
G	Social Phobia (social anxiety disorder)	Current (past month)	☐	300.23	F40.1
H	Obsessive compulsive disorder	Current (past month)	☐	300.3	F42.8
I	Post traumatic stress disorder (optional)	Current (past month)	☐	309.81	F43.1
J	Alcohol dependence	Past 12 months	☐	303.9	F10.2x
	Alcohol abuse	Past 12 months	☐	305.00	F10.1
K	Substance dependence (non alcohol)	Past 12 months	☐	304.00-.90/305.20-.90	F11.1-F19.1
	Substance abuse (non alcohol)	Past 12 months	☐	304.00-.90/305.20-.90	F11.1-F19.1
L	Psychotic disorders	Lifetime	☐	295.10-295.90/297.1	F20.xx-F29
		Current	☐	297.3/293.81/293.82/ 293.89/298.8/298.9	
	Mood disorder with psychotic features	Lifetime	☐	296.24/296.34/296.4	F32.3/F33.3/
		Current	☐		F30.2/F31.2/F31.5 F31.8/F31.9/F39
M	Anorexia Nervosa	Current (past 3 months)	☐	307.1	F50.0
N	Bulimia Nervosa	Current (past 3 months)	☐	307.51	F50.2
	Anorexia nervosa, binge eating/purging type	Current		307.1	F50.0
O	Generalised anxiety disorder	Current (past 6 months)	☐	300.02	F41.1
	Antisocial personality disorder optional	Lifetime	☐	301.7	F60.2

General Instructions

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10.Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

Interview

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

General format

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

- At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
- At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

Conventions

- *Sentences written in* « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.
- *Sentences written in* « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.
- *Sentences written in* « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.
- *Answers with an arrow above them* (➨) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.
- When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).
- *Phrases in (parentheses*) are clinical examples of the symptom. These may be read to the patient to clarify the question.

Rating instructions

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear. The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

A. Major Depressive Episode

➡ means: Go to the diagnostic boxes, circle NO in all diagnostic boxes and move to the next module.

A1	Have you been consistently depressed or down, most of the day, nearly every day for the last 2 weeks?	No	Yes
A2	In the past 2 weeks have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	No	Yes
	Is **A1** or **A2** coded YES? ➡	No	Yes

A3 **Over the past two weeks, when you felt depressed or uninterested:**

a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)? IF **YES** TO EITHER, CODE **YES**.	No	Yes*
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	No	Yes
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	No	Yes*
d	Did you feel tired or without energy almost every day?	No	Yes
e	Did you feel worthless or guilty almost every day?	No	Yes
f	Did you have difficulty concentrating or making decisions almost every day?	No	Yes
g	Did you repeatedly consider hurting yourself,, feel suicidal, or wished you were dead?	No	Yes

ARE 5 OR MORE ANSWERS **(A1-A3)** CODED YES?

NO	**YES***
MAJOR DEPRESSIVE EPISODE, CURRENT	

IF PATIENT HAS MAJOR DEPRESSIVE EPISODE CONTINUE TO A4, OTHERWISE MOVE TO MODULE B:

A4 a	During your lifetime, did you have other periods of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about? ➡	No	Yes
b	Did you ever have an interval of at least 2 months without any depression and any loss of interest between 2 episodes of depression?		

NO	**YES***
MAJOR DEPRESSIVE EPISODE, RECURRENT	

*If patient has Major Depressive Episode, Current, code **YES** in corresponding questions on next page.

Major Depressive Episode with Melancholic Features (optional)

➡ means: Go to the diagnostic box, circle NO in all diagnostic boxes and move to the next module.

IF THE PATIENT CODES YES FOR A CURRENT MAJOR DEPRESSIVE EPISODE (A3=YES),EPLORE THE FOLLOWING

A5a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?	No	Yes
b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up?	No	Yes
		➡	
	Is **A5a** or **A5b** coded YES?	No	Yes

A6	**Over the past two weeks, when you felt depressed or uninterested:**		
a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	No	Yes
b	Did you feel regularly worse in the morning, almost every day?	No	Yes
c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	No	Yes
d	IS **A3c** CODED **YES** (PSYCHOMOTOR RETARDATION OR AGITATION)?	No	Yes
e	IS **A3a** CODED **YES** FOR ANOREXIA OR WEIGHT LOSS?	No	Yes
f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	No	Yes

ARE 3 OR MORE **A6** ANSWERS CODED **YES**?

NO	**YES**
MAJOR DEPRESSIVE EPISODE, WITH MELANCHOLIC FEATURES CURRENTCURRENT	

B. Dysthymia

➡ means: Go to the diagnostic box, circle NO in all diagnostic boxes and move to the next module.

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESIVE EPISODE SO NOT EXPLORE THIS MODULE

B1	Have you felt sad, low depressed most of the time for 2 years?	➡ No	Yes
B2	Was this period interrupted by your feeling ok for 2 months or more?	No	Yes
B3	**During this period of feeling depressed most of the time:**		
a	Did your appetite change significantly?	No	Yes
b	Did you have trouble sleeping or sleep excessively?	No	Yes
c	Did you feel tired or without energy?	No	Yes
d	Did you lose your self-confidence?	No	Yes
e	Did you have trouble concentrating or making decisions?	No	Yes
f	Did you feel hopeless?	No	Yes
	ARE 2 OR MORE **B3** ANSWERS CODED YES?	➡ No	Yes
B4	Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?	➡ No	Yes

IS **B4** CODED **YES?**

NO	**YES**
	DYSTHYMIA
	CURRENT

C. Suicidality

	In the past month did you?			**Points**
C1	Think that you would be better off dead or wish you were dead?	No	Yes	1
C2	Want to harm yourself?	No	Yes	2
C3	Think about suicide?	No	Yes	6
C4	Have a suicide plan?	No	Yes	10
C5	Attempt suicide?	No	Yes	10
	In your lifetime:			
C6	Did you ever make a suicide attempt?	No	Yes	4

IS AT LEAST 1 OF THE ABOVE CODED **YES**?

IF YES ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C6) CHECKED "YES" AND SPECIFY THE LEVEL OF SUICIDE RISK AS FOLLOWS:

NO	**YES**
SUICIDE RISK CURRENT	
1-5 points	**Low** ☐
6-9 points	**Moderate** ☐
≥ 10 points	**High** ☐

D. (Hypo) Manic Episode

➡ means: Go to the diagnostic boxes, circle NO in all diagnostic boxes and move to the next module.

D1a	Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper'or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior. IF NO, CODE NO TO **D1b**: IF **YES** ASK:	No	Yes
b	Are you currently feeling 'up' or 'high' or 'hyper' or full of energy?	No	Yes
D2a	Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? IF NO, CODE NO TO **D2b**: IF **YES** ASK:	No	Yes
b	Are you currently feeling persistently irritable?	No	Yes
	IS **D1a** OR **D2a** CODED **YES**?	No	Yes

D3	IF **D1b** OR **D2b** = **YES**: EXPLORE ONLY **CURRENT** EPISODE, OTHERWISE IF **D1b** AND **D2b** = **NO**: EXPLORE THE MOST SYMPTOMATIC **PAST** EPISODE **During the times when you felt high, full of energy, or irritable did you:**		
a	Feel that you could do things others couldn't do, or that you were an especially important person?	No	Yes
b	Need less sleep (for example, feel rested after only a few hours sleep)?	No	Yes
c	Talk too much without stopping, or so fast that people had difficulty understanding?	No	Yes
d	Have racing thoughts?	No	Yes
e	Become easily distracted so that any little interruption could distract you?	No	Yes
f	Become so active or physically restless that others were worried about you?	No	Yes
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	No	Yes
	ARE **3** OR MORE **D3** ANSWERS CODED **YES** (OR **4** OR MORE IF **D1a** IS **NO** (IN RATING PAST EPISODE) OR IF **D1b** IS **NO** (IN RATING CURRENT EPISODE)) ?	No	Yes

D4 Did these symptoms last at least a week and cause significant problems at home, at work, socially, or at school, or were you hospitalized for these problems?

No Yes

THIS EPISODE EXPLORED WAS A ☐ ☐

HYPOMANIC EPISODE MANIC EPISODE

IS **D4** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO	**YES**
HYPOMANIC EPISODE	
CURRENT ☐	
PAST ☐	

IS **D4** CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO	**YES**
MANIC EPISODE	
CURRENT ☐	
PAST ☐	

E. Panic Disorder

➡ means: Circle NO in E5, E6 and E7 and skip to F1

E1a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ No	Yes
b	Did the spells peak within 10 minutes?	➡ No	Yes
E2	At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ No	Yes
E3	Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack?	No	Yes
E4	**During the worst spell can you remember:**		
a	Did you have any skipping, racing or pounding of your heart?	No	Yes
b	Did you have sweating or clammy hands?	No	Yes
c	Were you trembling or shaking?	No	Yes
d	Did you have shortness of breath or difficulty breathing?	No	Yes
e	Did you have a choking sensation or lump in your throat?	No	Yes
f	Did you have chest pain, pressure or discomfort?	No	Yes
g	Did you have nausea, stomach problems or diarrhea?	No	Yes
h	Did you feel dizzy, unsteady, lightheaded or faint?	No	Yes
i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	No	Yes
j	Did you fear you were losing control or going crazy?	No	Yes
k	Did you fear you were dying?	No	Yes
l	Did you have tingling or numbness in parts of your body?	No	Yes
m	Did you have hot flushes or chills?	No	Yes
E5	ARE BOTH **E3,** AND **4** OR MORE **E4** ANSWERS, CODED **YES**?	No	Yes Panic disorder lifetime
	IF YES TO E5 SKIP TO E7		
E6	IF **E5** = **NO,** ARE ANY E4 ANSWERS CODED **YES**?	No	Yes Limited symptom attacks lifetime
	THEN SKIP TO **F1**		
E7	In the past month, did you have such attacks repeatedly (2 or more) followed by persistent concern about having another attack?	No	Yes Panic disorder current

F. Agrophobia

F1	Do you feel anxious or uneasy in places or situations where you might have a panic attack NO YES or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?	No	Yes

IF **F1** = **NO**, CIRCLE **NO** IN **F2**

F2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	No	Yes Agrophobia current

IS **F2** (CURRENT AGROPHOBIA) CODED **NO**

AND

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO

YES

PANIC DISORDER

IS **F2** (CURRENT AGROPHOBIA) CODED **YES**

AND

IS **E7** (CURRENT PANIC DISORDER) CODED **YES?**

NO

YES

PANIC DISORDER

IS **F2** (CURRENT AGROPHOBIA) CODED **YES**

AND

IS **E5** PANIC DISORDER LIFETIME) CODED **NO**?

NO

YES

AGROPHOBIA,

G. Social Phobia (social anxiety disorder)

➡ means: go to the diagnostic box, circle NO and move to next module

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ No	Yes
G2	Is this fear excessive or unreasonable?	➡ No	Yes
G3	Do you fear these situations so much that you avoid them or suffer through them?	➡ No	Yes
G4	Does this fear disrupt your normal work or social functioning or cause you significant distress?		

NO **YES**

SOCIAL PHOBIA

(social anxiety disorder)

CURRENT

H. Obsessive Compulsive Disorder

➡ ABOVE a NO means go to the diagnostic box, circle NO and move to next module

H1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing?(For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though you didn't want to, **or** fearing you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOTINCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	No to H➡	Yes
H2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	No to H4 ➡	Yes
H3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	No	Yes **obsessions**
H4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking compulsions things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	No	Yes **compulsion**
	IS **H3** or **H4** CODED **YES**?	➡ No	Yes
H5	Did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➡ No	Yes
H6	Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, occupational functioning, usual social activities, or relationships, or did they take more than one hour a day?	**NO** **YES** **O.C.D** **CURRENT**	

I. Posttraumatic stress disorder (optional)

➡ means: go to the diagnostic box, circle NO and move to next module

I1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, SUDDEN DEATH OF SOMEONE CLOSE TO YOU, WAR, OR NATURAL DISASTER.	➡ No	Yes
I2	Did you respond with intense fear, helplessness or horror?	➡ No	Yes
I3	During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?	➡ No	Yes
I4	**In the past month:**		
a	Have you avoided talking or thinking about the event?	No	Yes
b	Have you avoided activities, places or people that remind you of the event?	No	Yes
c	Have you had trouble recalling some important part of what happened?	No	Yes
d	Have you become much less interested in hobbies or social activities?	No	Yes
e	Have you felt detached or estranged from others?	No	Yes
f	Have you noticed that your feelings are numbed?	No	Yes
g	Have you felt that your life will be shortened or that you will die sooner than other people?	No	Yes
	ARE **3** OR MORE **I4** ANSWERS CODED **YES**?	➡ No	Yes
I5	**In the past month:**		
a	Have you had difficulty sleeping?	No	Yes
b	Were you especially irritable or did you have outbursts of anger?	No	Yes
c	Have you had difficulty concentrating?	No	Yes
d	Were you nervous or constantly on your guard?	No	Yes
e	Were you easily startled?	No	Yes
	ARE **2** OR MORE **I5** ANSWERS CODED **YES**?	➡ No	Yes
I6	During the past month have these problems significantly interfered with your work or social activities or caused significant distress?		

NO	YES
POSTTRAUMA	

J. Alcohol Abuse and Dependence

➡ means: go to the diagnostic boxes, circle NO in both and move to next module

		➡	
J1	**In the past 12 months**, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?	NO	YES

J2 **In the past 12 months:**

a	Did you need to drink more in order to get the same effect that you got when you first started drinking?	No	Yes
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? IF **YES** TO EITHER, CODE **YES**.	No	Yes
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	No	Yes
d	Have you tried to reduce or stop drinking alcohol but failed?	No	Yes
e	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	No	Yes
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	No	Yes
g	Have you continued to drink even though you knew that the drinking caused you health or mental problems?	No	Yes

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

NO	YES*
ALCOHOL DEPENDENCE CURRENT	

f ***** IF YES, SKIP J3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE

J3 **In the past 12 months:**

a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	No	Yes
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?		
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	No	Yes
d	Did you continue to drink even though your drinking caused problems with your family or other people?	No	Yes

ARE **1** OR MORE **J3** ANSWERS CODED **YES**?

NO	N/A	YES
ALCOHOL ABUSE CURRENT		

K. Non –Alcohol Psychoactive Substance Use Disorders

➡ means: go to the diagnostic boxes, circle NO in all diagnostic boxes and move to next module

	Now I am going to show you/read to you a list of street drugs or medicines.		
K1a	**In the past 12 months:**did you take any of these drugs more than once to get high, to feel better, or to change your mood?	➡ No	Yes

Circle each drug taken

Stimulants: amphetamines, "speed", crystal meth, "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("Angel Dust", "peace pill"), psilocybin, STP, "mushrooms", ecstasy, MDA, or MDMA

Inhalants: "glue", ethyl chloride, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown

Miscellaneous: steroids, nonprescription sleep or diet pills, GHB. Any others?

SPECIFY MOST USED DRUGS:

ONLY ONE DRUG / DRUG CLASS HAS BEEN USED ☐

ONLY THE MOST USED DRUG CLASS IS INVESTIGATED ☐

EACH DRUG CLASS USED IS EXAMINED SEPARATELY (COPY K2 AND K3 AS NEEDED) ☐

b	SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXPLORED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE:		
K2	**Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**		
a	Have you found that you needed to use more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	No	Yes
b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	No	Yes
	IF **YES** TO EITHER CODE **YES**		
c		No	Yes

Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?

d Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed? No Yes

e On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug? No Yes

f Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? No Yes

g Have you continued to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused you health or mental problems? No Yes

ARE **3** OR MORE **K2** ANSWERS CODED **YES**?

SPECIFY DRUG(S):

NO	**YES***
SUBSTANCE DEPENDANCE	
CURRENT	

***** IF YES, SKIP K3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX FOR THIS SUBSTANCE AND MOVE TO THE NEXT DISORDER.
DEPENDENCE PREEMPTS ABUSE.

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

K3a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? No Yes
Did this cause any problem?

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? No Yes

C Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? No Yes

d Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused problems with your family or other people? No Yes

ARE **1** OR MORE **K3** ANSWERS CODED **YES**?

SPECIFY DRUGS:

NO	**N/A**	**YES**
SUBSTANCE ABUSE		
CURRENT		

L. Psychotic Disorders and Mood Disorder with Psychotic Features

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF

PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

	Now I am going to ask you about unusual experiences people have			Bizarre
L1a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? **NOTE**: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING	No	Yes	YES
b	**IF YES:** do you currently believe these things?	No	Yes	YES →L6
L2a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	No	Yes	YES
b	**IF YES:** do you currently believe these things?	No	Yes	YES →L6
L3a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	No	Yes	YES
b	**IF YES:** do you currently believe these things?	No	Yes	YES →L6
L4a	Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?	No	Yes	YES
b	**IF YES:** do you currently believe these things?	No	Yes	YES →L6

				Bizarre
	Now I am going to ask you about unusual experiences people have			
L5a	Have your relatives or friends ever considered any of your beliefs strange or unusual? INTERVIEWER**:** ASK FOR EXAMPLES. ONLY CODE **YES** IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS L1 TO L4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITIUTION, ETC.	No	Yes	YES
b	**IF YES:** do they currently consider your beliefs strange?	No	Yes	YES
L6a	Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING:	No	Yes	
	IF YES: did you hear a voice commentating on your thoughts or behavior or did you hear 2 or more voices talking to each other?			YES
b	**IF YES:** have you heard these things in the past month?	No	Yes	YES
b	**IF YES:** do you currently believe these things?	No	Yes	YES →L8b
L7a	Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE**.**	No	Yes	
b	**IF YES:** have you seen these things in the last month?	No	Yes	
	CLINICIANS JUDGEMENT			
L8b	IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS?	No	Yes	
L9b	IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR?	No	Yes	
L10b	ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW?	No	Yes	

L11a ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L7a CODED **YES OR YES BIZARRE** AND IS EITHER

MAJOR DEPRESSIVE EPISODE, (CURRENT OR RECURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED YES?

No →L13 Ye

IF NO TO L11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO L13.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).

Were the beliefs and experiences you just described (SYMPTOMS CODED **YES** FROM **L1**a TO **L7**a) restricted exclusively to times when you were feeling depressed/high/irritable?

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO L12 AND MOVE TO L13

NO Y

MOOD DISORD WITH PSYCHOT FEATURES

LIFETIME

L12 ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L7b CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED **YES**?

IF THE ANSWER IS YES TO THIS DISORDER, CIRCLE NO TO L13 AND L14 AND MOVE TO THE NEXT MODULE

NO **YES**

MOOD DISORDER WITH PSYCHOTIC FEATURES

CURRENT

L13 ARE 1 OR MORE « b » QUESTIONS CODED **YES BIZARRE**?
OR
ARE 2 OR MORE « b » QUESTIONS CODED **YES** (RATHER THAN **YES BIZARRE**)?

NO **YES**

PSYCHOTIC DISORDER

CURRENT

L14 IS **L13** CODED **YES**
OR
ARE 1 OR MORE « a » QUESTIONS CODED **YES BIZARRE**?
OR
ARE 2 OR MORE « a » QUESTIONS CODED **YES** (RATHER THAN **YES BIZARRE**) AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME TIME PERIOD?

NO **YES**

PSYCHOTIC DISORDER

LIFETIME

M. Anorexia Nervosa

➡ means: go to the diagnostic box, circle NO and move to next module

M1	How tall are you? **cm**	
b	What is your lowest weight in the last 3 months? **Kg**	
c	IS PATIENT'S WEIGHT LOWER THAN THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	NO YES

In the past 3 months

M2	In spite of this low weight have you tried not to gain weight?	No Yes
M3	Have you feared gaining weight or becoming fat, even though you were underweight?	No Yes
M4a	Have you considered yourself fat or that part of your body was too fat?	No Yes
b	Has your body weight or shape greatly influenced how you felt about yourself?	No Yes
c	Have you thought that your current low body weight was normal or excessive?	No Yes
M5	ARE 1 OR MORE ITEMS FROM **M4** CODED **YES**?	No Yes
M6	FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	NO YES No Yes

FOR WOMEN: ARE **M5 AND M6** CODED **YES**?
FOR MEN: IS **M5** CODED **YES**?

NO	YES
ANOREXIA NERVOSA	
CURRENT	

Female Height/Weight

cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	38	39	39	40	41	42	43	44	45	46	47	49	50	51

Male Height/Weight

cm	155	156	160	163	165	168	170	173	175	178	180	183	185	188	191
kgs	47	48	49	50	51	51	52	53	54	55	56	57	58	59	61

The weight thresholds above are calculated as a 15% reduction below the normal range for the patient's height and gender as required by DSM-IV. This table reflects weights that are 15% lower than the low end of the normal distribution range in the Metropolitan Life Insurance Table of Weights.

N. Bulimia Nervosa

➡ means: go to the diagnostic boxes, circle NO in all diagnostic boxes and move to next module

N1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➡ No	Yes
N2	In the last 3 months, did you have eating binges as often as twice a week?	➡ No	Yes
N3	During these binges, did you feel that your eating was out of control?	➡ No	Yes
N4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➡ No	Yes
N5	Does your body weight or shape greatly influence how you feel about yourself?	➡ No	Yes
N6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	No ↓ Skip to N8	Yes
N7	Do these binges occur only when you are under (lbs./kgs.)? NO YES INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE	No	Yes

N8 IS **N5** CODED **YES** AND **N7** CODED **NO** OR SKIPPED?

IS **N7**CODED **YES**?

NO	**YES**
ANOREXIA NERVOSA	

O. Generalised Anxiety Disorder

➡ means: go to the diagnostic box, circle NO and move to next module

O1a	Have you worried excessively or been anxious about several things over the past 6 months?	No ➡	Yes
b	Are these worries present most days?	No ➡	Yes
	IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	No	Yes ➡
O2	Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	No ➡	Yes
O3	FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT**.**		
	When you were anxious over the past 6 months, do you, most of the time:		
a	Feel restless, keyed up or on edge?	No	Yes
b	Feel tense?	No	Yes
c	Feel tired, weak or exhausted easily?	No	Yes
d	Having difficulty concentrating or find your mind going blank?	No	Yes
e	Feel irritable?	No	Yes
f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively?	No	Yes

ARE **3** OR MORE **O3** ANSWERS CODED **YES**?

NO	YES
GENERALISED ANXIETY DISORDER CURRENT	

P. Antisocial Personality Disorder (optional)

➡ means: go to the diagnostic box, and circle NO

P1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight?	No	Yes
b	repeatedly lie, cheat, "con"others, or steal?	No	Yes
c	start fights or bully, threaten or intimidate others?	No	Yes
d	deliberately destroy things or start fires?	No	Yes
e	deliberately hurt animals or people?	No	Yes
f	force someone to have sex with you?	No	Yes

ARE **2** OR MORE **P1** ANSWERS CODED **YES**? ➡ No / Yes

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY
POLITICALLY OR RELIGIOUSLY MOTIVATED**.**

P2 **Since you were 15 have you:**

a	repeatedly behaved in a way that others would consider irresponsible, like NO YES failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	No	Yes
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	No	Yes
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	No	Yes
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	No	Yes
e	exposed others to danger without caring?	No	Yes
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	No	Yes

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO	YES
ANTISOCIAL PERSONALITY DISORDER LIFETIME	

THIS CONCLUDES THE INTERVIEW

GRID HAMD -17

1. Depressed Mood

Frequency				
This item assesses feelings of sadness, hopelessness, helplessness and worthlessness. Note: This is not a global rating of depressive illness.	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild Feelings of sadness, discouragement, low self esteem, pessimism	**0**	**1**	**1**	**2**
Moderate Clear non verbal signs of sadness (such as tearfulness) feelings of hopelessness, helplessness or worthlessness about some aspects of life		**1**	**2**	**3**
Severe Intense sadness, weeping, hopelessness about most aspects of life, feelings of complete helplessness or worthlessness		**2**	**3**	**4**
Very Severe Extreme sadness, intractable hopelessness or helplessness		**3**	**4**	**4**

Whats your mood been like this week (compared to when you feel ok)?
Have you been feeling down or depressed? Sad or hopeless? Helpless? Worthless? (Can you describe what this feeling has been like for you? How bad is the feeling?) Does the feeling lift at all if something good happens? (Does it go away completely or is it just less intense?)
How long have you been feeling this way?
How are you feeling about the future?
Have you been crying at all? if YES how often?

Frequency

- During the last week how often did you feel this way?
- How much of the time did you feel this way?
- How many days in the past week was it? (Was it every day? How much of each day?)

Notes

Conventions
This item should not be considered a global measure of depression severity. Item 1 assesses one of several core symptoms of depression.

- Normal mood fluctuations without clinical significance should be rated "0"
- Rate depressed mood even if patient attributes mood to real life problems (e.g. depressed due to bad job marital conflict)
- Some patients describe feelings of low mood without acknowledging "sadness" or "depression" (e.g. "down," "blah," "numb"). Rate as symptomatic.
- Non vernal signs (e.g.slumped posture, infrequent eye contact, frowning, sad facial expression) are also considered in assessing severity.

Do not rate angry, irritable or anxious mood on this item.

Item score	

2. Guilt

Frequency				
Guilt is defined as the sense of having done something bad or wrong and is accompanied by feelings of regret or shame. Guilt is rated only if it is excessive or unrealistic.	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild Self critical, self-reproach (e.g. "I've let people down.")	**0**	**1**	**1**	**2**
Moderate Feelings of guilt, remorse, shame, belief that one has done something bad or wrong		**1**	**2**	**3**
Severe Pervasive feelings of guilt; feels the illness is a punishment for sinful deeds		**2**	**3**	**4**
Very Severe Delusions, hallucinations			**4**	**4**

Have you been especially critical of yourself this past week, or feeling like you've let others down?
IF YES: What have your thoughts been?
In the past week, have you been feeling guilty about anything you've done or not done?
(IF YES: What have you been feeling guilty about?) (What about things that happened a long time ago?)
How guilty have you been feeling this past week?
Do you feel that your depression is a punishment for something bad that you've done?
(Have you been hearing voices or seeing visions in the last week? IF YES: Tell me about them.)

Frequency

- During the last week how often did you feel this way?
- How much of the time did you feel this way?
- How many days in the past week was it? (Was it every day? How much of each day?)

Notes

Conventions

- Realistic self-reproach is not rated (e.g., feeling bad to some degree about falling behind in work or not attending to children when this is really a problem) unless the patient dwelled on this excessively.
- Vague feelings of low self-esteem (e.g., feeling unattractive to the opposite sex) are not rated unless the low self-esteem is associated with self-reproach or criticism.
- Distinguish between the belief that the patient has brought the depression on themselves by mistakes they have made in their lives (mild or moderate intensity) and the belief that the depression is a punishment for bad things they have done (severe intensity).
- Feelings of worthlessness are an aspect of depressed mood (item 1) and are not rated here unless accompanied by guilt.

Item score	

3. Suicide

Frequency				
This item assesses the full range of severity of suicidal ideation and behaviour	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild Feels life is not worth living, but expresses no wish to die e.g. "I don't care if I live or die".)	**0**	**1**	**1**	**2**
Moderate Wishes to be dead; thoughts of dying but no specific plan or intent (e.g. "if i go thit by a bus I wouldn't care", "I'd like to go to sleep and never wake up.")		**1**	**2**	**3**
Severe Clear suicidal plan or intent; suicidal gesture (e.g. taking a few sleeping pills).		**3**	**3**	**4**
Very Severe Attempts at suicide		**4**	**4**	**4**

This week, have you had thoughts that life is not worth living?
IF YES: What have you thought about?
What about thinking that you'd be better off dead?
IF YES: Can you tell me more about that?
Have you had thoughts of hurting or killing yourself?
IF YES: What have you thought about? Have you actually done anything to hurt yourself?
Frequency

- During the last week how often did you feel this way?
- How much of the time did you feel this way?
- How many days in the past week was it? (Was it every day? How much of each day?)

Notes

Conventions
Note that some patients may attempt to conceal or minimize suicidal thoughts or behaviors.
• Do not rate feelings of discouragement and alienation (e.g., "what's the use," "nobody cares," etc.) unless associated with thoughts that life is not worth living.
• Preoccupation with death, in the absence of wishing to die, is rated as mild intensity.
• Feeling like life is a burden and the wish to escape, without clear thoughts of suicide or death, is rated as mild intensity.
• Suicidal gestures or attempts are rated positively even if the patient describes the behaviors as a cry for help or an act of revenge.
• Suicidal thoughts or plans are rated positively regardless of rationale (e.g., terminal illness).

Item score	

4. Insomnia Early

Frequency				
Time to first falling asleep	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild 30-59 minutes to fall asleep	**0**	**1**	**1**	**2**
Marked 1 hour or more to fall asleep		**1**	**2**	**2**

I'd like to ask you about your sleep in the past week.
What were your usual hours of going to sleep and waking up before this began?
In the past week, have you had trouble falling asleep at the beginning of the night?
How long has it taken you to fall asleep?
Have you changed the time at which you try to get to sleep since you've been depressed?

Frequency

- During the last week how often have you had trouble falling asleep?
- How many nights in the last week was it? (Was it every night?).

Notes

Conventions
Nighttime insomnia is rated even if the patient attributes this to daytime napping.
• Do not rate difficulty falling or staying asleep due to unambiguous external causes, e.g., baby crying, neighbor's party, etc.
• Early insomnia is rated even if the patient goes to bed later because he is unable to fall asleep.
• If the patient used sleeping pill(s) during the past week, rate the intensity and frequency of insomnia as it occurred with the use of the sleeping pill(s). If the patient used sleeping pills fewer than 7 nights during the past week, base your rating on an average of the intensity and frequency of insomnia over the entire week, including those nights on which the patient did not use sleeping pill(s).

Item score	

5. Insomnia Middle

Frequency				
After falling asleep and until 2 hours prior to the usual hour of waking.	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild 30-59 minutes awake	**0**	**1**	**1**	**2**
Marked 1 hour or more awake		**1**	**2**	**2**

In the past week, have you been waking up in the middle of the night?
IF YES: How long has it taken you to fall back asleep?
Has your sleep been restless or disturbed?
IF YES: How many nights this week has your sleep been restless?
Frequency• During the past week, how many times each night have you woken up?
• How many nights in the past week did this occur?

Notes

Conventions
• Nighttime insomnia is rated even if the patient attributes this to daytime napping.
• Do not rate difficulty falling or staying asleep due to unambiguous external causes, e.g., baby crying, neighbor's party, etc.
• Rate all insomnia items that apply. E.g., if a patient wakes in the middle of the night and can't fall back to sleep at all, rate middle and late insomnia.
• Don't rate waking to use the bathroom, unless it takes ≥30 minutes to fall back to sleep.
• Getting out of bed is not required for a rating of 2.
• For frequent, brief awakenings, sum the total time awake (e.g., 10 + 10 + 10 = 30 minutes).
• Restlessness, without being awake more than a total of 30 minutes, can merit a maximum rating of 1 only if it occurs much of the time or almost all of the time.
• If the patient used sleeping pill(s) during the past week, rate the intensity and frequency of insomnia as it occurred with the use of the sleeping pill(s). If the patient used sleeping pills fewer than 7 nights during the past week, base your rating on an average of the intensity and frequency of insomnia over the entire week, including those nights on which the patient did not use sleeping pill(s).

Item score	

6. Insomnia Late

Frequency				
Within 2 hours of usual hour of waking. May stay awake during this time frame or may return to sleep after full awakening.	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild 30-59 minutes awake	**0**	**1**	**1**	**2**
Marked 1 hour or more awake		**1**	**2**	**2**

This past week, what time have you been waking up in the morning for the last time? (COMPARE TO PREMORBID WAKE TIME)
IF EARLY: Is that with an alarm clock or do you wake up yourself?
Are you able to fall back asleep?
How long does it usually take you to fall back asleep?
Frequency• During the past week, how many mornings did you wake up earlier than is usual for you?

Notes

Conventions
• Nighttime insomnia is rated even if the patient attributes this to daytime napping.
• Do not rate difficulty falling or staying asleep due to unambiguous external causes, e.g., baby crying, neighbor's party, etc.
• Don't rate waking to use the bathroom, unless it takes ≥30 minutes to fall back to sleep.
• Getting out of bed is not required for a rating of 2.
• For frequent, brief awakenings, sum the total time awake (e.g., 10 + 10 + 10 = 30 minutes).
• If the patient used sleeping pill(s) during the past week, rate the intensity and frequency of insomnia as it occurred with the use of the sleeping pill(s). If the patient used sleeping pills fewer than 7 nights during the past week, base your rating on an average of the intensity and frequency of insomnia over the entire week, including those nights on which the patient did not use sleeping pill(s).

Item score	

7. Work and Activities

Frequency				
This item assesses loss of interest or pleasure and impairment in functioning at work inside and outside the home, leisure activities, and family and social relationships.	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild Some reduction in interest or pleasure but no clear impairment in functioning.	**0**	**1**	**1**	**2**
Moderate Significant reduction in interest or pleasure or clear impairment in functioning.		**1**	**2**	**3**
Severe Profound reduction in interest, pleasure and functioning.		**2**	**3**	**4**
Very Severe Unable to work; needs help performing self care activities; unable to function without assistance.		**3**	**4**	**4**

How have you been spending your time this past week (when not at work)?
Have you felt interested in doing (those things), or do you feel you have to push yourself to do them?
Before this (depression) began, what types of things did you enjoy doing? Have you stopped doing anything you used to do?
What about hobbies? IF YES: Why?
IF WORKING (IN OR OUT OF THE HOME): Have you been able to get as much (work) done as you usually do? IF NO: How much less?
Do you have to push yourself to get things done? IF YES: How hard?
How much time have you been spending with your family and friends? Is this less than usual?

Severity

- How much less interested in things have you been during this past week? How much less do you enjoy them?
- How much harder has it been for you to do your work this past week?

Frequency

- During the past week, how often did you feel this way?
- How much of the time did you feel this way?
- How many days in the past week? (Was it every day? How much of each day?)

Conventions
This item assesses three dimensions that may sometimes be independent: loss of interest, loss of pleasure, and impairment. Severe and very severe intensity require disturbance in all three domains.

- Consider multiple domains of functioning (job, home, recreational activities), giving greater weight to roles that take up most time or are most important to the patient.
- Impairment is evidenced by decreased time spent in activities, decreased productivity, or both.
- Severe intensity requires impairment in primary role functioning or in multiple domains.
- If unemployed, consider reasons why the patient is not working. Rate very severe only if the patient is unable to work due to the depression.
- Do not rate inactivity that is better accounted for by fatigue or low energy (e.g., when patient tries to work but is too tired to continue).

Notes	**Item score**	

8. Psychomotor Retardation

		Conventions This item rates behavioral indicators of psychomotor retardation. Do not assess the patient's subjective feelings of being slowed down. • Consider delays in verbal responses and rate of speech as well as physical movements. • The rater should take into account the full range of psychomotor retardation that occurs in people with depression. Note: Retardation and Agitation (item 9) occasionally coexist, but only at mild intensity.
This item assesses retardation in movement and speech observed during interview		
Symptom intensity		
Absent	**0**	
Mild Rate of speech slightly reduced	**1**	
Moderate Rate of speech clearly reduced with noticeable pauses	**2**	
Severe Interview clearly prolonged; all movements very slowed	**3**	
Very Severe Interview cannot be completed	**4**	
RATE BASED ON OBSERVATION		
Notes	**Item Score**	

9. Psychomotor Agitation

		Conventions This item rates behavioral indicators of psychomotor agitation. Do not assess the patient's subjective feelings of agitation and/or restlessness. Note: Agitation and Retardation (item 8) occasionally coexist, but only at mild intensity.
This item assesses agitation in motor behaviour and speech observed during interview.		
Symptom intensity		
Absent Movements within normal range (e.g., occasionally shifts position in seat)	**0**	
Mild Doubtful or slight agitation, mild restlessness (e.g., frequently changing position in seat, foot-tapping, playing with hair, hands, or clothes)	**1**	
Moderate Moderate to marked restlessness or agitation (e.g. wringing hands, excessive scratching or picking)	**2**	
Severe Cannot sit still or stay seated even for a short period of time; pacing	**3**	
Very Severe Interview cannot be completed	**4**	
RATE BASED ON OBSERVATION		
Notes	**Item Score**	

10. Anxiety, Psychic

Frequency				
This item assesses apprehension, fear, panic and worry as well as irritability. Note: Do not rate physical symptoms of panic attacks here. Rate in item 11: anxiety somatic.	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild Some feelings of worry or irritability	**0**	**1**	**1**	**2**
Moderate Excessive worry or irritability; anxiety causes distress; may cause some impairment in functioning		**1**	**2**	**3**
Severe Pervasive worry or dread; fearing the worst; apprehension obvious in demeanor or behaviour; significant impairment in functioning; feelings of panic		**2**	**3**	**4**
Very Severe Incapacitating		**3**	**4**	**4**

Have you been feeling especially tense or irritable this past week?
IF YES: In what kinds of situations? Is this more than is normal for you?

Have you been worrying a lot this past week? (About what?)
Do you worry about what's going to happen in the future? IF YES: What do you worry about happening?
Have you been feeling panicky this past week? IF YES: What's that feeling been like?

Severity
- How bad has this been this past week?
- How much difficulty has this caused you this past week?

Frequency
- During the past week, how often did you feel this way?
- How much of the time did you feel this way?
- How many days in the past week? (Was it every day? How much of each day?)

Conventions

Excessive worry is out of proportion, either in time spent worrying or in intensity of worry.

• If a patient has a few panic attacks with no anxiety at other times, this is rated as severe but occasional (e.g., 2 or 3).

• Psychic anxiety associated with a comorbid anxiety disorder (generalized anxiety disorder, panic disorder, social anxiety disorder, specific phobia) is rated even if this disorder preceded the depression and did not worsen with the onset of depression.

Notes	**Item score**	

11. Anxiety Somatic

Frequency				
This item assesses physical symptoms associated with anxiety. **Gastrointestinal** - dry mouth, gas, indigestion, diarrhea, constipation, stomach cramps, belching **Cardiovascular** - heart pounding or racing **Respiratory** - sighing, hyperventilation **Other** - headaches, urinary frequency, sweating, lightheadedness	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild Some distress	**0**	**1**	**1**	**2**
Moderate Marked distress may cause some impairment in functioning		**1**	**2**	**3**
Severe Significant impairment in functioning		**2**	**3**	**4**
Very Severe Incapacitating		**3**	**4**	**4**

Tell me if you've had any of the following physical symptoms in the past week. (READ LIST FROM GRID, PAUSING AFTER EACH SYMPTOM)

Assess Severity for Each Symptom
- How bad has it been? (Did you have to take medicine for it?)
- How much has it bothered you this past week?
- Has it gotten in the way of your doing the things you usually do? (How much? In what way?)

Assess Frequency for Each Symptom
- During the past week, how often did you feel this way?
- How much of the time did you feel this way?
- How many days in the past week? (Was it every day? How much of each day?)

Conventions
In general, it is the overall impact of the combined symptoms that determines the level of intensity for this item.

- Headaches are rated in this item (and not in item 13, Somatic Symptoms, General). Rate all headaches here, regardless of type (e.g., tension, migraine).

Notes	**Item score**	

12. Loss of Appetite (somatic symptoms, gastrointestinal)

Frequency				
(Somatic symptoms, Gastrointestina). This item assesses appetite (e.g. hunger, desire for food, enjoyment of food). Note: do not rate other gastrointestinal symptoms here. Rate in item 11; anxiety somatic.	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild Some loss of appetite but eating without encouragement; less interest or pleasure in eating	**0**	**1**	**1**	**2**
Marked Marked loss of appetite, very little interest or pleasure in eating (e.g. forcing self to eat)		**1**	**2**	**2**

How has your appetite been this past week (compared to your usual appetite)? IF LESS: How much less than usual has it been?
Have you enjoyed eating as much as usual?
Have you had to push yourself to eat?
Have other people had to urge you to eat? Have you skipped meals?

Frequency
• During the past week, how much of the time was your appetite less than usual?
• How many meals did you just not feel like eating?
• How many days in the past week were like this? (Was it every day? How much of each day?)

Notes

Conventions

Change in quantity of food eaten may or may not indicate change in appetite. Some patients with decreased appetite may skip meals or eat less at meals. Others continue to eat, but feel they have to push themselves to eat. Both are rated.

• Do not count as symptomatic a patient whose depression has been associated with increased appetite and who is currently improving, with appetite decreasing to normal (pre-depression) levels.

Item score	

13. Somatic Symptoms General

Frequency				
This item assesses tiredness, loss of energy, fatigue and muscular aches and pains	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild Mild tiredness, loss of energy, fatigue, feelings of heaviness in limbs or being weighted down, or muscular aches and pains	**0**	**1**	**1**	**1**
Marked Prominent tiredness, loss of energy, fatigue, feelings of heaviness in limbs or being weighted down, or muscular aches and pains		**1**	**2**	**2**

How has your energy been this past week, compared to before you were depressed? IF LESS THAN USUAL: How much less energy than usual have you had?
Have you felt tired? (How bad has it been?)
This week, have you had any muscle aches or pains?
Have you felt any heaviness in your limbs, back, or head this past week? Or have you felt weighted down this past week?
How bad has it been?

Frequency
• During the past week, how often did you feel this way?
• How much of the time did you feel this way?
• How many days in the past week? (Was it every day? How much of each day?)

Notes

Conventions

Note that this item rates loss of physical energy as opposed to lack of interest, which is rated in item 7 (Work and Activities), although many patients have both symptoms.
• Any of the symptoms listed (e.g., decreased energy, heaviness in limbs, muscle aches) is sufficient to earn a positive rating on this item.
• Do not rate fatigue or muscle aches due to extra exertion or other causes clearly unrelated to depression (e.g., the flu, working very long hours).
• Headaches are not rated here, but are rated in item 11 Anxiety, Somatic.

Item score	

14. Sexual Interest, (Genital Symptoms)

<table>
<tr><td colspan="2"></td><td rowspan="11">Conventions

Problems with sexual performance are not rated here, as long as interest remains unchanged.

• This item does not assess other symptoms (e.g., menstrual difficulties) categorized as genital in some versions of the HAMD.

• For a person without a partner, decreased interest may be evidenced by decreased thoughts about sex.

• Sexual interest is not limited to desire for intercourse, but includes desire for other sexual behaviors, e.g., masturbation.

• The non-depressed level of sexual interest varies considerably. Do not rate unless current interest is lower than non-depressed levels.

• A change from a very high level of interest to an average level of interest is still a decrease and is rated.

• Do not rate avoidance of partner due to interpersonal conflict if sexual interest remains unchanged.

• A person who has sex regularly despite reduced interest (e.g., to accommodate a partner) is still rated as symptomatic.</td></tr>
<tr><td colspan="2">This item assesses loss if interest or pleasure in sex; not amount of activity</td></tr>
<tr><td>Symptom intensity</td><td></td></tr>
<tr><td>Absent</td><td>0</td></tr>
<tr><td>Mild
Some loss of interest or pleasure</td><td>1</td></tr>
<tr><td>Marked
Marked loss of interest or pleasure</td><td>2</td></tr>
<tr><td colspan="2">How has your interest in sex been in this past week? I’m not asking about actual sexual activity, but about your sexual interest or pleasure.

IF LOW OR NO INTEREST OR PLEASURE: Is this a change, compared to when you feel well?

Is it a little less or a lot less?</td></tr>
<tr><td colspan="2">Notes</td></tr>
<tr><td></td><td>Item Score</td><td></td></tr>
</table>

15. Hypochondriasis

Frequency				
This item assesses unjustified preoccupation with having a general medical illness regardless of whether present or not.	**Absent** Not occurring or clinically insignificant	**Occasional** Infrequent; less than 3 days; up to 30% of the week	**Much of the time** Often; 3-5 days; 31%-75% of the week	**Almost all of the time** Persistent; 6-7 days; More than 75% of the week
Symptom intensity				
Absent	**0**			
Mild Preoccupation with bodily functions and sensations, but no concern about a specific illness	**0**	**1**	**1**	**2**
Moderate Excessive or unrealistic worry about having an illness (e.g. "I worry that these headaches are from a brain tumor)		**1**	**2**	**3**
Severe Severe unrealistic conviction of having an illness (e.g. "I am convinced I have cancer)		**2**	**3**	**3**
Very Severe Somatic delusions or hallucinations (e,g. " My insides are rotting")		**4**	**4**	**4**

In the last week, how much have your thoughts been focused on your physical health or how your body is working?
What have your thoughts been? Have you thought about this more than you did before you became depressed?
Have you worried that you might be sick or have some type of physical illness? IF YES: What are you afraid you have?
Have you seen a doctor about these problems?IF YES: What did the doctor say?
Severity• How much time have you spent thinking about this?
• How worried have you been about this?
• How sure are you that you have (illness)?
Frequency• During the past week, how often did you think about this?
• How much of the time did you think about this?
• How many days in the past week? (Was it every day? How much of each day?)

Conventions
Somatic symptoms, themselves (e.g., stomach aches) are rated under Anxiety, Somatic (Item 11). Rate here the patient's worry about or preoccupation with having the condition.
• Concerns about physical appearance (e.g., being overweight) are not rated in this item.
• Concerns about depressive symptoms, such as being tired or not sleeping, are rated only if the patient worries that these symptoms suggest a nonpsychiatric medical disease.
• Do not rate fears of getting or catching an illness; only the belief that the patient is already ill.
• A person who still strongly believes they have a specific illness despite overwhelming evidence to the contrary (e.g., repeated medical tests) is rated as having hypochondriasis.

Notes	**Item score**	

16. Loss of weight

Rate A or B but not both. DO not rate weight loss due to dieting and non depression related circumstances (e.g. weight loss due to general medical conditions).

A. When rating by history. At initial assessment compare to premorbid weight. At follow up compare to previous visit.		**B. When rating by actual weight changes.** Guidelines provided below apply to individuals who are of average weight.	
No weight loss	**0**	**Less than 1 lb. (0.5kg)loss per week since last visit**	**0**
Probable weight loss	**1**	**1-2 lb. (0.5-1.0kg) loss per week since last visit.**	**1**
Definite weight loss	2	**More than 2 lb. (>1kg) per week since last visit**	**2**

Have you lost any weight since this depression began?
AT INITIAL ASSESSMENT: Have you lost any weight since this began? IF YES: Do you think it was because of feeling depressed or down? How much did you lose?

IF NOT SURE: Do you think your clothes are any looser on you? IF YES: How much looser?

AT FOLLOW-UP: Have you lost any weight since your last visit? IF YES: Do you think it was because of feeling depressed or down? How much did you lose?

IF NOT SURE: Do you think your clothes are any looser on you? IF YES: How much looser?

Have you gained any of the weight back? IF YES: How much?

NOTE: RATE 1 or 2 ONLY IF PATIENT LOST WEIGHT AND HAS NOT BEGUN TO GAIN IT BACK.

Notes

Conventions

At follow-up visit: If patients are still under their premorbid weight, the previous rating is carried forward, even if they have not lost additional weight (assuming that they have not gained any weight back).

- If patients were rated positive for weight loss at initial assessment, and have begun to gain weight but are still under their premorbid weight, decrease the score in the following manner: a probable (e.g., 1-2 lb) weight gain would lower the score by one point. For example, a 2 would be lowered to a 1 or a 1 would be lowered to a 0. A definite (greater than 2 lb) weight gain would reduce either a 2 or a 1 to a 0.
- If weight loss was rated at initial assessment with a score of 1 (probable weight loss) and at a follow-up visit the patient definitely weighs less (compared to her usual self), score 2.
- Some patients "rationalize" weight loss after the fact (e.g., feeling pleased and stating that the weight loss was beneficial because they needed to lose weight). This is still rated as symptomatic.
- When onset of the depressive episode is accom-panied by weight gain, do not rate subsequent weight loss unless it falls below the pre-depres-sion weight.
- If the patient was rated 0 at initial assessment and began to lose weight during the study, rate with the guidelines provided (e.g., probable weight loss in the past week would merit a score of 1, definite weight loss, a score of 2).

Item score	

17. Insight

		Conventions
This item assesses pathological denial of illness. do not rate denial that reflects cultural norms.		This item measures the presence of severe denial of being depressed only in patients who are clearly symptomatic. Rate 0 for patients who are not clearly depressed. • This item is rated based on prior questioning. This symptom is not often positive in outpatients and should be rated conservatively. • Do not rate as symptomatic, denial that reflects cultural norms, e.g., in some cultures, admitting to feeling depressed is not generally accepted. • Score a 0 if the patient recognizes they are in a depressed state - even if their explanation for why they are depressed seems implausible ("I'm depressed because I'm not getting enough vitamins"). • Some patients know something is wrong, but are not sure what depression is or if their symptoms are a result of being depressed or due to something else. Score a 0 if the patient allows for the possibility that they may be depressed. In this case, they are not denying they are depressed - they just don't know.
Symptom intensity		
Absent Any recognition of depressive symptoms with or without attribution to any cause (e.g. "I'm depressed because my partner always argues with me")	**0**	
Mild Denies illness but accepts possibility of being ill (e.g. "I don't think theres anything wrong but other people think there is")	**1**	
Marked Complete denial of having illness (e.g. "I'm not depressed I'm fine")	**2**	
Notes		
	Item Score	

Young Rating Scale for Mania

For each item, select the code number which best characterises the patient:

ITEM	CODE	Score
1. ELEVATED MOOD	0 = Absent 1 = Mildly or possibly increased on questioning 2 = Definite subjective elevation: optimistic; self-confident; cheerful, appropriate to content 3 = Elevated, inappropriate to content; humorous 4 = Euphoric; inappropriate laughter; singing	
2. INCREASED MOTOR ACTIVITY ENERGY	0 = Absent 1 = Subjectively increased 2 = Animated; gestures increased 3 = Excessive energy; hyperactive at times; restless (can be calmed) 4 = Motor excitement; continuous hyperactivity (cannot be calmed)	
3. SEXUAL INTEREST	0 = Normal; not increased 1 = Mildly or possibly increased 2 = Definite subjective increase on questioning 3 = Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report 4 = Overt sexual acts (towards patients, staff or interviewer)	
4. SLEEP	0 = Reports no decrease in sleep 1 = Sleeping less than normal amount by up to one hour 2 = Sleeping less than normal by more than one hour 3 = Reports decreased need for sleep 4 = Denies need for sleep	
5. IRRITABILITY	0 = Absent 1 = Subjectively increased 2 = Irritable at times during interview; recent episodes of anger or annoyance on ward 3 = Frequently irritable during interview; short, curt throughout 4 = Hostile; uncooperative; interview impossible	
6. SPEECH RATE AND AMOUNT	0 = No increase 1 = Feels talkative 2 = Increased rate or amount at times; verbose at times 3 = Push; consistently increased rate and amount; difficult to interrupt 4 = Pressured; uninterruptable; continuous	

ITEM	CODE	Score
7. LANGUAGE - THOUGHT DISORDER	0 = Absent 1 = Circumstantial; mild distractibility; quick thoughts 2 = Distractible; loses goal of thought; changes topics frequently; racing thoughts 3 = Flight of ideas; tangentiality; difficult to follow; rhythm; echolalia 4 = Incoherent; communication impossible	
8. CONTENT	0 = Normal 1 = Questionable plans; new interests 2 = Special project(s); hyperreligious 3 = Grandiose or paranoid ideas; ideas of reference 4 = Delusions; hallucinations	
9. DISRUPTIVE – AGGRESSIVE BEHAVIOUR	0 = Absent; cooperative 1 = Sarcastic; loud at times; guarded 2 = Demanding; threats on ward 3 = Threatens interviewer; shouting; interview difficult 4 = Assaultive; destructive; interview impossible	
10. APPEARANCE	0 = Appropriate dress and grooming 1 = Minimally unkempt 2 = Poorly groomed; moderately dishevelled; overdressed 3 = Dishevelled; partly clothed; garish make-up 4 = Completely unkempt; decorated; bizarre garb	
11. INSIGHT	0 = Present; admits illness; agrees with need for treatment 1 = Possibly ill 2 = Admits behaviour change but denies illness 3 = Admits possible change in behaviour, but denies illness 4 = Denies any behaviour change	
	SCORING: Items 1, 2, 3, 4, 7, 10 and 11 are multiplied by 1 **Items 5, 6, 8 and 9 are multiplied by 2** **SCORE**	

Additional notes (including reason for exclusion if made):

The Pittsburgh Sleep Quality Index

Instructions:

The following questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month. Please answer all the questions.

1. During the past month, when have you usually gone to bed at night?	Usual bedtime:
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?	Number of minutes:
3. During the past month, when have you usually got up in the morning?	Usual getting up time:
4. During the past month, how many hours of *actual* sleep did you get at night? (This may be different than the number of hours you spend in bed).	Hours of sleep per night:

For each of the remaining questions, check the one best response. Please answer *all* questions.

5. During the past month, how often have you had trouble sleeping because you……

	Not during the last month	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
a) Cannot get to sleep within 30 minutes				
b) Wake up in the middle of the night or early morning				
c) Have to get up to use the bathroom				
d) Cannot breath comfortably				
e) Cough or snore loudly				
f) Feel too cold				
g) Feel too hot				
h) Had bad dreams				
i) Have pain				
j) Other reasons – please describe				
How often have you had trouble sleeping because of this?				

	Very good	Fairly good	Fairly Bad	Very bad
6. During the past month how would you rate your sleep quality overall?				

	Not during the last month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				

Scoring

	Score
Component score 1 – Subjective sleep quality	
Component score 2 – Sleep latency	
Component score 3 – Sleep duration	
Component score 4 – Habitual sleep efficiency	
Component score 5 – Sleep disturbances	
Component score 6 – Use of sleeping medication	
Component score 7 – Daytime dysfunction	
Global PSQI score	

The Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you.

Use the following Scale to choose the most appropriate number for each situation:

0 - would never doze

1 - slight chance of dozing

2 - moderate chance of dozing

3 - high chance of dozing

	Situation Chance of Dozing (0-3)
Sitting and reading _____	_____
Watching TV _____	_____
Sitting, inactive in a public place (e.g. Cinema) _____	_____
As a passenger in a car for an hour without a break ___	_____
Lying down to rest in the afternoon when given a chance	_____
Sitting and talking to someone _____	_____
Sitting quietly after lunch without alcohol _____	_____
In a car, while stopped for a few minutes in traffic _____	_____

Total Score | |

Appendix B Healthy Volunteer Case Report Form 1

The Association between Sleep and Cognitive Function in Bipolar Disorder and Insomnia.

(The ASCRIBE study)

Case Report Form (Health Volunteer) – Visit 1

Participant Study Code:

Date:

Raters initials:

Contents

Demographics

Date of birth: **Age:**

Ethnicity:

Weight(Kg): **Height (cm):**

BMI(Kg/m^2):

NART(IQ):

Years in full time education: **Highest level of education achieved:**

Employment status:

Number of hours worked per day:

Usual work hours:

Smoking Status: **Number smoked per day:**

Alcohol (Units per week):

Current medications

Medication	Dose	Date started

Additional notes:

Edinburgh Handedness Inventory

Edinburgh Handedness Inventory (revised)					
Please mark the box that best describes which hand you use for the activity in question					
	Always left	*Usually left*	*No preference*	*Usually right*	*Always right*
Writing					
Throwing					
Scissors					
Knife (without fork)					
Spoon					
Match (when striking)					
Computer mouse					

Scoring:

Always left = -50
Usually left = -25
No preference = 0
Usually right = +25
Always right = +50

Handedness:
Score:
Left = < -200
Mixed = -200 to + 200
Right = > +200

Handedness:

Beck Depression Inventory

On this questionnaire are groups of statements. Please read each group of statements carefully, then pick out the one statement in each group which best describes the way you have been feeling over the PAST WEEK. Circle the number beside the statement you picked. If several statements in the group seem to apply equally well then circle each one.

Be sure to read all the statements in each group before making your choice.

1.
0 I do not feel sad
1 I feel sad
2 I feel sad all the time
3 I am so sad or unhappy that I can't stand it

2.
0 I am not particularly discouraged about the future
1 I feel discouraged about the future
2 I feel I have nothing to look forward to
3 I feel that the future is hopeless and that things cannot improve

3.
0 I do not feel like a failure
1 I feel I have failed more than the average Person
2 As I look back on my life all I can see is a lot of failures.
3 I feel I am a complete failure as a person

4.
0 I get as much satisfaction out of things as I used to
1 I don't enjoy things the way I used to
2 I don't get real satisfaction out of anything now
3 I am dissatisfied or bored with everything

5.
0 I don't feel particularly guilty
1 I feel guilty a good part of the day
2 I feel guilty most of the time
3 I feel guilty all of the time

6.
0 I don't feel I am being punished
1 I feel I may be being punished more than I used to
2 I expect to be punished
3 I feel I am being punished

7.
0 I don't feel disappointed in myself
1 I am disappointed with myself
2 I am disgusted with myself
3 I hate myself

8. 0 I do not feel I am worse than anyone else
1 I am critical of myself for my weaknesses or mistakes
2 I blame myself all the time for my faults
3 I blame myself for everything bad that happens

9. 0 I do not have any thoughts of killing myself
1 I have thoughts about killing myself but I not carry them out
2 I would like to kill myself
3 I would kill myself if I had the chance

10. 0 I don't cry anymore than usual
1 I cry more now than I used to
2 I cry all the time now
3 I used to be able to cry but now I can't even though I want to

11. 0 I am no more irritated now than I ever am
1 I get annoyed or irritated more easily now than I used to
2 I feel irritated all the time now
3 I don't get irritated at all by things that used to irritate me.

12. 0 I have not lost interest in other people
1 I am less interested in other people than I used to be
2 I have lost most of my interest in other people
3 I have lost all of my interest in other people

13. 0 I make decisions about as well as I ever could
1 I put off making decisions more than I used to
2 I have greater difficulty making decisions than before
3 I can't make decisions at all anymore

14. 0 I don't feel I look any worse than I used to
1 I am worried that I am looking old or unattractive
2 I feel that there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly

15. 0 I can work about as well as before
1 It takes some extra effort to get started at doing something
2 I have to push myself very hard to do anything
3 I can't do any work at all

16. 0 I can sleep as well as usual
1 It don't sleep as well as I used to
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
3 I wake up several hours earlier than I used to and cannot get back to sleep

17. 0 I don't get more tired than usual
1 I get tired more easily than I used to
2 I get tired from doing almost anything

3 I am too tired to do anything

18. 0 My appetite is no worse than usual
1 My appetite is not as good as it used to be
2 My appetite is much worse now
3 I have no appetite at all anymore

19. 0 I havn't lost any weight lately
1 I have lost more than 5 pounds
2 I have lost more than 10 pounds
3 I have lost more than 15 pounds
I am purposely trying to lose weight by eating less yes …….. no ……..

20. 0 I am no more worried about my health than usual
1 I am worried about physical problems such as aches and pains, upset stomach constipation
2 I am very worried about physical problems and it's hard to think of much else
3 I am so worried about my physical problems that I can't think about anything else

21. 0 I have not noticed any recent changes in my interest in sex
1 I am less interested in sex than I used to be
2 I am much less interested in sex now
3 I have lost interest in sex completely

Beck Depression Score_____

Altman Self Rating Mania Scale (ASRM)

Instructions - On this questionnaire are groups of five statements; read each group of statements carefully.

- Choose the one statement in each group that best describes the way you have been feeling for the **past week**.
- Circle the number next to the statement you picked.
- *Please note:* The word "occasionally" when used here means once or twice; "often" means several times or more, "frequently" means most of the time.

---

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.

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 most of the time
4 I feel extremely self-confident all of the time

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

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

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

ASRM Total Score_____

State and Trait Anxiety Inventory

Directions - State:

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right now*, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

Directions - Trait

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally* feel.

	Not at all	Somewhat	Moderately so	Very much so
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I feel "calm , cool and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that doesn't really matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I cannot put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

Biological Rhythm Interview of Assessment in Neuropsychiatry (BRIAN)

From the options below, check the one that better describes the patient's behavior *in the last 15 days*.

Sleep

	Not at all 1	Seldom 2	Sometimes 3	Often 4
1. Do you have problems falling asleep at your usual time?				
2. Do you have problems waking up at your usual time? How often?				
3. Do you have problems getting out of bed after you wake up? How frequently?				
4. Do you feel rested with the amount of sleep you usually get (including subjective perception of being rested and actual performance in daily activities such as driving, working)? How frequently?				
5. Do you feel you have difficulty switching off at the time of resting? How frequently?				

Activity

	Not at all 1	Seldom 2	Sometimes 3	Often 4
6. Do you have difficulties completing activities at your work? How frequently?				
7. Do you have difficulties in completing your household activities? How frequently?				
8. Do you have difficulties in keeping your usual rhythm of physical activity (e.g. taking a bus, metro or practicing sports)? How frequently?				
9. Do you have difficulties in completing your daily activities in the time scheduled? How frequently?				
10. Do you have difficulties in keeping your usual level of libido / sexual activity? How frequently?				

Social

	Not at all 1	Seldom 2	Sometimes 3	Often 4
11. Do you have difficulties in communicating and having interpersonal relationships with significant others? How frequently?				
12. Do you overly use electronic devices to the point that it impairs your interpersonal relationships (such as the television or the internet)? How frequently?				
13. Do you have difficulties in synchronizing daily routines and sleep patterns with significant others (family, friends, spouse)? How frequently?				
14. Do you have difficulties in giving attention to significant others (family, friends, spouse)? How frequently?				

Eating Pattern

	Not at all 1	Seldom 2	Sometimes 3	Often 4
15. Do you have difficulties in keeping the scheduled times for meals? How frequently?				
16. Do you skip meals? How frequently?				
17. Do you have difficulties in eating a regular amount during meals? How frequently?				
18. Do you have difficulties in using stimulants in moderation (such as coffee , coke and chocolate)? How frequently?				

Predominant rhythm (chronotype)

Consider the last 12 months for the following questions.

	Never 1	Seldom 2	Often 3	Always 4
19. Tends to be more energized for work and interpersonal relationships at night.				
20. Feels more productive in the morning.				
21. Do you have your day/night cycle reversed?				

BRIAN Summary Scores

	Score
Sleep	
Activity	
Social	
Eating pattern	
BRIAN total (items 1-18)	
Predominant rhythm (chronotype)	

Functioning Assessment Short Test (FAST)

To what extent is the patient experiencing difficulties in the following aspects? Ask the patient about the areas of difficulty in functioning and score according to the following scale: (0): no difficulty, (1): mild difficulty, (2): moderate difficulty, (3): severe difficulty. The timescale is over the last 15 days.

AUTONOMY	
1. Taking responsibility for a household	(0) (1) (2) (3)
2. Living on your own	(0) (1) (2) (3)
3. Doing the shopping	(0) (1) (2) (3)
4. Taking care of yourself (physical aspects, hygiene)	(0) (1) (2) (3)
OCCUPATIONAL FUNCTIONING	
5. Holding down a paid job	(0) (1) (2) (3)
6. Accomplishing tasks as quickly as necessary	(0) (1) (2) (3)
7. Working in the field in which you were educated	(0) (1) (2) (3)
8. Occupational earnings	(0) (1) (2) (3)
9. Managing the expected work load	(0) (1) (2) (3)
COGNITIVE FUNCTIONING	
10. Ability to concentrate on a book, film	(0) (1) (2) (3)
11. Ability to make mental calculations	(0) (1) (2) (3)
12. Ability to solve a problem adequately	(0) (1) (2) (3)
13. Ability to remember newly-learned names	(0) (1) (2) (3)
14. Ability to learn new information	(0) (1) (2) (3)
FINANCIAL ISSUES	
15. Managing your own money	(0) (1) (2) (3)
16. Spending money in a balanced way	(0) (1) (2) (3)
INTERPERSONAL RELATIONSHIPS	
17. Maintaining a friendship or friendships	(0) (1) (2) (3)
18. Participating in social activities	(0) (1) (2) (3)
19. Having good relationships with people close you	(0) (1) (2) (3)
20. Living together with your family	(0) (1) (2) (3)
21. Having satisfactory sexual relationships	(0) (1) (2) (3)
22. Being able to defend your interests	(0) (1) (2) (3)
LEISURE TIME	
23. Doing exercise or participating in sport	(0) (1) (2) (3)
24. Having hobbies or personal interests	(0) (1) (2) (3)

The Quality of Life in Bipolar Disorder (QoL.BD) Questionnaire

The following items ask about a range of experiences, behaviors and feelings related to quality of life. Please tell us about your quality of life by rating how much you agree with each of the statements below. Circle the number that best describes your experience over the *last 7 days.* Do not spend too long on each item, it is your first impressions we are interested in.

Over the past 7 days I have	**Strongly disagree**	**Disagree**	**Neutral**	**Agree**	**Strongly agree**
1. Had plenty of exercise	1	2	3	4	5
2. Had the right amount of exercise for me	1	2	3	4	5
3. Felt physically well	1	2	3	4	5
4. Been content with my sex life	1	2	3	4	5
5. Woken up feeling refreshed	1	2	3	4	5
6. Had no problems getting out of bed	1	2	3	4	5
7. Had about the right amount of sleep for me	1	2	3	4	5
8. Kept a routine in my sleep/wake cycle	1	2	3	4	5
9. Felt happy	1	2	3	4	5
10. Enjoyed things as much as I usually do	1	2	3	4	5
11. Felt able to cope	1	2	3	4	5
12. Felt emotionally balanced	1	2	3	4	5
13. Thought clearly	1	2	3	4	5
14. Had good concentration	1	2	3	4	5
15. Had no difficulties with my memory	1	2	3	4	5
16. Made plans without difficulty	1	2	3	4	5
17. Enjoyed my leisure activities	1	2	3	4	5
18. Been interested in my leisure activities	1	2	3	4	5
19. Had fun during my leisure activites	1	2	3	4	5
20. Expressed my creativity	1	2	3	4	5
21. Enjoyed spending time with other people	1	2	3	4	5
22. Been interested in my social relationships	1	2	3	4	5

Over the past 7 days I have	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
23. Had meaningful friendships	1	2	3	4	5
24. Been able to share feelings or problems with a friend	1	2	3	4	5
25. Been satisfied with the spiritual side of my life	1	2	3	4	5
26. Expressed my spirituality as I wish	1	2	3	4	5
27. Practised my spirituality as I wished	1	2	3	4	5
28. Kept routine in my spiritual life	1	2	3	4	5
29. Had enough money for basic needs	1	2	3	4	5
30. Had enough money for extras	1	2	3	4	5
31. Felt secure about my current financial situation	1	2	3	4	5
32. Had no difficulties with debts	1	2	3	4	5
33. Done my daily household chores	1	2	3	4	5
34. Been organised around my home	1	2	3	4	5
35. Kept my home tidy	1	2	3	4	5
36. Kept my home clean	1	2	3	4	5
37. Felt respected	1	2	3	4	5
38. Felt accepted by others	1	2	3	4	5
39. Felt as worthwhile as other people	1	2	3	4	5
40. Felt able to cope with stigma	1	2	3	4	5
41. Had a sense of freedom	1	2	3	4	5
42. Felt safe in my home environment	1	2	3	4	5
43. Travelled around freely (e.g. driving or using public transport)	1	2	3	4	5
44. Felt others have allowed me my independence	1	2	3	4	5
45. Had a strong sense of self	1	2	3	4	5
46. Had a stable sence of what I am really like	1	2	3	4	5
47. Had a clear idea of what I want and don't want	1	2	3	4	5
48. Had control over my life	1	2	3	4	5

Are you currently engaged in any paid of voluntary work? Please circle Yes No

If yes

Over the past 7 days I have	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
49. Been confident in my abilities at work	1	2	3	4	5
50. Met demands at work	1	2	3	4	5
51. Been satisfied with the quality of my work	1	2	3	4	5
52. Been reliable at work	1	2	3	4	5

Are you currently engaged in any educational activities? Please circle Yes No

If yes

Over the past 7 days I have	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
53. Enjoyed my educational activities	1	2	3	4	5
54. Felt confident about finishing my educational activities	1	2	3	4	5
55. Performed to my usual standards educationally	1	2	3	4	5
56. Organised my educational activities adequately	1	2	3	4	5

Morningness/Eveningness Scale

Read each question carefully. Select the most appropriate answer and note the corresponding value next to it.

1. If you were entirely free to plan your evening and had no commitments the next day at what time would you choose to go to bed?

    1. 2000hrs - 2100hrs..... 5
    2. 2100hrs - 2215hrs..... 4
    3. 2215hrs - 0030hrs..... 3
    4. 0030hrs - 0145hrs..... 2
    5. 0145hrs - 0300hrs..... 1

2. You have to do 2 hours physically hard work. If you were entirely free to plan your day, in which of the following periods would you choose to do the work?

    1. 0800hrs - 1000hrs..... 4
    2. 1100hrs - 1300hrs..... 3
    3. 1500hrs - 1700hrs..... 2
    4. 1900hrs - 2100hrs..... 1

3. For some reason you have gone to bed several hours later than normal, but there is no need to get up at a particular time the next morning. Which of the following is most likely to occur?

    1. Will wake up at the usual time and not fall asleep again.....4
    2. Will wake up at the usual time and doze thereafter.....3
    3. Will wake up at the usual time but will fall asleep again.....2
    4. Will not wake up until later than usual.....1

4. You have a 2 hour test to sit which you know will be mentally exhausting. If you were entirely free to choose, in which of the following periods would you choose to sit the test?

    1. 0800hrs - 1000hrs.....4
    2. 1100hrs - 1300hrs.....3
    3. 1500hrs - 1700hrs.....2
    4. 1900hrs - 2100hrs.....1

5. If you had no commitments the next day and were entirely free to plan your own day, what time would you get up?

    1. 0500hrs - 0630hrs.....5
    2. 0630hrs - 0745hrs.....4
    3. 0745hrs - 0945hrs.....3
    4. 0945hrs - 1100hrs.....2
    5. 1100hrs - 1200hrs.....1

6. A friend has asked you to join him twice a week for a work-out in the gym. The best time for him is between 10pm - 11pm. Bearing nothing else in mind other than how you normally feel in the evening, how do you think you would perform ?

    1. Very well.....1
    2. Reasonably well.....2
    3. Poorly.....3
    4. Very poorly.....4

7. One hears about 'morning' and 'evening' types of people. Which of these types do you consider yourself to be?

    1. Definitely morning type..... 6
    2. More a morning than an evening type.....4
    3. More an evening than a morning type.....2
    4. Definitely an evening type.... 0

Now add the scores together to get your total and compare your total score with the table below to get an idea of your Chronotype :

1. Definitely morning type .....32 - 28
2. Moderately morning type .....27 - 23
3. Neither type .....22 - 16
4. Moderately evening type.....15 - 11
5. Definitely evening type.....10 - 6

Summary of Scores

(Take HAM-D, YMRS, PSQI & ESS from eligibility screening).

Mood Ratings

HAMD-17: **BDI:** **YMRS:**

ASRM: **STAI: State:** **Trait:**

Sleep Ratings

PSQI: Subjective sleep quality: **Sleep latency:** **Sleep duration:**
Habitual sleep efficiency: **Sleep disturbances:**

Use of sleep medication: **Daytime dysfuntion:** **PSQI Global:**

ESS:

Chronotype, function & QoL

Morningness/evening scale:

FAST:

Qol.BD

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