Quantifying Objective Sleep Measures and Their Associations with Memory in Older Adults with Depression

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Thesis Overview

Disturbed sleep is a key symptom of depression in older adults and is a risk factor for the recurrence of depressive episodes. However, the nature of the changes to sleep macro-architecture (sleep stages and timings) and sleep micro-architecture (electroencephalogram (EEG) changes) in this population have not been fully characterised. Older adults with depression also demonstrate changes in brain integrity and associated impairments in memory. Though prior studies support the functional role of sleep in memory consolidation processes there is a lack of research investigating the specific links between sleep and memory, particularly emotional memory, in older adults with depression. This is important as biases in emotional memory are believed to contribute to maladaptive schemas and the worsening of depressive symptoms. Therefore, the overarching aims of this thesis were to characterise objectively measured abnormalities in sleep macro- and micro-architecture observed in older adults with depression and to explore the relationships between sleep, emotional and episodic memory, and brain integrity.

The first study aimed to systematically review and meta-analyse data from studies that objectively measured sleep using polysomnography in adults and older adults in people with depression. We showed that compared to controls, adults with depression had worse sleep initiation and continuity (less total sleep time, lower sleep efficiency, delayed sleep onset, higher wake after sleep onset) and greater rapid eye movement (REM) density. Older adults with depression also had poor sleep continuity (greater stage 1 and less stage 2 sleep) and shorter REM onset latency.

The second study explored differences in objectively measured sleep in 66 older adults with and 106 without depression attending a memory clinic and the associations between sleep and episodic memory, and MRI-based measures of brain integrity in a sub-set of participants. It showed that older adults with depression had delayed sleep onset and REM onset. In those with depression, less time spent in slow-wave sleep (SWS) was associated with poorer memory. However, there were no relationships between sleep and hippocampal volume and prefrontal cortex thickness.

The final study employed innovative high-density EEG to measure regional brain activity during sleep and overnight emotional memory consolidation in 12 older adults with and 10 without depression. In the emotional memory task, the depression group rated negative images more negatively in the morning and showed increased self-rated arousal response to negative images in the morning, relative to the evening. The study found a global loss of EEG delta power during (non-REM) NREM sleep in the depression group, with regional analysis revealing a reduction in delta power in the frontal brain region.

This thesis contributes to the literature by characterising the abnormalities in objectively measured sleep in depression, as well as those observed in older people with depression which are above and beyond the changes seen in healthy older people. The global and regional deficits in delta power suggests that the sleep homeostatic process may be disrupted in older adults with depression. This work also highlights how SWS appears to contribute to memory processes in older adults with depression. It underscores the potentially utility of interventions targeted at enhancing SWS and delta frequency oscillations in NREM and how this may affect the consolidation of overnight memory processing observed in this population.

Declaration of Originality

This thesis comprises a systematic review and meta-analysis and two empirical studies. For all Chapters, I was responsible for determining study aims and design, completing data analysis and Chapter writing. In Chapter II, I conducted the systematic review, meta-analysis, and risk of bias analysis. For Chapter III, a retrospective data analysis of existing clinical data I was responsible for statistical data analysis and in Chapter IV, I completed participant recruitment, sleep and memory data collection, sleep scoring, data processing and statistical analysis. This research was conducted under the supervision of Dr. Angela D'Rozario (co-primary supervisor), Professor Sharon Naismith (co-primary supervisor), Dr Rick Wassing (auxiliary supervisor) and Dr Fiona Kumfor (auxiliary supervisor). Research was approved by the University of Sydney Human Research Ethics Committee and conducted at the Brain and Mind Centre and Woolcock Institute of Medical Research, Sydney Australia.

I declare that to the best of my knowledge the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes. I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

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Co-author Declaration

Dr Angela D'Rozario and Professor Sharon Naismith provided substantial support in the design of research studies, oversight of analysis and interpretation of data and revision of the thesis. Dr Rick Wassing made substantial contributions to the development of analysis and interpretation of data. Dr Fiona Kumfor contributed to the planning and design of Chapter IV. Dr Tancy Kao provided contributions to the high-density EEG analysis and statistical analysis and interpretation. Dr Jun Zhi Teh, Dr Aaron Lam and Associate Professor Nathaniel Marshall provided considerable contribution to the planning, data collection and interpretation of the systematic review and meta-analysis study (Chapter II). Dr Loren Mowszowski and Dr Haley LaMonica performed neuropsychological testing on participants in Chapter III. Miss Zoe Menczel Schrire and Dr Carla Haroutonian performed mood assessments. Dr Carla Haroutonian and Dr Aaron Lam contributed to sleep data analysis for Chapter III. Dr Andrew McKinnon provided training and contribution to both neuropsychological tasks and data analysis and interpretation of MRI data (Chapter III and IV). Dr Catriona Ireland, Associate Professor Delwyn Bartlett, and Professor Ron Grunstein provided guidance on clinical aspects of the project and contributed to the planning of Chapter IV.

The listed co-authors contributed to reviewing and revising relevant Chapters of the thesis for intellectual content.

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The effect of sleep disturbance on cognition in late-life depression. Ricciardiello, A., D'Rozario, A., Wassing, R., Kumfor, F., &. Naismith, S (2021). Sleep, 44 (Supplement 2), A15-A15.

Conference Abstract: Australasian Sleep Association Sleep Down Under Conference, October 2022

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List of Abbreviations

AHI	Apnea Hypopnea Index
BMI	Body Mass Index
C-AVLT	Cognitive-Affective Verbal Learning Task
CIRS-G	Cumulative Illness Rating Scale- Geriatric
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyography
EO	Early-onset (depression)
EOG	Electrooculography
ESS	Epworth Sleepiness Scale
GDS-15	Geriatric Depression Scale-15 item
hdEEG	High-density electroencephalography
HBA	Healthy Brain Ageing (Clinic)
Hz	Hertz
IAPS	International Affective Picture System
ICD	International Classification of Diseases
LO	Late-onset (depression)
MD	Major depression

MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
ODI	Oxygen desaturation index
N1	Stage 1 sleep
N2	Stage 2 sleep
N3	Stage 3 sleep
NREM	Non-rapid eye movement
PFC	Prefrontal cortex
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
qEEG	Quantitative electroencephalography
RAVLT	Rey Auditory Verbal Learning Test
REM	Rapid eye movement
SWA	Slow-wave activity
SWS	Slow-wave sleep
SOL	Sleep onset latency
TFCE	Threshold-free cluster enhancement
TST	Total sleep time
uV	Microvolts
WASO	Wake after sleep onset
WTAR	Wechsler Test of Adult Reading

Chapter 1- Introduction

This section introduces the prevalence and economic impact of depression in older adults. It emphasizes the challenges of treatment, the significance of prevention for healthy aging, and provides a concise overview of the definition and diagnosis of depression. The links between depression and cognitive decline and neurodegeneration are explored. Additionally, it introduces the connection between sleep and depression, which will be explored in further detail throughout this thesis.

1.1 Prevalence and economic impact of depression

Major depression (MD) is the third highest cause of burden of disease both in Australia (Australian Institute of Health and Welfare, 2018) and globally (World Health Organization, 2017) and as such is a significant public health issue. Major depression prevalence rates in adults over 65 years are estimated at 5.5-7.5% (World Health Organization, 2017), however, epidemiological studies suggest the prevalence of MD in older adults is much higher than reported, between 10 and 20%, as older adults do not often meet traditional MD criteria (Beekman et al., 1995; Copeland et al., 2004; Luijendijk et al., 2008). As the population of Australians over the age of 65 has increased significantly over time, 5.1% from 1990 to 2020, it is crucial to focus on optimising healthy ageing (Australian Bureau of Statistics, 2019, 2021).

In Australia, mental health disorders are the fourth most costly group of diseases (Australian Institute of Health and Welfare, 2019). A meta-analysis of healthcare utilisation and total healthcare costs in older adults with depression reported higher healthcare utilisation and total healthcare cost by one-third compared to non-depressed older adults (Luppa et al., 2012). Further, healthcare costs increase with depression severity (Druss & Rosenheck, 1999; Johnson et al., 1992). Older adults with depression use more health resources for related comorbidities than those without depression (Vasiliadis et al., 2013) and stay longer when hospitalised (Beekman et al., 2002). The disabling effects of depression in older adults also causes other direct and indirect costs including, but not limited to, increased number of days out of work or life roles, decreased daily functioning and diminished quality of life and financial achievement (Balsamo et al., 2018; Kessler, 2012). Depression in older adults is associated with a higher

level of individual and social burden (Beekman et al., 2002; Unützer et al., 1997). Treating depression in older adults to the point of remission is difficult with only 20-30% reaching remission with multiple pharmacological treatments, therefore focus on prevention is needed to optimise healthy ageing (Baldwin, 2010; Roose & Schatzberg, 2005; Whyte et al., 2004). For the purpose of this thesis the use of the term depression indicates participants have depressive symptoms but may not meet criteria for major depression according to accepted diagnostic criteria.

1.2 Symptoms and diagnosis of depression

Major depression is a syndrome defined by a cluster of co-occurring symptoms. Despite multiple diagnostic tools, there is no one universal definition of major depression. The common core symptoms, depressed mood and loss of interest or pleasures, are presumed to be representative of underlying common pathology although there is heterogeneity in the phenotypes of those with unipolar major depression, a phenomenon which is not yet fully understood (Paykel, 2008). Unipolar major depression can be diagnosed using a combination of validated criteria and clinician-based methods (El-Den et al., 2018). It can also be categorised by severity depending on the level of symptomology (Middleton et al., 2005). Minor, subsyndromal or subthreshold depression is defined by the presence of one of the core symptoms and one to three additional symptoms, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Table 1.1) (Bell, 1994; World Health Organization, 2010).

Table 1.1 Unipolar Major Depressive Disorder Diagnostic and Statistical Manual of Mental Disorders Criteria (Bell, 1994)

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or another medical condition.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

1.3 Symptoms and diagnosis of depression in older adults

Depression in older adults, defined as over 50 years of age (Naismith et al., 2012), differs in its symptom expression, risk factors and outcomes compared to depression in earlier life (Mitchell & Subramaniam, 2005). Apathy, withdrawal, lack of vigour and somatic symptoms are more commonly seen in older adults with depression and are not covered in standard depression criteria, therefore, many cases in this group are underdiagnosed (Adams, 2001; Copeland et al., 2004; Hegeman et al., 2012; Hybels et al., 2012; Mitchell & Subramaniam, 2005). Although older patients are more likely to exhibit these symptoms there is no specific phenotype or diagnostic criteria for older adults with depression (Hybels et al., 2012). In a large sample of older adults aged over 60 years the prevalence of depression, including all severity groups, was assessed by different tools: International Classification of Diseases-10 (ICD-10), Diagnostic and Statistical Manual of Mental Disorders Four Text Revision (DSM-IV-TR), Montgomery and Asberg Depression Rating Scale (MADRS) and the Geriatric Depression Scale (GDS). The prevalence of depression was similar across tools except the ICD-10 which underestimated the prevalence (ICD-10: 4.2%, DSM-IV-TR: 9.3%, MADRS: 10.6% and GDS: 9.2%) (Sjöberg et al., 2017). Those with subthreshold depression are still at risk of physical and psychosocial impairments similar to those meeting criteria for major depression (Beekman et al., 1995; Hybels et al., 2001; Jongenelis et al., 2004).

Depression episode onset age has been shown to predict clinical features of depression, such as agitation and being non-interactive, and may indicate potentially differing underlying pathology (Brodaty et al., 2001). Studies have defined early-onset depression (EO) and late-onset depression (LO) groups as having a first depressive episode before or after 50 years of age, respectively (Blazer, 2003). In this thesis the definition for late-onset depression is also 50 years and is based on the previous work identifying vascular risk factors in older adults with depression which appear at a higher rate after the age of 50, compared to early-onset depression (Kendler et al., 2009). Those with early-onset depression are more likely to present with a genetic history of mental illness, personality abnormalities and anxiety features (Brodaty et al., 2001; Naismith et al., 2012). Whereas those with late-onset depression present with memory impairment, psychomotor, executive function changes, apathy, and a greater treatment

resistance (Beats et al., 1996; Blazer, 2003; Naismith et al., 2012). There is a delineation of genetic pathways between earlier and later onset groups with the hazard ratio for vascular disease being twice as high in those aged 47-65 compared to 13-46 years (Kendler et al., 2009). Risk factors for the development of depression in older adults includes sleep disturbance, other disability, bereavement, and female gender (Cole & Dendukuri, 2003). However, no one risk factor can wholly explain the etiopathogenesis.

The understanding of depression from a neurobiological perspective has focused on cerebrovascular disease because of its associations with structural and functional brain changes (Aizenstein et al., 2016). The vascular depression hypothesis (Alexopoulos et al., 1997), proposes that cardiovascular pathology causes lesions which disturb corticostriatal circuits and affect cognitive functioning in older adults with depression, especially evident in those with later ages of onset (Delaloye et al., 2010; Salo et al., 2019). Based on this, there has been interest in categorising a subgroup of late-life depression as 'vascular depression'. However, there is a lack of consensus on the phenotype classification. The most consistent criteria being the evidence of deep white matter hyperintensities on brain magnetic resonance imaging (MRI) which are assumed to be caused by vascular factors (Sneed & Culang-Reinlieb, 2011). A longitudinal community study found that older adults with a score of two or more on the Fazekas scale for white matter lesions were 8.1 times more likely to develop depression at follow-up (Park et al., 2015). More severe white matter hyperintensities have been observed in those with late-onset depression compared to those with early-onset depression (Hickie et al., 1997). This is consistent with the characteristic psychomotor changes, memory and cognitive dysfunction and apathy seen in older adults with depression and may account for the associated increased risk of progression to dementia (Butters et al., 2000; Naismith et al., 2012). Although many older adults with cerebrovascular disease do not develop depression, it is possible that other mechanisms may mediate this relationship (Teper & O'Brien, 2008). It is still not known at what stage these lesions develop, whether they are a symptom of neurodegenerative pathology or causative of depression symptoms in older adults. More research is needed to ascertain the significance of exact brain lesion location and severity to define neuropathological impairments in vascular depression and risk of neurodegenerative progression.

1.4 Cognitive impairment in older adults with depression

1.4.1 Cognitive impairment in older adults with depression incidence and proposed mechanisms

Depression has been linked to cognitive impairment and dementia risk in neuroimaging studies, suggesting similar brain pathology in older adults depression and neurodegeneration (Naismith et al., 2012). Mild cognitive impairment is present in up to 75% of health-seeking adults over 50 years with depressive disorders (Jayaweera et al., 2015) and a lifetime history of depression or depressive symptoms is linked with a 2-fold increased risk of cognitive decline in older adults (Byers & Yaffe, 2011). Further, individuals with both late-onset depression and cognitive impairment are at a greater risk of developing dementia at a rate of 40% within 3-5 years (Alexopoulos, 2005; Schweitzer et al., 2002). Older adults with depression demonstrate more severe memory impairments than those with depression in earlier adult life, independent of the effect of ageing alone (Thomas et al., 2009). These memory deficits have been shown to persist after clinical recovery and may be a core part of depressive illness (Bhalla et al., 2006). A longitudinal study over 7 years, found that poorer delayed recall predicted a steeper increase in affect suggesting a prospective association in which depression preceded poor memory performance (Brailean et al., 2017). Given the high incidence of depression in mild cognitive impairment, studies have posited that depressive symptoms may be an early sign of dementia, potentially due to the neuropathology that causes dementia also causing depressive symptoms (Panza et al., 2010). A recent Lancet commission report stated depression as a risk factor for dementia and suggested that depression in older adults causes dementia (Livingston et al., 2020).

Studies of older adults with depression have found significant degradation of white matter tracts that are important for emotion regulation, memory, executive function, and self-referential thinking (Sebastian Köhler et al., 2010; Sheline et al., 2008; Tadayonnejad & Ajilore, 2014). These include the white matter tracts involved in the structural connectivity of the default mode network, fronto-limbic network, and cortico-striatal network (Dalby et al., 2010; Sheline et al., 2008; Tadayonnejad & Ajilore, 2014). There has been some consensus in the presentation of those with late-onset depression exhibiting a much higher degree of structural brain changes and vascular risk factors. In participants over the age of 65 with a history of depression, deficits such as poor processing speed, attention, executive function,

verbal fluency, vocabulary, and episodic memory are observed. Moreover, worse cognition is observed with increased depression severity (Koenig et al., 2015; Panza et al., 2010). Together these studies suggest that structural brain changes in older adults with depression may mediate changes in cognition.

1.4.2 Overview of memory processes

Traditional models of memory suggest information is encoded, consolidated and fixed into a static memory, although we now understand that memory formation and storage is a more labile process (Nadel et al., 2012). Memories can be short-term, held for a period of a few seconds, or long-term which require structural and functional changes in neural networks (Alberini, 2009). During initial encoding, representations of the stimulus in cortical systems and the hippocampus are activated (Nadel et al., 2012; O'Reilly & Rudy, 2001). The hippocampal system attributes spatial and temporal characteristics to the stimulus and stores information for future retrieval (O'Reilly & Rudy, 2001). Investigations in animal models, as well as in humans, have characterised the hippocampal memory system which involves pathways leading from relevant associated sensory neocortical areas to the parahippocampal region and finally the hippocampus which facilitates plasticity in numerous brain areas (Eichenbaum, 2000; Restivo et al., 2009). The hippocampus is vital to specific declarative memory processing, with those who have had hippocampal removal displaying anterograde amnesia, or an inability to retain information for long periods (Squire & Bayley, 2007). The links between cortical and hippocampal regions are crucial to efficient encoding, consolidation and retrieval (Nadel et al., 2012). The newly encoded information can become strengthened, stabilised, and consolidated over time (Alberini & LeDoux, 2013; Nadel et al., 2012; Tronson & Taylor, 2007). More recent studies report memories becoming more labile with reactivation and then stabilised again with reconsolidation, although it is not known whether this is a distinct process due to the engagement of different brain regions (Alberini, 2005; Alberini & LeDoux, 2013; Tronson & Taylor, 2007). When memory is reactivated it can be weakened, erased, strengthened, or altered depending on the stimulus conditions. The retrieval of memories also involves the reactivation of stored memory traces, referred to as engrams, via external or internal cues (Frankland et al., 2019). Memory failure can be caused by a breakdown in any of the

memory processes including encoding, consolidation, reconsolidation, or retrieval (Frankland et al., 2019).

1.4.3 Memory impairment in older adults with depression

Memory deficits have been observed in studies of older adults with depression, and also persist in those with remitted depression (Dillon et al., 2014; Koenig et al., 2015; Pantzar et al., 2014). There is some evidence for increasing severity of memory impairments with later ages of onset of depression, although this has not been consistent (Herrmann et al., 2007; S Köhler et al., 2010). Greater hippocampal volume loss is evident in older adults with depression compared to controls when measured cross-sectionally and at longitudinal time-points (Hickie et al., 2005; Steffens et al., 2011). Hippocampal volume loss has been associated with declarative memory impairment but is not correlated with depression severity (Hickie et al., 2005; O'Brien et al., 2004). In a longitudinal cohort, older adults with depression had worse memory impairment at baseline but did not decline more rapidly than healthy controls, whereas late-onset depression performed worse at baseline and also declined more rapidly over time (Ly et al., 2021).

1.4.4 Overview of emotional memory processes

Emotional memories carry a certain valence (e.g. positive and negative) and produce a physiological arousal response (Bogie et al., 2019). The tendency to remember an emotionally salient stimulus compared to a neutral stimulus is well documented in healthy adults and may be explained by prioritising emotional events that are more relevant to survival (Flaisch et al., 2016; Tambini et al., 2017). The amygdala and hippocampus are involved in the encoding and retrieval of emotionally salient memories (Dere et al., 2010; Tambini et al., 2017). Exposure to emotional stimuli connections from the sensory cortical regions (e.g. visual cortex) causes the relay of information to the amygdala which is responsible for initial encoding (LaBar & Cabeza, 2006). The amygdala produces a response to the emotional stimuli, before conscious awareness and attention, and provides feedback that enhances later perception (Phelps et al., 1997). By altering the perception of a specific hippocampal-dependent episodic memory the amygdala enhances the priority of the emotional information (Phelps et al., 1997).

The hippocampus is responsible for the retention and storage of information which is set or consolidated over time (Phelps et al., 1997).

Stress hormones, such as noradrenaline activate areas of the locus coeruleus, modulate the activity of the hippocampal-dependent emotional memory consolidation as well as prefrontal cortex activation (Germain & Kupfer, 2008; Keller et al., 2006; LaBar & Cabeza, 2006). Increases in sympathetic nervous system arousal during emotional stimuli encoding have been associated with greater memory for salient information (Tambini et al., 2017; Walker & Van Der Helm, 2009). Drug alterations of the noradrenergic system in humans have highlighted the important role of sympathetic arousal in supporting information recall (Clewett et al., 2017; Krenz et al., 2021).

1.4.5 Emotional memory impairment in depression

In addition to presenting with cognitive deficits such as impairments in memory and executive function, studies suggest that cognitive biases may be a specific domain affected within major depression in younger and older adults (Bogie et al., 2019; Callahan et al., 2016; LeMoult & Gotlib, 2019). The mood congruency phenomenon observed in depression hinges on the proclivity of individuals with depression to remember negative emotional information compared to positive or neutral stimuli (Bradley et al., 1995; Ellwart et al., 2003; Gaddy & Ingram, 2014; Hamilton & Gotlib, 2008; Matt et al., 1992). This memory bias is believed to perpetuate the self-referent maladaptive schemas, or memory systems, that reinforce negative beliefs about the world, the self and the future (Bogie et al., 2019). In major depression, the tendency to selectively highlight negative information and interpret ambiguous information as negative contributes to the maintenance of symptoms, physiological autonomic responses and dysthymic behaviours (Mogg et al., 2006; Payne & Kensinger, 2010). Participants with depression suffer from a lack of attentional inhibition for negative emotional information, which is thought to be related to a reduction in activation of the anterior cingulate and dorsolateral prefrontal cortex regions, responsible for task-related decisions (Goeleven et al., 2006; MacDonald et al., 2000). This is thought to be one of the mechanisms behind rumination symptoms in depressed patients (Goeleven et al., 2006). A study by Hamilton and Gotlib (2008) found depressed patients, compared to

controls, demonstrated better recollection of negative information, and an increase in right amygdala activity and greater functional connectivity with the hippocampus with the successful encoding of negative information only. Further, due to changes in stress hormone levels observed in people with depression and the white matter abnormalities in frontal subcortical and limbic networks in older adults with depression, it is important to consider the effect of sympathetic nervous system arousal on the consolidation of emotional memories (Keller et al., 2006; Sexton et al., 2013).

1.4.6 Emotional memory and ageing

A decline in episodic memory function is characteristic of ageing, although, contrary to previous literature the current research suggests emotion processing in healthy ageing is preserved especially for positive information (Mather, 2012, 2016). Despite numerous studies reporting on this finding, the neurobiological evidence for the mechanisms behind the preservation of positive information in healthy adults is limited (Mammarella et al., 2016). Although emotional valence and arousal mechanisms are heavily dependent on the amygdala, it is possible for patients with amygdala lesions to preferentially remember affective words in memory tasks (Phelps et al., 1997). In these cases, patients utilise other strategies including semantic cohesion and organisation that are more dependent on the medial temporal lobe and prefrontal cortex, which are responsible for the perception of emotional stimuli (LaBar & Cabeza, 2006). A study using intracranial electrodes in epileptic patients to study emotional pattern separation identifying the amygdala-hippocampal network showing strong alpha and theta signals during memory discrimination trials (Zheng et al., 2019). In older age, with damage to the amygdala, there is a move toward this dependency on the prefrontal cortex which is responsible for the perception of affective stimuli and short-term working memory (Leigland et al., 2004; Shaw et al., 2005). There are no studies of emotional memory in older adults with depression therefore, the effect of depression and its associated emotional biases within the context of neurodegeneration is largely unknown.

1.4.7 Executive Function in depression

Executive function encapsulates cognitive control of behaviour in domains such as attention and task management. The top down modulation of activity by the pre-frontal cortex (PFC) supports executive function with damage to these areas causing impairment in executive function performance (reviewed in Funahashi and Andreau (2013)). Executive function is a cognitive domain affected within major depression especially in older adults (Elderkin-Thompson et al., 2011; Lockwood et al., 2002). In older adults with depression, especially those with late-onset depression, both the loss of volume within the prefrontal cortex and increased amounts of white matter hyperintensities are related to deficits in executive function (Elderkin-Thompson et al., 2009; Sebastian Köhler et al., 2010; Salloway et al., 1996). Theories of poor executive function in older adults with depression have suggested hypothalamic–pituitary–adrenal (HPA) axis dysfunction and hypercortisolemia may be responsible for neuronal atrophy (Butters et al., 2022). Further, executive dysfunction in depression has been linked to the persistence of symptoms and treatment resistance, highlighting the importance of intervention targeting this specific domain (Baldwin et al., 2004).

1.5 Depression and sleep disturbance: a bidirectional link

The relationship between sleep disturbance and depression is complex and bidirectional, with approximately 50-90% of patients with depression reporting sleep problems (Boivin, 2000; Monteleone et al., 2011; Poole & Jackowska, 2018). Sleep disturbance is a key symptom of major depression(Bell, 1994). A meta-analysis found that sleep disturbance was a risk factor for depression in older adults with a population-attributable risk of 57% (Cole & Dendukuri, 2003). Sleep disturbance is a risk factor for not only the onset but also the recurrence of depression in older adults (Cho et al., 2008; Lee et al., 2013). For example, persistent sleep disturbance in community-dwelling older adults predicted depression remission, at an odds ratio of 5.2, at one year follow-up (Lee et al., 2013).

Insomnia and hypersomnia are highly prevalent in depression and are risk factors for the onset and maintenance of depressive symptoms. A meta-analysis investigating the incidence of depression in adults found that 11.3% of individuals with insomnia at baseline developed depression at follow-up

(12-84 months) compared to only 2.4% in those without sleep disturbances (Baglioni et al., 2011). Conversely, subjective hypersomnia and excessive daytime sleepiness are prevalent sleep complaints in depression, however, assessing the frequency of hypersomnia is difficult to quantify as objective tests often fall within normal ranges (Lopez et al., 2017). Comorbid depression is prevalent in sleep disorders such as sleep apnea (22.4%) and restless legs syndrome (46-52%) (Auvinen et al., 2018; Jackson et al., 2019). For example, a study of older adults with depression and subjective sleep complaints found 90% of patients with improved sleep after interpersonal psychotherapy remained well after a year compared to only 33% with persistent sleep disturbance (Franzen & Buysse, 2008). Although the relationship between sleep disturbance and depression is reliably and consistently found, the exact mechanisms are still undefined. However, it is likely that there are multiple mechanistic pathways underpinning this bidirectional relationship. It is possible that sleep disturbance may mediate the development or severity of depression (Cole & Dendukuri, 2003; Mayers & Baldwin, 2006). The treatment of sleep problems represents an opportunity for the prevention of future depression episodes, reduction of future depression severity and acceleration of recovery (Franzen & Buysse, 2008; Geoffroy et al., 2018; Lopez et al., 2017; Nutt et al., 2022; Perlis et al., 2006).

The following section introduces the assessment of sleep using electroencephalography (EEG) and the neuronal mechanisms behind sleep states and oscillations. Furthermore, it highlights the changes in sleep characteristics observed in normal aging and depression.

1.6 Assessing sleep EEG and understanding the origins from the brain

Polysomnography is the gold standard sleep assessment and includes physiological recordings of brain activity measure by electroencephalography (EEG), eye movements (electrooculography, EOG), chin and leg muscle activation (electromyography, EMG) and heart rhythm electrocardiography (ECG). Breathing is also measured using nasal respiratory airflow, thermistor, thoracic and abdominal respiratory effort and oxygen saturation (pulse oximetry).

1.6.1 Electroencephalography recordings

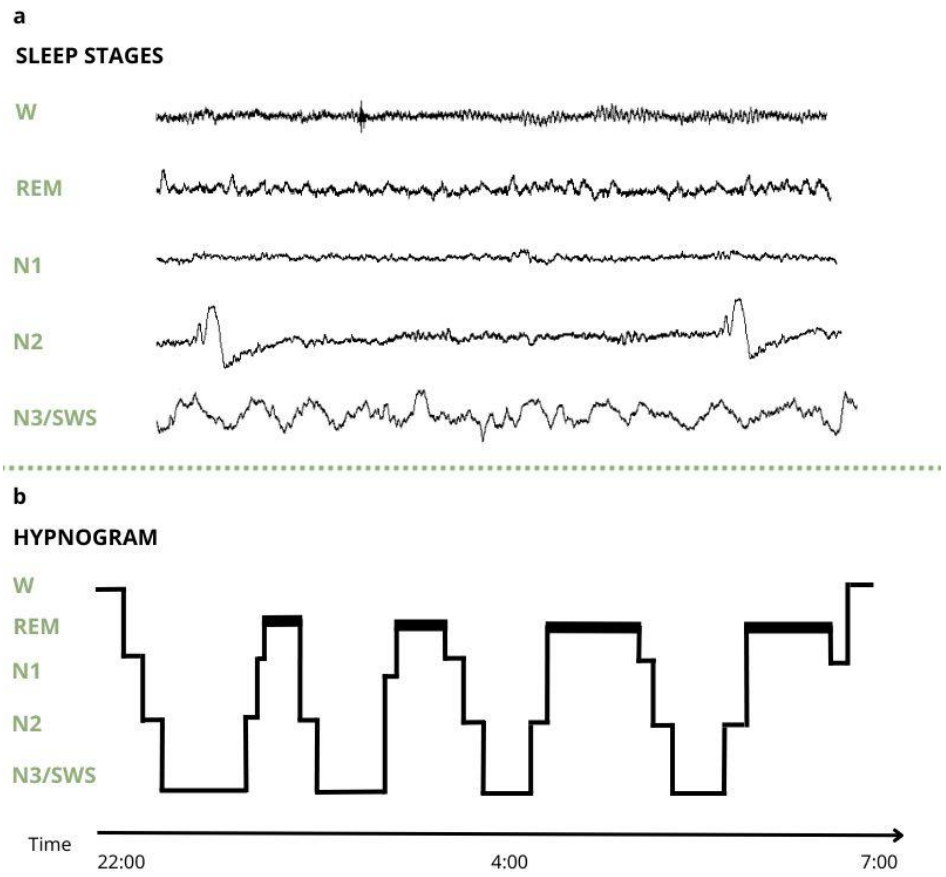
As a part of a routine polysomnographic study, EEG data is derived from electrodes placed on the scalp over the frontal, central and occipital regions according to the 10-20 electrode-placement system (Jasper, 1958). Sleep architecture is the temporal distribution of sleep stages, which is scored in 30-sec epochs based on American Academy of Sleep Medicine (AASM) guidelines (Berry et al., 2012). Sleep stages (Figure 1.1) include:

- Wake- the total time spent awake during recording
- Stage 1 (N1) – the initial stage of sleep where EEG frequency slows compared to wake and alpha and theta rhythms are often prominent.
- Stage 2 (N2) - makes up majority of sleep in normal adults and is characterised by the presence of distinct EEG oscillations k- complexes and sleep spindles.
- Stage 3 (N3) or slow-wave sleep (SWS) – characterised by slow frequency high amplitude delta waves.
- Rapid eye movement (REM) sleep- characterised by rapid eye movements and high frequency low amplitude waves and muscle atonia.

Macro-architectural outcomes can be derived from EEG recordings to describe the quality of sleep initiation and continuity (Berry et al., 2012). These include;

- Total sleep time (TST)- total time spent asleep
- Sleep onset latency (SOL) - the time from lights out until first sleep onset
- Sleep efficiency (SE)– the percentage of total sleep time divided by the amount of time spent in bed
- Wake after sleep onset (WASO)- the amount of time spent in wake after the initial sleep onset and before lights on
- REM onset latency (ROL)- the time between sleep onset and the onset of the first REM sleep period

Figure 1.1 Image of Sleep Stages Macro-architecture and Hypnogram



Note: Panel a displays typical EEG signals from wake (W), rapid eye movement (REM) sleep, stage 1 (N1) sleep, stage 2 (N2) sleep and stage 3 (N3) or slow-wave sleep (SWS). Panel b shows a typical hypnogram of sleep stages as a function of time.

Normative sleep architecture has been described in the general population, however, there is a high level of inter-individual variation (Danker-Hopfe et al., 2005; Ohayon et al., 2004). Normal sleep architecture involves cycling between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep throughout the night (Figure 1.1, part b) (Carskadon & Dement, 2005). In young adults, SWS is the predominant sleep stage at the beginning of the night and REM sleep is predominant in the later part of the night (Figure 1.2, part a)(Carskadon & Dement, 2005). The proportion of time spent in sleep stages in healthy young adults is approximated at stage 1: 2-5%, stage 2: 45-55%, stage 3: 13-23%, REM 20-25% (Carskadon & Dement, 2005).

One major conceptual framework underlying the structure of sleep is the two-process model of sleep regulation (Borbély, 1982). This concept highlights two interacting factors, "process S", a homeostatic sleep/wake process and "process C", a circadian process which regulates sleep timing (Borbély, 1982). Normal ageing is associated with changes in sleep initiation and continuity reflective of both homeostatic and circadian misalignment (Dijk et al., 1999; Mander et al., 2017). Older adults tend to exhibit a longer sleep onset latency, more sleep fragmentation, less slow-wave and REM sleep and less frequent cycling between non-rapid eye movement (NREM) sleep and REM (Conte et al., 2014; Crowley, 2011; Ohayon et al., 2004). The proportion of time spent in sleep stages in older adults (55-70+ years) is estimated at stage 1: 5.7-6.3%, stage 2: 60.4-61.8%, stage 3: 11.4-12.6 %, REM: 18.3-19.7% (Conte et al., 2014; Ohayon et al., 2004).

1.6.2 Neuronal mechanisms for sleep states and oscillations

Thalamocortical brain regions are involved in the generation of electrical potentials measured at the level of the scalp (Steriade, 2003). Using quantitative electroencephalography (EEG) analysis signals can be derived and organised into the frequency components of EEG spectral power using Fast-Fourier transform (Cooley & Tukey, 1965). Frequency bands can be categorised into delta (slow-wave activity, SWA): 0.5-4.5 Hz, theta: 4.5-8 Hz, alpha: 8-12Hz, sigma: 12-15Hz, beta: 15-25 Hz, gamma: 25-40Hz and each relates to certain sleep states and neural pathway activation. Across the literature there is no consensus on the exact frequency definitions of each band, creating issues when comparing studies (Steriade, 2006; Steriade & McCarley, 2005). Spectral EEG activity varies across sleep periods with NREM having characteristically more delta and sigma activity, REM having more beta and gamma activity and wake having a higher alpha activity.

State switching between wake and sleep stages involves intricate interactions between multiple dorsal and ventral neural pathways. The dorsal pathway encompasses the activation of the thalamus and in turn the cortex while the ventral pathway incorporates the activation of the hypothalamus and forebrain structures which then activate the cortex (Eban-Rothschild et al., 2018). The switching between wake, NREM and REM is also driven by neurotransmitter fluctuations (Eban-Rothschild et al., 2018) (Figure

1.2). The activity of the noradrenergic locus coeruleus (LC) is proportional to the arousal levels seen in distinct brain states with silent LC activity associated with low arousal levels during REM sleep, tonic wake states associated with low-frequency noradrenergic activity and phasic states in response to stimuli which are associated with activation of global networks (Aston-Jones & Cohen, 2005; Devilbiss & Waterhouse, 2011). The basal forebrain contains cholinergic neurons which are activated during both wake and REM sleep and are posited to reduce delta EEG activity during NREM sleep (Chen et al., 2016; Lee et al., 2005).

1.6.3 Slow-wave activity and slow oscillations

Slow oscillations (<1 Hz) are large hyperpolarisations and depolarisations occurring in the delta frequency range, which are representative of synchronised excitation and inhibition of cortical networks (Figure 1.2) (Steriade et al., 1993). Thalamocortical inputs are involved in the generation of the upstate of slow oscillations and theta waves often travel from anterior to posterior cortical regions (Amzica & Steriade, 1995; Steriade, 2003). Functionally, slow oscillations have been linked to sleep homeostasis and synaptic plasticity and its contribution to memory formation in both animal and human studies (Diekelmann & Born, 2010; Dijk, 2009; Niethard et al., 2018; Tononi & Cirelli, 2006).

Sleep is a homeostatic process that is dependent on the preceding wake time and quality. The sleep-wake process (process S) can be modelled to calculate sleep pressure which builds during wake and is reflected in slow-wave activity (or delta activity, typically 0.5-4.5 Hz) during sleep (Borbely & Achermann, 1999; Deboer, 2013; Jones, 2005; Vyazovskiy et al., 2009). This theory is supported by sleep deprivation studies which demonstrate a compensatory enhancement of delta power and nap studies which reduce the SWA the following night (Achermann & Borbély, 2003; Borbély et al., 1981). Tononi and Cirelli (2003) proposed the synaptic homeostasis hypothesis which highlights the significance of slow wave delta power in homeostatic regulation via synaptic potentiation and downscaling. The synaptic pruning that occurs during delta frequency is projected to strengthen current neural connections and facilitate new learning in the proceeding wake period (Tononi & Cirelli, 2006).

Normal ageing produces changes in micro-architecture resulting in an overall reduction of absolute power across spectral frequencies (Sprecher et al., 2016). There are also prominent reductions of delta power and slow oscillation events observed predominantly in the pre-frontal cortex region compared to younger adults (Dijk et al., 1999; Mander et al., 2013; Sprecher et al., 2016). There are marked reductions in not only delta EEG power but also the amplitude and incidence of slow waves. NREM delta power has been associated with prefrontal cortex (PFC) activation and PFC-dependent executive tasks in older adults (Anderson & Horne, 2003; Dang-Vu et al., 2008; Maquet et al., 1997). The exponential decline of slow wave dissipation over the night that is seen in younger adults is also not observed in older adults (Landolt & Borbély, 2001), suggestive of reduced homeostatic slow-wave activity regulation (Dijk et al., 1999).

1.6.4 Sleep Spindles

Sleep spindles are typified by waxing and waning oscillations occurring in the sigma frequency with a duration of approximately 0.5 to 3 seconds (Figure 1.2) (Steriade et al., 1993). Sleep spindles can also be categorised into fast and slow spindles (fast: 13-16 Hz and slow: 11-13 Hz) with potentially differing functions (Pisarenco et al., 2014). Sleep spindles are representative of thalamic events which project to cortical regions (Caporro et al., 2012). Sleep spindles, a proposed marker of synaptic plasticity, are involved in the consolidation of memory, sensory processing and cognitive function as reviewed by Fernandez and Lüthi (2020).

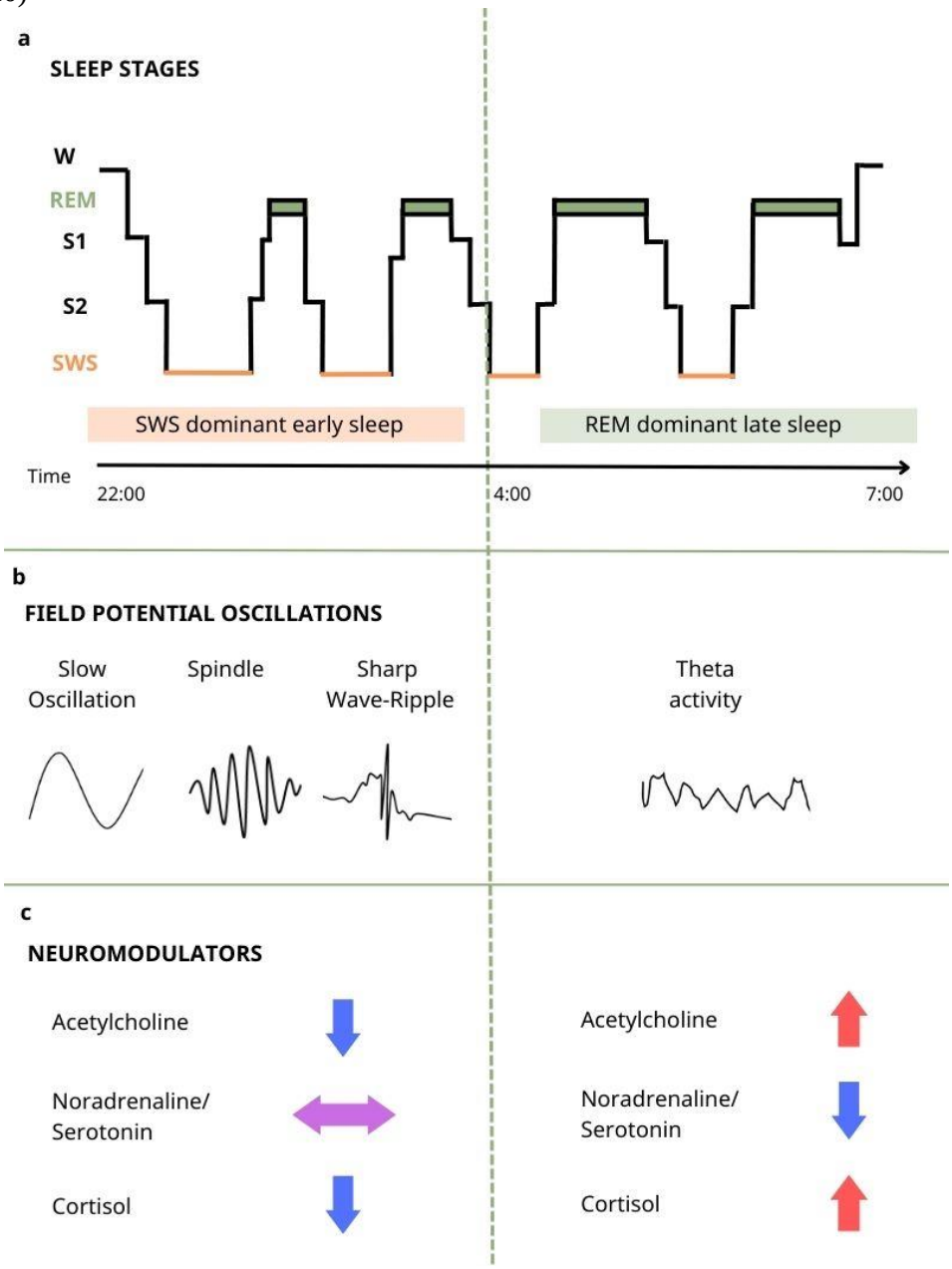
Sleep spindle density is associated with cognitive outcomes and are a potential target for overnight enhancement of memory consolidation (reviewed in Fernandez and Lüthi (2020)). Sigma power, sleep spindle density and amplitude show decline, especially in frontal areas, in normal ageing (Landolt & Borbély, 2001; Martin et al., 2013). A higher density of fast spindles has been reliably associated with learning in stage 2 sleep (Clemens et al., 2005; Cox et al., 2012; Mednick, 2013; Nishida & Walker, 2007). Imaging studies have found associations between fast spindles and activation in memory pathways including the sensory cortical areas, the medial frontal cortex, and hippocampus (Schabus et al., 2007). Fast spindles are thought to have a priming role in sleep-dependent memory processing,

occurring predominantly in stage 2 sleep before SWS periods (Fogel & Smith, 2006; Mölle & Born, 2011).

1.6.5 Sleep Oscillation Coupling

Individually, slow oscillations and sleep spindles are linked to memory although their co-occurrence is considered to be a marker of synaptic plasticity and memory reorganisation and consolidation (Mölle & Born, 2011; Siapas & Wilson, 1998). The temporal precision of slow oscillations, sleep spindles and hippocampal ripples is thought to assist in the information transfer in long-term memory formation (Clemens et al., 2005; Diekelmann & Born, 2010). Older adults are less likely to demonstrate precise fast spindle and slow oscillation coupling compared to younger adults which are necessary for memory consolidation (Muehlroth et al., 2018). Atrophy in brain areas responsible for the generation of spindles and slow oscillations, the medial PFC, thalamus, hippocampus, and entorhinal cortex, is detrimental for spindle-slow oscillation coupling (Helfrich et al., 2018; Muehlroth et al., 2019; Wei et al., 1999). The active system hypothesis focuses on the repetitive reactivation of the hippocampus during non-REM sleep that synchronises with sharp wave ripples and thalamo-cortical spindles during information reactivation (Diekelmann & Born, 2010). Newly encoded neural traces formed in the hippocampus undergo cortical reactivation during overnight memory reprocessing (Antony et al., 2019; Jegou et al., 2019). Hippocampal ripple events are coupled with thalamocortical fast spindles and slow-waves facilitating crosstalk between cortical and subcortical memory systems (Antony & Paller, 2017; Diekelmann & Born, 2010; Fernandez & Lüthi, 2020; Klinzing et al., 2019). More recent work is aiming to manipulate sleep spindles and slow oscillations using medication and auditory and electrical stimulus to improve overnight memory consolidation in humans (Mednick, 2013; Ngo et al., 2013) and optogenetically in rats (Mednick, 2013; Miyamoto et al., 2016).

Figure 1.2 Sleep architecture and the neurophysiology of sleep stage adapted from Diekelmann and Born (2010)



Note: Panel a demonstrates a hypnogram of sleep stages across time, highlighting slow-wave sleep (SWS) dominant early sleep and rapid eye movement (REM) late sleep. Panel b demonstrates trait sleep oscillations evident in SWS (slow oscillation, sleep spindle and sharp wave ripple) and REM sleep (theta activity). Panel c indicates the relative levels of neuromodulators evident in SWS and REM sleep. Arrows indicate whether neuromodulator levels are increased, decreased or the same compared to other sleep stages.

1.7 Characterisation of sleep in depression

1.7.1 Sleep macro-architecture in depression

Despite the bidirectional relationship between sleep and depression being very well documented, the characterisation of objective sleep disturbance within depression has only relatively recently been investigated. The quantification of objective sleep measures in older adults is especially understudied. Sleep alterations are evident in most mental disorders, with many overlapping measures of sleep disturbance occurring in many disorders (Baglioni et al., 2016). Sub-optimal sleep duration, both longer and shorter, can predict depressive symptoms longitudinally (Jackowska & Poole, 2017). Sleep disturbance is observed in adults with depression who exhibit sleep phase advancement in a 24-hour cycle, changes in sleep onset latency and sleep fragmentation (Armitage, 2007; Baglioni et al., 2016; Benca et al., 1992; Boivin, 2000; Monteleone et al., 2011; Poole & Jackowska, 2018).

Research has tried to uncover trait sleep markers in depression as potential target mechanisms for treatment. Early research in younger adults emphasised the importance of rapid eye movement (REM) latency as a marker of depression although later research argued REM density as the most sensitive and specific marker of depression (Giles et al., 1987; Groch et al., 2013; Lauer et al., 1991; Pillai et al., 2011; Rumble et al., 2015). Two separate meta-analyses have found earlier REM onset latency, increased REM density and REM duration are found in young adults with affective disorders (Baglioni et al., 2016; Benca et al., 1992). The limitations of these meta-analyses are explored further in Chapter II. Research has proposed that increased REM density in combination with reduced time spent in slow-wave sleep (SWS) could be biomarkers for major depression which are persistent even in remitted individuals (Baglioni et al., 2016; Pillai et al., 2011). Increased central cholinergic activity observed in depression has been suggested as a driving mechanism behind the increased number of rapid eye movements with REM suppression being a mechanism of many antidepressant treatments (Baglioni et al., 2016; Palagini et al., 2013; Steiger et al., 2015). Less SWS in the first non-REM period and a decreased amount of time spent in SWS, have been observed in some studies in adults with depression but is not reliably found (Rumble et al., 2015).

Differentiating the EEG characteristics in normal ageing and the effects of depression which are beyond the level of normal ageing is crucial, given the relationship between sleep and neurodegeneration. One study of older adults with depression found later sleep latency and latency to REM relative to controls (Hoyos et al., 2020), however a second study found no differences in sleep architecture in older adults with early-onset and late-onset depression. As with younger adults, research focusing on REM measures has cited reductions in REM onset latency and time spent in REM in older adults with depression compared to controls (Dykierek et al., 1998). However, few studies have explored NREM sleep characteristics in older adults with depression, despite dissipation of delta EEG power and SWS in normal ageing. Generally, there are a very limited number of studies objectively measuring sleep EEG in older adults with depression, therefore it is difficult to conclude if there are definitive characteristic sleep measures for intervention targets in this group. This gap will be addressed further in Chapter II.

1.7.2 Sleep micro-architecture in depression

In adults with depression, studies of slow-wave activity in adults with depression have inconsistent findings in both increased, decreased, and showing no difference compared to healthy controls (Armitage et al., 2000; Borbély et al., 1984; Hoffmann et al., 2000; Plante, Landsness, Peterson, Goldstein, Wanger, et al., 2012). Studies of slow wave dynamics in younger adults with depression have found decreased delta amplitude in the first half of the night as well as elevated EEG fast frequency and reduced interhemispheric coherence, indicating potential homeostatic interruptions and defects in cortical plasticity (Armitage, 1995; Ferrarelli & Tononi, 2020). Quantitative EEG is understudied and under-reported in older adults with depression, despite known changes to delta power in ageing.

Sleep spindle measures in depression are not consistently measured or reported in studies adults with depression and therefore no consensus on the characterisation of spindle measures in this group. One high density (hdEEG) study of younger adults with major depression found increases in parietal and frontal sleep spindle density compared to control participants most evident in female participants (Plante et al., 2013). Whereas another found lower total sleep spindle density in younger adults with depression compared to controls (De Maertelaer et al., 1987). In one study of older adults there was no

difference in sleep spindle density compared to controls (Reynolds et al., 1985). Due to the lack of consensus of the definition of sleep macro- and micro-architectural markers in depression and dearth of literature defining sleep in older adults with depression and we conducted a meta-analysis to quantify characteristic EEG in depression and address this gap (see Chapter II).

The following section provides an overview of the function of sleep in declarative and emotional memory. It includes a comprehensive review and critical evaluation of sleep and memory studies in younger and older adults with depression and sleep and emotional memory studies in younger adults with depression and healthy adults.

1.8 Sleep's role in declarative and emotional memory

Sleep provides favourable conditions to support the consolidation of long-term memories (Diekelmann & Born, 2010). Several independent hypotheses about the mechanisms of sleep-dependent memory consolidation have been proposed from a combination of animal and human research. The dual-process hypothesis of memory consolidation states that REM sleep preferentially consolidates non-declarative memories, including emotional memories, whereas SWS is beneficial for declarative memory (Ackermann & Rasch, 2014; Plihal & Born, 1997). Although some studies have implicated REM sleep and SWS in separate memory processes, it is likely that the interaction between the continuous sleep stages is important for processing different aspects of memory (Hornung et al., 2007). A recent animal study by Hauer et al. (2019) examined the functional role of the nucleus reuniens showing slow rhythmic patterns during deactivated brain states coupled with slow-wave oscillations. These neurons connect the medial prefrontal cortex and the hippocampus which are key areas in memory processing suggesting SWS may be important in strengthening memories (Hauer et al., 2019). The reduction of time spent in non-REM sleep and the reduced slow-wave spectral activity that is associated with major depression may influence the hippocampal sleep-dependent memory consolidation pathways (Armitage, 1995; Hickie et al., 2005; Plante et al., 2013). The sequential hypothesis argues that the cyclic nature of REM and NREM is imperative in providing complementary functions for memory formation (Giuditta et al., 1995). Slow-wave sleep is posited to depotentiate or reduce synaptic connections while high-frequency EEG during REM sleep strengthens synaptic connections (Giuditta et al., 1995).

Sleep has been found to assist the preferential retention of the most emotionally salient information compared to wake (Cellini et al., 2016; Hu et al., 2006; Payne & Kensinger, 2010; Wagner et al., 2006). Research explaining the relationship between emotional memory and sleep has focused on REM sleep

and its involvement in reprocessing valence and arousal aspects of emotional stimuli. Rat models have elucidated the role of the LC in sleep-wake cycles, which, when activated results in less noradrenaline and more high-frequency, low-amplitude theta EEG activity (Aston-Jones et al., 2007; Berridge & Foote, 1991). Sleep deprivation studies have found increased emotional dysregulation with congruent amplification in amygdala response (Motomura et al., 2013; Yoo et al., 2007). The increase in amygdala response was associated with reduced connectivity in the medial PFC and increases in sympathetic connections in the locus coeruleus (Motomura et al., 2013; Yoo et al., 2007). Together this suggests that the combination of the reactivation of the amygdala-hippocampal networks and the suppression of adrenergic neurotransmitters during REM is responsible for reprocessing and dampening of emotional reactivity and subjective emotional response to previous salient events (Van Der Helm et al., 2011). This study also proposes that REM sleep gamma EEG activity may act as a surrogate marker for adrenergic activity (Van Der Helm et al., 2011). The amount of overnight theta EEG activity has been associated with increased emotional memory performance (Nishida et al., 2009). Theta EEG activity is posited to be representative of an "offline" brain state which allows selective strengthening of emotional memories (Hu et al., 2006; Walker & Van Der Helm, 2009). As well as strengthening emotional memory, REM sleep also dampens or depotentiates the arousal response to emotional stimuli (Van Der Helm et al., 2011). Successful overnight emotional memory depotentiation has been associated with low REM gamma in rats, another proposed measure of adrenergic activity (Berridge & Foote, 1991; Cape & Jones, 1998). Collectively this indicates that fragmentation of REM sleep or changes in arousal during REM may interrupt emotional processing, which is significant for both sleep and mental health disorders (Riemann et al., 2012).

1.9 Sleep and declarative memory in depression

Many studies have determined the value of sleep in supporting memory processes in healthy adults. However, the literature explaining objective sleep measures and memory in depression in adults and older adults is limited, despite evidence of both impaired sleep and poor memory performance in these groups. Support from neuroimaging studies indicate that task-specific brain areas are potential targets for overnight EEG measurements and intervention. Volume loss in the PFC and hippocampus combined with memory deficits and self-reported sleep disturbance have been observed in older adults with depression. (Chang et al., 2011; DiNapoli et al., 2017; Hickie et al., 2005; Hou et al., 2012; McKinnon et al., 2018; Naismith et al., 2009; Steffens et al., 2011) These studies suggest that sleep disturbance may also be a contributing factor to or a product of changes in memory processing in older adults.

Table 1.2 summarises the few studies that have assessed the associations between memory and objective sleep measures using polysomnography (PSG) in adults with depression and self-report or actigraphy studies in older adults with depression (Dresler et al., 2011; Göder et al., 2011; Naismith et al., 2009; Naismith et al., 2011; Nishida et al., 2016; Sutter et al., 2012). Two studies in young adults with depression tested the relationship between non-declarative memory using a sleep-dependent paradigm and objective sleep EEG measures (Dresler et al., 2011; Nishida et al., 2016). Both studies found that participants with depression had worse overnight non-declarative memory compared to controls. However, only Nishida et al. (2016) found SWS duration was positively correlated with non-declarative memory in the depression group and slow spindles positively associated with non-declarative memory in both depression and control groups. These two studies have different outcomes potentially due to the effect of benzodiazepines in the study by Dresler et al. (2011) which have a REM suppressant effects and increase SWS.

Dresler et al. (2011) also measured declarative memory and found there was no change in overnight declarative memory in the depression group and no associations with memory. However, another study found SWS duration was positively correlated with declarative verbal memory in the depression group at the pre-treatment PSG (baseline) (Göder et al., 2011). This study also tested the effect of REM suppressant medication on next morning declarative verbal memory performance in depression,

however, no effects were observed after 1 week of REM suppressive medication. This study is limited by the lack of a control group and small sample sizes in each group. The two studies are difficult to compare, as the memory tasks used in each study measure different domains of learning and memory. In summarising, two of three studies suggest that SWS duration may be involved in declarative and non-declarative memory consolidation, although studies are limited by medications and study design (Dresler et al., 2011; Göder et al., 2011; Nishida et al., 2016). Generally, more studies, with well-matched cases and controls, and a consistent study design, are needed to understand the relationship between sleep and memory consolidation in adults with depression, especially in older adults.

There have been no studies assessing objective sleep EEG measures in older adults with depression. However, three studies in older depressed adults have used self-report or actigraphy measures of sleep quality and run cross-sectional associations between sleep measures and memory. One study assessed older adults with depression and characterised insomnia in this group as early insomnia (issues with sleep initiation) or late insomnia (issues with early morning waking) and found adults with depression and late insomnia had worse declarative memory recall, especially in adults with depression and later ages of depression onset (Naismith et al., 2009). A second study using actigraphy and self-reported sleep quality found older adults with depression had higher wake after sleep onset (WASO), lower sleep efficiency (SE), and lower sleep quality compared to controls (Naismith et al., 2011). Further higher WASO and lower SE were associated with lower declarative verbal and visual memory in older adults with depression. Conversely, a third study assessing self-report sleep quality found no associations between declarative memory recall and sleep quality(Sutter et al., 2012). Two out of three studies demonstrate sleep continuity issues in older adults with depression and associate poor sleep continuity with worse declarative memory performance. Sutter et al. (2012) was limited by a sample with a subclinical depression severity level and two studies (Naismith et al., 2009; Sutter et al., 2012) did not use a control sample. Self-report subjective and objective actigraphy do not measure the same outcome as participants are not always able to accurately estimate their sleep quality (Armitage et al., 1997). These studies use one-off cross-sectional designs, therefore temporality of associations between sleep and memory cannot be interpreted. These limitations in the literature make it difficult to interpret the

relationship between sleep and memory in older adults with depression and reveal a need for studies measuring objective sleep EEG and associations with memory in this population. Further, no studies have assessed objective sleep EEG and memory in early-onset and late-onset depression groups, despite further cognitive deficits reported in those with late-onset depression. Addressing this knowledge gap is essential in understanding the potential impacts of poor sleep on neurodegenerative processes in this group which will be explored further in Chapter III

Table 1.2 Studies assessing sleep and declarative and non-declarative memory in adults and older adults with depression

Reference	Aims	Sample	Diagnostic criteria	Sleep measure	Memory task	Outcome
Studies of younger adults with depression using polysomnography (PSG)						
Dresler et al. (2011)	To understand the relationship between sleep and declarative and nondeclarative memory in MD	Medicated inpatients MD (n=37) (mean age=48.3), HC (n=31) (mean age=48.1),	ICD-10	PSG	SDM non-declarative sequential finger tapping task and declarative paired association task	No association between sleep and memory
Nishida et al. (2016)	To understand the functions of fast and slow spindles in memory processing in MD	MD (n=11) (mean age= 33.76), HC (n=17) (mean age=30)	ICD-10	PSG and qEEG analysis	SDM non-declarative finger-tapping sequence test	SWS duration was positively correlated with memory consolidation in MD. Slow spindles were associated with reduced memory consolidation in both groups
Göder et al. (2011)	To test the pharmacological REM suppressant effects on memory in MD	MD (n=41) (mean age = 31.4)	DSM-IV-SCID	Baseline PSG with qEEG analysis night then allocation to 1 week SSRI, SNRI, or interpersonal psychotherapy then PSG	Next morning declarative Rey Auditory-Verbal Learning Test	SWS duration was positively correlated with memory in MD at baseline. No effects of REM suppression on memory performance
Studies of older adults with depression using actigraphy/ self-report sleep measures						
Naismith et al. (2009)	To assess the relationship between sleep disturbance and neuropsychological functioning in older adults with MD	MD (n=48) (mean age=59.6)	DSM-IV	Insomnia items (Hamilton Depression Rating Scale)	Declarative RAVLT measured at clinically at one time-point	Depressed participants with late insomnia (early awakening) had worse memory recall, especially in later depression onset ages

Naismith et al. (2011)	To assess the relationship between sleep-wake disturbance and neuropsychological functioning in older adults with MD	MD (n=44) (mean age=62.7), HC (n=22) (mean age= 61.4)	DSM-IV	Actigraphy, sleep diary and PSQI	Declarative Rey Complex Figure Test, Wechsler Memory Scale-III - logical memory subtest, RAVLT measured at one time-point before actigraphy	Poor sleep efficiency and WASO on actigraphy was related to poorer verbal and visual learning in MD
Sutter et al. (2012)	To assess the relationship between sleep quality and cognitive performance in older adults with subclinical depression	Older adults with subclinical depression (n=107) (mean age = 61)	GDS-15 >6	PSQI	Declarative Verbal Learning and Memory Test (German-RAVLT) measured at one time-point	No association between subjective sleep quality and memory

Key: MD- major depression, HC- healthy control, DSM-IV- Diagnostic and Statistical Manual of Mental Disorders, SCID- Structured Clinical Interview, GDS-15- Geriatric Depression Scale 15-item, SDMC- sleep-dependent memory consolidation, RAVLT- Rey-Auditory Verbal Learning Test, SWS- slow-wave sleep, PSG- polysomnography, EEG- electroencephalography, qEEG- quantitative EEG, PSQI- Pittsburgh Sleep Quality Index, WASO- wake after sleep onset

1.10 Sleep and emotional memory

As shown in Table 1.3, few studies have assessed the relationship between sleep and emotional memory consolidation in adults with depression. Three studies have assessed the relationship between sleep and memory for emotional information in young adults with mild to moderate depression using different methodologies. One study assessed sleep deprivation in comparison to normal sleep and found young adults with depression had no difference in objective sleep, or emotional memory recall, arousal, and valence measures compared to controls, but better identified all information after sleep compared to participants with depression who were sleep deprived (Harrington, Nedberge, et al., 2018). Two studies compared REM and NREM-rich sleep periods in young adults with affective disorders (McNamara et al., 2010) and mild depressive symptoms (Harrington, Johnson, et al., 2018). Neither study reported between-group differences in sleep measures. One study reported negative memories were more frequently recalled after REM sleep compared to NREM in both affective disorder and control groups (McNamara et al., 2010), whereas a further study reported depression participants consolidated more neutral memories during NREM-rich sleep than low depression symptom participants (Harrington, Johnson, et al., 2018). Both these studies are limited by very small sample sizes in each condition and all three studies use university student samples.

These studies suggest that sleep is beneficial to the consolidation of both emotional and non-emotional information. However, none of these studies report any specific sleep stages on emotional information. All studies are also limited by reduced alertness after sleep deprivation or night testing conditions, potentially biasing emotional memory results and making it difficult to measure the effect of depression symptoms and sleep on memory. These studies also do not account for circadian factors that may affect testing in early versus late sleep. Previous meta analyses have found that the use of recall over recognition and the timing of learning and recollection phases can moderate the effect of sleep on emotional memory (Lipinska et al., 2019). Understanding the effects of sleep on emotional memory consolidation in depression is difficult given such a small number of studies in a limited age range, highlighting the need for further research into the associations between sleep-dependent emotional memory in adults with depression, especially older adults.

When casting a broader net, over emotional memory studies in healthy young adults, the predominant focus has been on research on the selective effects of REM sleep and arousal in emotional memory information recall, arousal, and valence processing. Baran et al. (2012) found sleep compared to wake facilitated better recognition of all information and that negative valence responses were preserved with more REM sleep compared to wake, however, did not find any effects of sleep on arousal. Three studies measured overnight changes in objective measures of arousal (Cunningham et al., 2014; Rosales-Lagarde et al., 2012; Van Der Helm et al., 2011). Using skin conductance and self-reported valence and arousal scores, Cunningham et al. (2014) found, more negative valence and larger arousal responses to negative information at encoding were related to better negative object recollection after sleep, compared to wake. However, this study did not identify specific relationships between sleep stages and emotional processing. Two studies used functional MRI (fMRI) during an emotional memory task to measure arousal in specific brain areas. Van Der Helm et al. (2011) used a sleep-dependent memory paradigm and found amygdala activity decreased, and connectivity between amygdala-ventromedial prefrontal cortex increased overnight, in the sleep group compared to wake. This study also linked lower REM-gamma EEG power to larger decreases in amygdala reactivity to emotional images. A second fMRI study found REM sleep deprivation increased emotional reactivity, and preserved REM sleep decreased emotional reactivity in brain areas, occipital and temporal lobes and ventrolateral prefrontal cortex, involved in emotion processing at recall trials compared to relative NREM controls (Rosales-Lagarde et al., 2012). However, there were no observed changes in amygdala activity. Taken together, these studies suggest that in healthy young adults, sleep, and specifically REM sleep, are important for the consolidation of emotional memory and arousal processing. Studies using fMRI during tasks were potentially more sensitive in capturing arousal compared to self-reported arousal and posit that REM gamma EEG activity may be a surrogate to measure arousal. Chapter IV utilises these concepts to assess emotional memory and sleep in older adults with depression using high-density EEG.

A further three studies used methodology comparing selective deprivation or consolidation of late sleep (REM-rich) and late sleep (NREM-rich) without objective measures of arousal. Two studies found better recognition of negative pictures in REM compared to NREM sleep (Wagner et al., 2001; Wiesner

et al., 2015), while a third found only an association between REM-rich sleep and more negative emotional valence ratings (Wagner et al., 2002). The two studies, which measured subjective arousal scores to emotional images, however, did not find any specific effects of whole night sleep, REM or NREM sleep (Wagner et al., 2002; Wiesner et al., 2015). Selectively waking and testing participants during the night and morning, in split-night paradigms, does not account for the circadian effects on emotional memory tasks as well as alertness, potentially accounting for the differences observed in arousal rating between studies. The potential role of circadian factors that occur across a whole night sleep is important to consider when assessing the relationship between sleep mechanisms and cognitive outcomes. This limitation is addressed further in Chapter IV.

Two studies have evaluated associations between NREM sleep and emotional memory consolidation using different methodologies. One study used targeted memory activation during encoding, recall and an afternoon nap (Cairney et al., 2014). Both SWS duration and spindles were related to better negative stimuli recognition when compared to neutral stimuli. Whereas a second study found SWS was beneficial to the consolidation of all stimuli in stressed young adults compared to controls (Denis et al., 2022). Slow wave oscillation and spindle coupling was also inversely related to memory consolidation, contrary to previous studies (Siapas & Wilson, 1998). Both studies suggest SWS is important in the consolidation of memory, however, only Cairney et al. (2014) reports specific effects on negative information (Cairney et al., 2014; Denis et al., 2022). These studies are difficult to compare due to methodologies, as one is a cued daytime nap study and does not account for daytime circadian factors and the potential impact on consolidation. Two studies do not provide enough evidence to conclude if NREM sleep is important in the consolidation of emotional memory. Measuring REM and NREM sleep, and their respective components of emotional processing and memory consolidation, independently, does not allow for a holistic understanding of the mechanisms underpinning overnight emotional memory consolidation. Chapter IV will address this gap.

Table 1.3 Studies assessing sleep and emotional memory in adults with depression and healthy adults

Reference	Aims	Sample	Diagnostic criteria	Sleep measure/ intervention	Emotional memory task	Outcome
Harrington, Nedberge, et al. (2018)	To investigate the effects of sleep deprivation on recognition of emotional stimuli	Moderate depression symptom group (n = 26, mean age = 20), low/ no depression symptom group (n = 28, mean age =19.6)	BDI-II score mean = 21 (moderate)	Half of the participants from each group were randomised into one full night of sleep deprivation or one night normal sleep conditions with PSG and PSQI	SDMC of IAPS (60 positive, 60 neutral, 60 negative) with subjective valence and arousal ratings before and after sleep deprivation or sleep, then 7 day retest	Depression participants in the sleep condition better identified negative and neutral images than the sleep deprived depression participants the morning after
Harrington, Johnson, et al. (2018)	To understand the effects of REM and NREM rich sleep on emotional memory consolidation	Mild depression symptom group (n =11, mean age = 21.3), low/ no depression symptom group (n = 12, mean age = 22.1),	BDI-II score mean = 18.6 (mild)	Half of the participants from each group were randomised into a PSG with early sleep (NREM-rich) or late sleep conditions (REM-rich) with PSG and PSQI	Learning and memory recognition using IAPS (100 positive, 100 neutral, 100 negative) before and after early or late sleep	Depression participants consolidated more neutral memories during NREM-rich sleep than low depression symptom participants
McNamara et al. (2010)	To test if REM sleep contributes to biased memory processing	Young adults with depression or anxiety symptoms (n = 20, mean age = 21.8), HC (n = 35, mean age = 20.8),	DASS score mean = 5.5 (mild)	Participants awoken during REM and NREM periods to recall information during PSG and PSQI	Autobiographical memory recall and self-other word recall task at 2 REM and 2 NREM time periods	Recall of negative memories was more frequent after REM sleep compared to NREM in both HC and depressed/ anxious groups

Healthy adult studies

Baran et al. (2012)	To examine the role of REM sleep in emotion processing	Healthy young adults (n= 106, mean age = 20.4)	N/A	Participants randomised into one of four; 12- hr sleep with PSG, daytime 12-hr wake condition, 45- min recognition morning or evening group	SDMC or short term recognition of IAPS (90 negative and 90 neutral pictures) with arousal and valence self-report	Sleep aided consolidation of all pictures. Sleep and especially REM sleep, preserved the emotional valence response to negative pictures compared to wake
Cunningham et al. (2014)	To investigate how arousal during emotional stimulus encoding would affect recollection after a sleep or wake period	Healthy university students (n = 46, age = N/A)	N/A	Participants underwent either sleep with PSG versus or 12-hr daytime wake condition	12-hr recognition of images with negative and neutral objects in the background. Skin conductance measures and self-report valence and arousal	Larger valence and arousal responses to negative information at encoding was related to better negative object recollection after sleep compared to wake
Van Der Helm et al. (2011)	To investigate the role of REM sleep in emotional arousal potentiation	Healthy young adults (n = 34, age = 18-30)	N/A	Participants randomised to sleep with PSG and qEEG or 12-hr daytime wake condition	SDMC paradigm using fMRI with simultaneous IAPS task (150 pictures)	Lower overnight levels of REM-gamma EEG power were associated with larger decreases in amygdala reactivity to emotional images
Rosales-Lagarde et al. (2012)	To test the effect of REM sleep deprivation on emotional stimuli	Healthy male adults (n = 20, mean age = 24.2)	N/A	All participants underwent a baseline night, intervention of either NREM interruption or REM sleep deprivation night and recovery night with PSG	fMRI with 24 hr recognition of IAPS (40 negative, 20 neutral) before and after sleep intervention night	REM sleep deprivation increased, and preserved REM sleep decreased emotional reactivity in brain areas involved in emotion processing at recall trials compared to relative NREM controls

Wiesner et al. (2015)	To examine the effect of NREM versus REM sleep on emotional stimuli ratings	Healthy university students (n = 62, mean age = 23.5)	N/A	Participants randomised into PSG night with selective deprivation of REM sleep, NREM sleep or a night wake condition	9-hr SDMC recognition of IAPS (80 negative and 80 neutral pictures) with arousal and valence self-report	Negative picture consolidation was better in participants with consolidated REM sleep compared to NREM. Arousal ratings reduced in recognition in all conditions. Affective ratings were unchanged in all conditions
Wagner et al. (2001)	To understand the effects of REM and NREM rich sleep on emotional memory consolidation	Healthy male adults (n = 23, mean age = 24.2)	N/A	Participants allocated to learning and retrieval before and after either early sleep (NREM) or late sleep (REM) or night wake condition with PSG	SDMC of a declarative memory task of standardised emotional texts with neutral and emotional content	REM rich sleep compared to NREM rich sleep and wake enhanced memory for emotional information compared to neutral information
Wagner et al. (2002)	To compare emotional stimuli processing in REM rich and NREM rich periods	Healthy male adults (n = 24, mean age = 23.4)	N/A	All participants underwent both early sleep (NREM) and late sleep (REM) learning and recognition conditions with PSG across two nights	SDMC of IAPS (200 moderate to highly negative pictures) with valence and arousal rating	REM rich sleep was related to more negative emotional valence ratings compared to NREM rich sleep. REM and NREM sleep did not selectively enhance arousal ratings
Cairney et al. (2014)	To investigate how auditory memory activation in SWS effects emotional memory	Healthy young adults (n = 15, mean age = 20.4)	N/A	Target memory activation with auditory cues played during encoding, retrieval, and SWS during an afternoon nap with PSG and qEEG	SDMC of IAPS (36 negative, 36 neutral) with auditory cues at encoding, SWS and retrieval	SWS duration and spindles were related to better negative stimuli recognition, compared to neutral stimuli, when cued with targeted memory activation
Denis et al. (2022)	To investigate the association between slow-wave and spindle coupling and emotional memory in stressed participants	Stressed adults (n= 32, mean age= 21.5), HC (n=32, age = 22.3)	Trier Social Stress Task	Full night sleep PSG with qEEG	SDMC of IAPS (100 positive, 100 neutral, 100 negative) afternoon testing encoding and recognition	SWS duration was associated with better memory for all stimulus in stressed participants. Spindle and slow oscillation coupling was associated with worse memory in the stressed group

Key: HC- Health control, SDMC – sleep-dependent memory consolidation, IAPS- International Affective Picture System, REM- rapid eye movement, NREM- non-rapid eye movement, SWS – slow-wave sleep, PSG – polysomnography, qEEG- quantitative electroencephalography

1.11 Limitations, Significance and Aims

Though prior research has emphasised the value of sleep and its importance for cognitive function in depression there are still many gaps in the literature. Studies have begun to define objective EEG measures of sleep in younger adults with depression, however, a consensus on the most sensitive and specific sleep-related markers of the disorder is lacking. The literature to date has also not fully characterised the changes in sleep micro-architecture in depression and limited studies have objectively measured sleep EEG activity in older adults with depression, despite known changes to sleep with normal ageing. It is important to pinpoint objective changes in sleep architecture measures in depression as these may be used as targets for sleep intervention in this at-risk group.

Research, using self-reported measures of sleep disturbance and actigraphy, has found associations between poor sleep continuity and declarative memory performance in older adults with depression. Yet, no studies have examined the effect of depression onset time on these relationships. This is imperative for understanding the impact of sleep disturbance on cognitive processes in this group.

Lastly, studies have examined the potential value of REM and NREM sleep in the consolidation of emotional memory in healthy young adults. However, limited studies have assessed these relationships in adults with depression and there are no studies in older adults with depression, despite reported sleep fragmentation and emotional processing issues in this population. There are also no studies utilising quantitative EEG (qEEG) analysis methods to measure brain activity-based markers of arousal in older adults with depression. Most studies evaluating sleep and emotional memory associations have focused on the individual contributions of REM and NREM sleep and used methodologies that do not account for the interaction between these temporally related sleep stages. Evaluating the role of sleep in emotional memory processes is key to understanding if sleep mediates mood symptoms in older adults with depression and findings may assist in identifying potential targets for intervention.

Therefore, the aims of this thesis are to:

1) Characterise objective sleep macro- and micro-architecture measures in adults and older adults with depression by conducting a systematic review and meta-analysis of the literature (Chapter II),

2) Identify whether sleep architecture differs in older adults with depression and late-onset depression compared to older adults without depression and explore relationship with performance on neuropsychological tasks (Chapter III),

3) Compare overnight emotional memory and EEG arousal measures during NREM and REM sleep using high-density EEG between older adults with depression and controls (Chapter IV),

4) Investigate the relationships between specific components of emotional memory and NREM and REM sleep arousal measures in older adults with depression (Chapter IV).

Chapter 2- Objective Measures of Sleep in Adults and Older Adults with and without Depression: A Systematic Review and Meta-Analysis

2.1 Abstract

Depression is intrinsically, bidirectionally linked to sleep, however, the exact nature of sleep macro- and microarchitectural disturbances in people with depression has been poorly defined, especially for older adults. Using published articles with electroencephalography (EEG) recordings from polysomnography, in adults with and without depression we aimed to determine whether objective measures of sleep macro- and micro-architecture differ. We also examined differences in these outcomes in older adults with and without depression.

A total of 2135 papers were identified through PubMed, Scopus, Web of Science and Embase databases. Two independent reviewers used the PRISMA framework to exclude 2062 papers at abstract review and 58 articles at full-text review. Fifteen articles met inclusion criteria, with all reporting sleep macro-architecture measures and two reporting sleep micro-architecture measures. We conducted a random effects model meta-analysis using Review Manager 5.4 software. NICE case-control guidelines manual was used to assess risk of bias.

Sleep data from 838 participants (406 depression and 432 control) were assessed. Out of the fifteen studies, two examined sleep EEG in 62 older adults over 50 years (31 depression and 31 control). Within the total sample (n=838), adults with depression had less total sleep time (mean difference (MD): 33.8 mins, 95% CI: 17.8, 49.8), lower sleep efficiency (SE) (MD: 7.8%, 95% CI: 4.5, 11.2), delayed sleep onset latency (MD: 9.0 mins, 95% : 5.7, 12.3), higher wake after sleep onset (MD: 14.69 mins, 95% CI: 6.0, 23.2), shorter rapid eye movement latency (ROL) (MD 10.4 mins, 95% CI: 1.2, 19.3) and greater REM density (MD 0.58 n/ REM min, 95% CI: 0.2, 1.0) than controls. No differences in the amount of N1, N2, slow-wave sleep (SWS) or rapid eye movement (REM) sleep were observed. In older adults, not all variables could be compared due to limited reporting however, the depression group had greater N1 (MD 6.9%, 95% CI: 1.8, 11.9), less N2 (MD 14.1%, 95% CI: 6.9, 21.3), shorter ROL (MD 25.5 mins, 95% CI: 13.5, 37.4) and no differences in SE, REM sleep or REM density. Risk of biases analyses demonstrated poor case-control selection across six studies, which when removed nullified the effects

of REM density and REM onset latency. Sleep micro-architecture measures were not analysed due to differing variable definitions.

Compared to controls, adults with depression had moderately worse sleep initiation and continuity. Shorter REM onset latency was also observed in adults with depression compared to control, although this effect was more strongly driven by older adults with depression. Based on limited available data at this time, objective EEG sleep macro-architecture is not consistently different in younger and older adults with depression compared to relevant controls.

2.2 Introduction

Sleep is imperative for optimal physiological functioning across the lifespan, with disruptions to the quality and quantity of sleep compromising physical and mental health (Medic et al., 2017). Depression is fundamentally linked to sleep disturbances, with sleep initiation and continuity issues being a part of the symptom profile within depression and also acting as risk factors for the recurrence of symptoms (Cho et al., 2008; Geoffroy et al., 2018). Sleep disturbance in depression has also been shown to remain after patients are in remission (Schennach et al., 2019). Insomnia and hypersomnia are common in depression therefore changes in sleep initiation, timing and sleep continuity are often observed in this population (Geoffroy et al., 2018). Alterations in rapid eye movement (REM) sleep are also frequently observed in adults with depression. Earlier research focused on shortened REM onset latency as a biomarker for depression (Kupfer, 1976; Kupfer & Foster, 1972), although more recent studies have identified increased REM density as a more specific biomarker (Feinberg et al., 1982; Lauer et al., 1991). Given the progress made in quantitative electroencephalography (EEG) analysis of sleep micro-architecture, it is important to assess these measures to characterise altered sleep physiology in depression. Previous literature has mostly focused on delta power during non-REM sleep which is reduced in depression, especially in the first non-REM period (Armitage, 1995; Hoffmann et al., 2000). Despite many cited differences in the sleep of depressed adults, there is still no consensus on which changes are sensitive and specific to the disorder and if these sleep measures change over the lifetime.

The majority of studies examining the changes in sleep macro- and micro-architecture in depression have focused on younger adults and thus the sleep of older adults with depression (>50 years old) has not yet been reliably characterised. Normal ageing is associated with difficulties in sleep initiation and continuity as well as a shift towards lighter stage 1 sleep (N1), rather than predominant stage 2 (N2) and 3 sleep or slow-wave sleep (N3/SWS) (Danker-Hopfe et al., 2005). Further reductions in slow wave-oscillation power is also observed in ageing samples (Mander et al., 2017; Sergeeva et al., 2020). The reduction of slow-wave sleep duration and power is thought to be representative of age-dependent neural atrophy (Mander et al., 2013). Understanding whether the changes in sleep in older adults with

depression are above and beyond the changes observed in normal ageing is crucial given the evidence supporting depression and sleep disturbance as risk factors for neurodegeneration and cognitive decline (as reviewed in Mander et al., 2017 and Naismith et al., 2012). However, there are a limited number of research studies in older adults with depression and the small sample sizes in each study make it difficult to conclude whether sleep is different compared to controls. Elucidating the alterations in sleep neurophysiology in depression may also inform future targeted treatment approaches to improve mental health outcomes and mitigate the impact of sleep disturbance in depression on associated comorbidities.

Previous meta-analyses have assessed objective sleep measures derived from polysomnography (PSG) in affective disorders more broadly (Baglioni et al., 2016; Benca et al., 1992). An early study by Benca et al. (1992) found that individuals with affective disorders had worse sleep continuity (less total sleep time (TST), lower sleep efficiency (SE)), alterations in sleep initiation (longer sleep onset latency (SOL) and earlier REM onset latency (ROL)), shorter SWS duration, longer REM duration, and higher REM density compared to controls. However, in participants over 50 years with affective disorders, differences in SWS, REM duration, and REM density were not observed. This study has limitations including the broad definition of affective disorders, the inclusion of children and adolescents, variations in sleep variable definitions, and a lack of control comparisons in some studies. A more recent meta-analysis by Baglioni et al. (2016) assessed participants with major depressive disorder and found they had worse sleep continuity (lower SE, later SOL and more WASO), lower sleep depth (more N1 and less N2 and N3 sleep) and higher REM pressure (shorter REM onset latency (ROL), increased REM density and longer REM sleep). The applicability of this study to the older population was also limited by the inclusion of children, and absence of case-control studies or groups matched in age and sex. Two studies of participants over 60 years with major depression were included (Dew et al., 1996; Dykierek et al., 1998), but the sleep measures were not reported separately. These studies were excluded from the current meta-analysis due to participants not meeting depression criteria and presence of other neuropsychological disorders. Finally, neither of these meta-analyses sought to measure quantitative EEG outcomes. Therefore, there is a gap in the literature for a systematic review of case control studies

critically assessing objective macro- and micro-architecture EEG measures in unipolar depression across younger and older adult groups.

This systematic review and meta-analysis evaluated the studies to date that have examined sleep EEG recordings from polysomnography in adults with and without unipolar depression. We aimed to determine whether objective measures of sleep macro-architecture and sleep micro-architecture differ between adults with and without depression, and between older adults (> 50 years old) with and without depression. Our primary sleep macro-architecture measures of interest were TST, SE and the amount of time spent in stage N1, N2, SWS and REM sleep, WASO, SOL and ROL and secondary measures included REM density and respiratory events (apnea-hypopnea index, arousal index, minimum oxygen saturation, oxygen desaturation index (ODI), mean desaturation). Our secondary sleep micro-architecture measures of interest were EEG spectral power in delta (slow-wave activity), theta, alpha and sigma frequency bands, number and density of sleep spindles, and K-complexes.

2.3 Methods

A search was conducted using PubMed, Scopus, Web of Science and Embase databases to identify studies examining objective measures of sleep in depression. The Boolean search terms used were formed around the key terms; 'depression' and 'sleep' or 'EEG', each transformed to suit the requirements of each database (see Appendix 6.1 Meta-Analysis Search Terms). No time or language limits were applied. The initial search was conducted on the 6th July 2020. A further search on the 23rd November 2021 did not reveal any new eligible studies. The analysis was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (Page et al., 2021). This study was prospectively registered on PROSPERO (CRD42020192585).

In order to be included in this review, studies had to meet the following criteria:

1. Population: Humans ≥ 18 years old.
2. Indicator: People diagnosed with current endogenous major depression, via clinician or researcher, according to accepted clinical criteria (listed in exclusion criteria).
3. Comparisons: Control participants were adults who were age-matched to the participants with depression (mean of ±2 years, at the group level). The criteria employed to diagnose depression must also have been applied to the control group (i.e., to ensure they did not meet the criteria for depression).
4. Outcomes: The primary (sleep macro-architecture) or secondary (sleep micro-architecture) outcome must be objectively measured sleep overnight via polysomnography (PSG) or polygraphy, including EEG assessment, without sleep or drug intervention. For sleep macro-architecture, the specific measures include total sleep time, sleep efficiency (total sleep time/ time in bed %), the amount of time spent in each stage of sleep (Wake, N1,2,3 and REM mins or %), wake after sleep onset, latency to sleep onset and latency to REM sleep, REM density (number of rapid eye movements per minute), apnea-hypopnea index, arousal index, minimum oxygen saturation, oxygen desaturation index (ODI), mean desaturation. Sleep micro-architecture measures were to be derived specifically using EEG power spectral analysis with

fast and slow frequency EEG activity across a range of bands (delta, theta, alpha and sigma) included. The number and density of spindles, and K-complexes during sleep were included.

5. Type of study: cohort, case-control study or interventional study with baseline PSG.

Studies were excluded if;

- Depression participants were not assessed using a clinician or researcher rated tool or did not meet criteria for current unipolar/ endogenous major depression using any of the following: Diagnostic and Statistical Manual of Mental Disorders-IV or III-R (Bell, 1994), International Classification of Diseases-10 (World Health Organization, 2010), Hamilton Rating Scale for Depression (cut-off score >8) (Hamilton, 1986), Montgomery–Åsberg Depression Rating Scale (cut-off score >7) (Montgomery & Åsberg, 1979) or Inventory of Depressive Symptomatology (cut-off score >6) (Rush et al., 1996) criteria or similar.
- Participants had a primary diagnosis of a neurocognitive disorder, neurodevelopmental disorder, schizophrenia spectrum or other psychotic disorder, bipolar or related disorder, anxiety disorder, obsessive-compulsive or related disorder, trauma-related disorder, dissociative disorder, eating disorder, conduct disorder, addictive disorder, personality disorder or paraphilic disorder.
- Participants had any significant medical comorbidities, e.g., neurological disease, traumatic brain injury, cancer.
- Participants had any sleep disorders such as obstructive sleep apnea, REM sleep behaviour disorder, shift work disorder or sleep disruption as a study design (e.g., SWS modulation)
- Participants were taking sleep affecting medication at the time of the study.

Following database searches, duplicate studies were removed. Each study was reviewed by two out of three reviewers (AR, JT, AL) in the initial phase where the title and abstract were reviewed, and disagreements were resolved by consensus. Subsequently, review of the full-text articles was performed by two of three reviewers (AR, JT, AL) and disagreements were resolved by consensus. Some attempt was made to contact the study authors in the case of missing macro- or micro-architecture data was unavailable, but no responses were received.

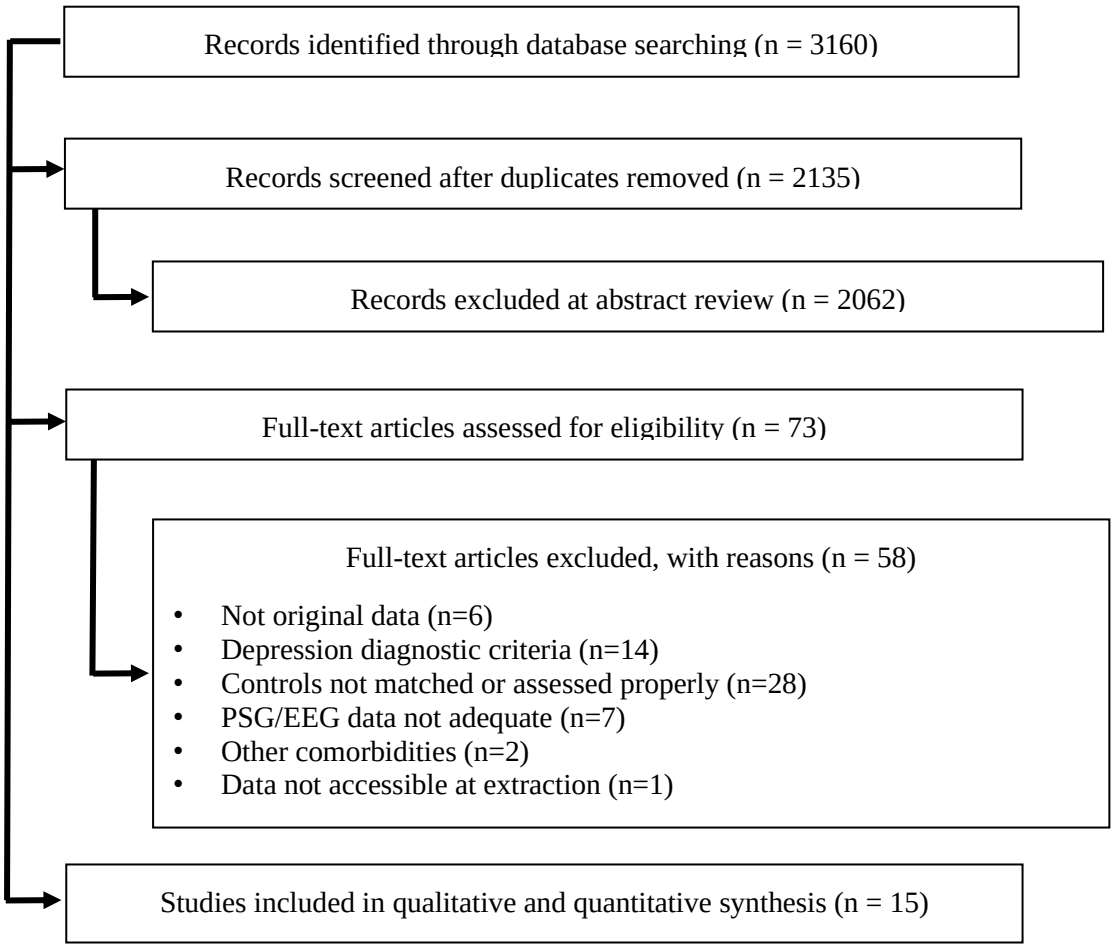
The study characteristics, measurements and outcomes were manually recorded from each paper and group data was tabulated as mean ± standard deviation. Studies reporting number of minutes spent in sleep stages were converted to a percentage of total sleep time for consistency across studies. In the case of different definitions of REM density across the studies, a sensitivity analysis was performed on studies with the same definition to report a consistent outcome. The standard error of the mean was converted to standard deviation where applicable using the formula in Chapter 6.5.2.2 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). Where necessary, we transformed data with multiple case or control groups into a single mean and standard deviation value for each group using formulas from chapter 6.5.2.10 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). Heterogeneity was assessed using the I^2 statistic, which represents the variation percentage across studies due to heterogeneity. The criteria were as follows; heterogeneity not important (I^2<40%), moderate heterogeneity (I^2= 40-60%), substantial heterogeneity (I^2=60-75%) and considerable heterogeneity (I^2>75%) (Higgins et al., 2003). The data was analysed, and forest plots were created using Review Manager 5.4.1 using the mean difference method and random effects model with 95% confidence interval analyses. Risk of bias assessment was undertaken (by AR and AL) using the National Institute for Health and Care Excellence (NICE) guidelines manual, appendix E, methodology checklist for case-control studies (Garbi, 2021). For criteria 1.8 and 1.9 of the NICE guidelines, the questions were adapted to suit the current research question 1.8 ‘Measures taken to prevent knowledge of depression influencing EEG/PSG scoring/outcomes?’ and 1.9 ‘Is EEG/PSG status measured in a standard, valid & reliable way?’ and used to assess risk of bias. Following quality appraisal through risk of bias and following the identification of a high risk of bias across most studies in case control and selection methods, sensitivity analyses was applied.

2.4 Results

2.4.1 Search

The initial search identified 3160 studies that met the search criteria (PubMed = 478, Scopus = 175, Web of Science = 2470, Embase = 37). Following duplicate removal, a total of 2135 papers were screened. A total of 2062 papers were excluded at the initial phase of the title and abstract review and 58 articles were excluded at the full-text review stage. Fifteen articles met inclusion criteria with all studies reporting sleep macro-architecture measures and three reporting sleep micro-architecture measures. See Figure 2.1 for a PRISMA flow diagram with reasons studies were excluded at the full-text review. Notably, three other studies assessing sleep micro-architecture in adults with depression could not be included due to overlapping samples with studies already included in the meta-analysis (Plante et al., 2013; Plante, Landsness, Peterson, Goldstein, Wanger, et al., 2012).

Figure 2.1 Systematic Review Flow Diagram



Legend- PSG- polysomnography, EEG- electroencephalography

2.4.2 Participant characteristics

A total of 406 depression and 432 control participants from 15 studies were analysed (Table 2.1). The average age of the depression group was 41.3 ± 8.6 years, and the control group were 41.1 ± 8.3 years. Females made up 52.5 % of the depression cases and 50.6% of the controls.

Three separate diagnostic structures were used within the studies to define depression. Most studies used a combination of two diagnostic structures to create a threshold for defining depression cases and to provide information about depression severity. The criteria used to define depression included the Diagnostic and Statistical Manual of Mental Disorders (n=10) (DSM-III-R and DSM-IV), Hamilton Depression Rating Scale (k = 2) (17-item) and the Schedule for Affective Disorders and Schizophrenia using Research Diagnostic Criteria (k = 2). Secondary depression severity criteria used included the Beck Depression Inventory (k = 3) (versions 1 and 2), Montgomery-Asberg Depression Rating Scale (k=1) and Hamilton Depression Rating Scale (k = 11) (17 and 24-item). Not accounting for the different diagnostic criteria used across the 15 studies, the depression severity across the studies was classified as moderate (k = 9), moderate to severe (k = 3) and severe (k = 3) (Beck et al., 1996; Beck et al., 1988; Zimmerman et al., 2013). Six of the 15 papers cited the age of first depressive episode onset, which in the six studies were classified as early-onset depression (<50 years).

All studies were age-matched at the group level ± 2 years in age to the cases. Two studies by Buysse et al. (1998) and Mendlewicz and Kerkhofs (1991) provided further case-matching details matching on age within 2 and 5 years, respectively. Six (40%) of the studies selectively defined controls as those without sleep- wake disturbance and did not apply this exclusion criteria to cases.

2.4.2.1 Older adults

Two studies with a total of 31 depression and 31 control participants contained data from adults over the age of 50 years. The average age of the older depression group was 64.6 ± 7.1 years, and older control group was 65.6 ± 5.8 years. However, the study by Reynolds et al. (1985) had more women in the depression group compared to controls (depression: 84%, control: 68%), whereas the participants

in Kupfer et al. (1989) were matched in gender. The average percentage of females per group across the two studies was 67% for the depression group and 59% for the control group. Both studies used the Hamilton Depression Rating 17-item scale to define depression severity. On average, the study by Kupfer et al. (1989) had a moderately depressed sample, while Reynolds et al. (1985) had a severely depressed sample. Kupfer et al. (1989) classified the group as early-onset depression based on the average age of first depressive episode onset (34 ± 15.9 years).

Table 2.1 Study characteristics of full text articles

Author and date	*Patient number, sex (% female), age (mean ±SD)*	*Depression criteria*	*Depression severity (mean score ±SD)*	*Depression patient severity*	*age of first depression onset*	*Control number, sex (% female), age (mean ±SD)*	*Controls depressive severity (mean score ±SD)*	*Case-match methods*	*Sleep setting methods*	*Sleep analysis methodology*
Armitage, 1992	n=9, 78% F, 32.0 ±7.1 years	DSM-III-R	HAM-D Scale 17-item score (22 ±3.5)	moderate	N/A	n=9, 78%, F, 32.0 ±7.1 years	HAM-D Scale 17-item score <7	Age and sex-matched controls selected from a pool of volunteers. Control exclusion criteria differed from depression in that they had no clinically identified sleep disturbance and regular sleep- wake cycles	EEG was recorded on FM tape and polygraph paper (Grass, Model 78). The sampling rate was 256Hz. Opposite mastoids were used. Band pass filters were 0.3-30 Hz with a 60Hz notch filter. R & K scoring criteria.	N/A
Borbely, 1984	n=6, 66% F, 31.6 ±7.5 years	HAM-D 17 score ≥30	HAM-D Scale 17-item score ≥30	severe	N/A	n=6, 66%, F, 31.6 ±7.5 years	Excluded for psychiatric disorder	Age and sex-matched controls. Controls were excluded for sleep-wake disturbance.	EEG was recorded on Hewlett Packard Model 3968 tape recorder. The sampling rate was 64 per second with a low-pass filter of 2.5 Hz, 24 dB/ octave. R & K scoring criteria.	N/A
Buysse, 1988	n=54, 100% F, 36.7±10.5 years	DSM-III-R or DSM-IV	HAM-D 17 score ≥ 15 (18.7 ±3.2)	moderate	23.2 ±7.1	n=54, 100% F, 36.7±10.5 years	HAM-D Scale 17-item score (1.6 ±1.6)	Age matched ±2 years and sex-matched controls	Mean data was taken from PSG nights 2 and 3. Single channel EEG, recorded at C3 or C4 referenced to A1 -A2, was collected through Grass Model 78 amplifiers filtered using 30Hz -0.3Hz and digitized at 256Hz.	N/A

Germain, 2004	n=12, 83%, F, 38.3 ±13.0 years	DSM-III-R SCID	HAM-D 17 score ≥ 15 (24 ±5.2)	severe	N/A	n=13, 77% F, 37.8 ±11.5 years	HAM-D Scale-17 item score (0.3 ±0.4)	Age and sex matched controls	EEG data from night 2 was used. EEG signals were collected from C4/A1-A2 using Grass 7P511 amplifiers and filtered between 0.3–100 Hz. Impedances were set at <5000 Ω. R & K scoring criteria.	N/A
Goldschmied, 2019	n=37, 56.7% F, 27.6 ±6.3 years	DSM-III-R or DSM-IV	BDI-II score (25.2 ±8.7)	moderate	N/A	n=59, 542% F, 29.0 ±5.7 years	BDI-II score (0.7 ±1.4)	Covaried for age and sex in the analysis	EEG channels C3, C4, F3, F4, P3, P4, O1, and O2 were collected with impedances were below 2 kΩ on GRASSTM P511 A/C amplifiers with a gain of 50,000. Band pass filters were 0.3-30Hz with a 60Hz notch filter. Signals were digitized at 256 Hz. R & K scoring criteria.	Fast Fourier transform was used for power spectral analysis from C3 electrodes processed in 2 sec epochs (512 samples). Delta power was defined as 0.5–3.9 Hz.
Hoffmann, 2000	n=13, 0% F, 33.1 ±7.8 years	DSM-III-R	HAM-D Scale 17-item score ≥ 17 (20.9±3.2)	moderate	25.5 ±8.7	n=13, 0% F, 31.3 ±5.1 years	HAM-D Scale 17-item score ≤2	Age and sex matched controls	Second night EEG was obtained from C3, and C4 referenced to the ear lobes with 10 KΩ resistance applied. GRASS P511 A/C amplifiers were used with a gain of 50,000. Band pass filters were set at 0.3-30Hz with a 60Hz notch filter. The sampling rate was 250 Hz. R& K scoring criteria.	N/A

Hubaln, 2006	n=67, 0% F, 43.4 ±12.3 years	SADS L RDC	HAM-D Scale 24-item score ≥20 (28 ±8.5)	moderate-severe	37.5 ±14	n=67, 0% F, 41.9 ±13.6 years	Absence of psychiatric disorder determined on interview	Men only. Age matched at a group level and was covaried for in the analysis	Night 3 EEG recordings were collected via Fz, Cz and Oz - A1/A2 channels. R & K scoring criteria.	N/A
Kupfer, 1989	n=6, 50% F, 59.3 ±7.6 years	HAM-D 17	HAM-D Scale 17-item score ≥30 (sum of 2 raters) (23 ±4.9)	moderate	34.0 ±15.9	n=6, 50% F, 62.2 ±6.6 years	HAM-D Scale 17-item score <5	Age and sex matched controls. Controls were excluded for sleep-wake disturbance.	EEG signals were measured using a Grass model 78B polygraph and were manually scored. R & K scoring criteria.	REM density defined as REM activity/time spent in REM sleep, where REM activity was an approximate measure of the frequency of rapid eye movement during REM sleep (each min of REM sleep is scored 0-8)
Kwon, 2019	n=30, 50% F, 50.5 ±14.5 years	DSM-IV	BDI score (26.4 ±5.6)	moderate	N/A	n=30, 50% F, 50.5 ±14.5 years	BDI score (8.6±4.1)	Age, sex and BMI matched controls	EEG were measured through C3 and O2 - A1/A2 electrodes. EEG signals were collected at a 250-Hz sampling rate. 2012 AASM scoring criteria.	REM criteria - max slope>1 μV/ms; duration of signal above <1.5 s; and opposite polarity and synchronization (within 70 ms) of both eye signals. REM density described as the ratio of 3-sec epochs per REM period including at least one rapid eye movement to the total amount of time spent in REM

Landolt, 2005	n=16, 50% F, 41.2 ±2.1 years	DSM-IV	BDI (23.3 ±2.3) and HAM-D Scale 17-item score (16.1 ±0.9)	moderate	22.3 ±2.8	n=16, 50% F, 41.2 ±2.1 years	BDI score (1.1 ±0.7) and HAM-D Scale 17-item score (0.7±0.3)	Age and sex matched controls	Night 2 EEG recordings used F4-C4, C4-P4, P4-O2, and C3-A2 electrodes. Signals filtered from 0.16-70 Hz at a sampling rate of 256Hz. R & K scoring criteria.	N/A
Leistedt, 2007	n=10, 0% F, 41.3 ±8.1 years	DSM-IV-TR	HAM-D Scale 24-item score ≥ 20 (24, range 20-56)	moderate-severe	39.1 ±3.5	n=14, 0% F, 42.4 ±5.7 years	HAM-D Scale 24-item score (0, range 0-3)	Men only. Age matched at group level. Depressed participants were required to have a PSQI score ≥5	Night 2 or 3 PSG was chosen based on artifact. EEG channels Fz, Cz and Oz referenced to A1/A2 was measured using Brainnet polygraph. A 0.3-35Hz filter was applied. Channels were sampled at 200 Hz. R & K scoring criteria.	No delta power definition reported.
Mendlewicz, 1991	n=67, 58% F, 42.6 years (no SD available)	RDC	HAM-D Scale 17-item score ≥ 17	moderate - severe	N/A	n=66, 55% F, 41.4 years	Controls were studied under the same conditions	Age matched ±5 years and sex matched	Night 3 EEG data was collected across different sites. R & K scoring criteria.	REM density = REM activity /time spent in REM sleep, where REM activity was an approximate measure of the frequency of rapid eye movement during REM sleep (each min of REM sleep is scored 0-8)

Plante, 2012	n=30, 63% F, 26.0 ±9.1 years	DSM-IV	HAM-D Scale 17-item score (19 ±2.7)	moderate	N/A	n=30, 63% F, 25.4 ±8.5 years	Evaluated with non-patient DSM-IV SCID	Age matched at a group level and sex-matched controls	High-density EEG channels were sampled at 500Hz. Net Station signals were high-pass filtered (0.1 Hz), down sampled to 128 Hz and band-pass filtered with 2-way least-squares FIR from 1–40 Hz. Channels were average referenced to the average scalp voltage in all channels. F3, F4, C3, C4, O1 and O2 channels were collection. AASM 2007 scoring criteria.	Delta power frequency band was defined as 0.5-4Hz, computed using half-wave zero analysis.
Reynolds, 1985	n=25, 84% F, 69.9 ±6.6 years	SADS-L RDC	HAM-D Scale 17-item score ≥15 (25 ±5.1)	severe	N/A	n=25, 68% F, 69.0 ±5.0 years	HAM-D Scale 17-item score < 5 (1.5 ±1.5)	Age and sex matched at a group level. Controls were excluded for sleep-wake disturbance.	Night 2 and 3 data was collected on one EEG channel (C3) using grass model 78-b at 50uV, with an impedance of 5,000 at 10mm/sec. R & K scoring criteria.	REM density = REM activity /time spent in REM sleep, where REM activity was an approximate measure of the frequency of rapid eye movement during REM sleep (each min of REM sleep is scored 0-8)
Staner, 2003	n=21, 48% F, 46.5 ±8.9 years	DSM-IV	MADRS (26.2 ± 9.7)	moderate	N/A	n=21, 48% F, 44.3 ±12.3 years	MADRS score (4.6 ± 2.7)	Age matched at a group level and sex matched. Depressed participants were required to have some level of sleep continuity or initiation issues whereas controls had a PSQI score <5	Night 2 EEG data were recorded via C3 and O1 - A1/A2 electrodes. Signals were digitized at 128 Hz. R & K scoring criteria.	N/A

Legend: MADRS- Montgomery-Asberg Depression Rating Scale, DSM- Diagnostic and Statistical Manual of Mental Disorders, BDI-Beck Depression Inventory, HAM-D - Hamilton Depression Rating Scale, SCID- Structured Clinical Interview for DSM, SADS-L -Schedule for Affective Disorders and Schizophrenia Lifetime, RDC- Research Diagnostic Criteria, R & K- Rechtschaffen and Kales, AASM - American Academy of Sleep Medicine, EEG- electroencephalography, REM- rapid eye movement, SD- standard deviation

2.4.3 Risk of Bias

Table 2.2 contains risk of bias outcomes for the case-control studies. Overall, studies performed poorly in the selection of participants. None of the studies reported participation rates. Further, sleep-scoring blinding methods were not reported by 10 of the 15 studies. EEG and PSG methodology varied between the studies, with some studies identified as high risk. Most studies were of moderate quality, therefore we included them in the meta-analysis and the outcome was interpreted with a level of uncertainty.

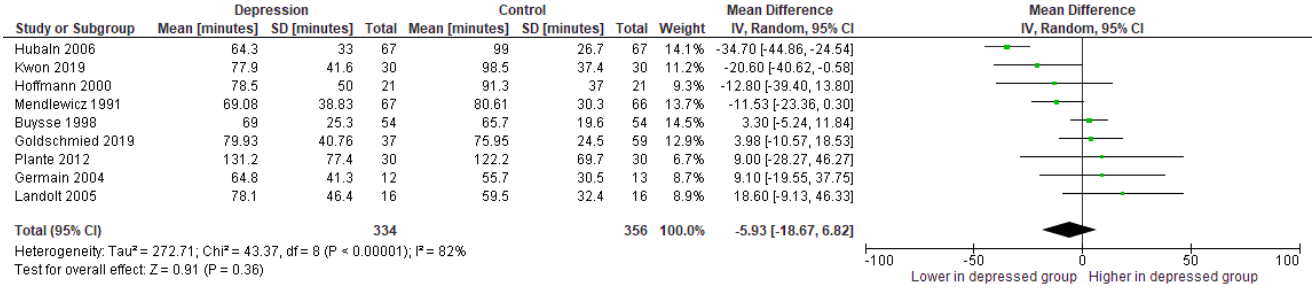
In eight studies, participants were either not recruited from comparable populations (e.g. severe inpatient cases and young healthy controls) or did not report the source of control participants (Armitage et al., 1992; Borbély et al., 1984; Germain et al., 2004; Hubain et al., 2006; Kupfer et al., 1989; Leistedt et al., 2007; Plante, Landsness, Peterson, Goldstein, Riedner, et al., 2012; Reynolds et al., 1985). The selective exclusion of cases and controls was the most problematic, as the definition of healthy controls varied across the studies. Some studies intentionally excluded controls without regular sleep-wake cycles or selected cases with evidence of sleep disturbances. To understand the effect of the studies which included 'healthy sleeping' controls, we performed a sensitivity analysis by removing these six studies (Armitage et al., 1992; Borbély et al., 1984; Kupfer et al., 1989; Leistedt et al., 2007; Reynolds et al., 1985; Staner et al., 2003). After removing studies with 'healthy sleeping' controls, the sensitivity analysis showed both REM onset latency (mean difference: 5.9, 95% CI = -18.7, 6.8, p = 0.36) and REM density (mean difference: 1.01, 95% CI = -0.08, 2.10, p = 0.07) were not different between cases and controls (Figure 2.2 and 2.3). The two studies of older adults both had poor case control selection and were removed in the sensitivity analysis, therefore a level of caution is needed in the interpretation of results. Other results were unchanged following the sensitivity analysis.

Table 2.2 Risk of Bias for k=15 studies

Author, year	The study addresses an appropriate and clearly focused question	Cases and controls are from comparable populations	The same exclusion criteria are used for cases & controls	Participation rate for cases & controls are similar	Comparison of participants & non-participants	Cases are clearly defined and differentiated from controls	Controls are not cases	Measures taken to prevent knowledge of depression influencing EEG/PSG scoring/outcomes	Is EEG/PSG status measured in a standard, valid & reliable way	Confounders are identified & taken into account in the design and analysis
Armitage, 1992	unclear	high risk	high risk	unclear	unclear	low risk	low risk	low risk	unclear	unclear
Borbely, 1984	low risk	high risk	high risk	unclear	unclear	low risk	low risk	unclear	unclear	low risk
Buysse, 1998	low risk	low risk	low risk	unclear	unclear	low risk	low risk	unclear	high risk	low risk
Germain, 2004	low risk	high risk	unclear	unclear	unclear	low risk	low risk	low risk	high risk	low risk
Goldschmied, 2019	low risk	low risk	low risk	unclear	low risk	low risk	low risk	unclear	low risk	low risk
Hoffmann, 2000	low risk	low risk	low risk	unclear	unclear	low risk	low risk	unclear	low risk	low risk
Hubaln, 2006	low risk	high risk	low risk	unclear	unclear	low risk	low risk	unclear	low risk	low risk
Kupfer, 1989	unclear	high risk	high risk	unclear	unclear	low risk	low risk	low risk	high risk	unclear
Kwon, 2019	low risk	low risk	low risk	unclear	unclear	low risk	high risk	unclear	low risk	low risk
Landolt, 2005	low risk	low risk	low risk	unclear	unclear	low risk	low risk	unclear	unclear	low risk
Leistedt, 2007	low risk	high risk	high risk	unclear	unclear	low risk	low risk	unclear	unclear	unclear
Mendlewicz, 1991	low risk	unclear	low risk	unclear	unclear	low risk	unclear	low risk	low risk	low risk
Plante, 2012	low risk	high risk	low risk	unclear	unclear	low risk	low risk	unclear	low risk	low risk
Reynolds, 1985	low risk	high risk	high risk	unclear	unclear	low risk	low risk	low risk	unclear	unclear
Staner, 2003	low risk	low risk	high risk	unclear	unclear	low risk	low risk	unclear	unclear	low risk

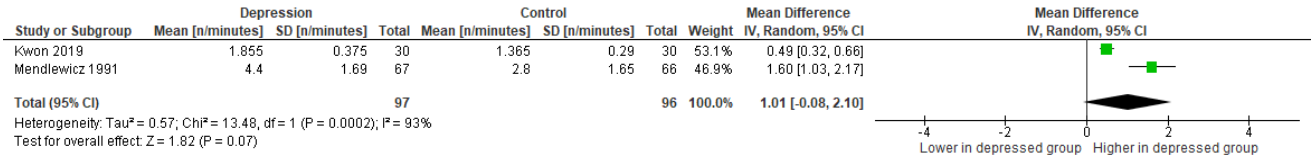
Risk of bias completed according to the National Institute for Health and Care Excellence (NICE) guidelines manual, appendix E, methodology checklist for case-control studies (Garbi, 2021).

Figure 2.2 Risk of bias sensitivity analysis forest plot of REM onset latency in adults with depression compared to control participants



REM onset latency (minutes) was reported by nine studies. There was no difference in REM onset latency between depression and controls (depressed participants reached their first REM period 5.93 minutes earlier than controls, 95% CI 6.82 to 18.67, $p < 0.00001$). There was moderate heterogeneity as represented by an I^2 value of 60%. The standard mean difference was 0.16 (95% CI 0.19 to 0.51, $p = 0.36$) indicating a small effect estimate.

Figure 2.3 Risk of bias sensitivity analysis forest plot of REM density in adults with depression compared to control participants



REM density was reported by two studies. There was no difference in REM density between depression and controls (depressed participants had a higher REM density by 1.01 rapid eye movements per minute compared to controls, 95% CI 0.08 to 2.10, $p = 0.07$). There was considerable heterogeneity as represented by an I^2 value of 95%. The standard mean difference was 1.14 (95% CI 0.68 to 1.61, $p < 0.00001$) indicating a large effect estimate.

2.4.4 Sleep measures

2.4.4.1 Primary measures

Pooled results indicated the depression group had 33.8 minutes less TST (95% CI: 17.8, 49.7), 7.9% lower sleep efficiency (SE) (95% CI: 4.5, 11.2), 14.6 minutes more WASO (95% CI: 6.0, 23.2), and SOL was 9.0 minutes later compared to the control group (95% CI: 5.7, 12.3), as indicated by mean difference (Figure 2.4-2.8) (ps.< 0.0001). The latency to REM sleep was 10.3 minutes earlier in the depression group compared to controls (95% CI: 1.2, 19.3, p = 0.03) (Figure 2.8).

There was no significant difference in any sleep stage (N1:0.71%, 95% CI: 0.21,1.64, N2:0.33%, 95% CI: 1.86, 2.25, SWS:1.1%, 95% CI: 0.08 to 2.28, or REM: 0.6%, 95% CI: 0.53, 1.74) between depression and control groups (see Figures 2.9-2.12).

2.4.4.2 Secondary measures

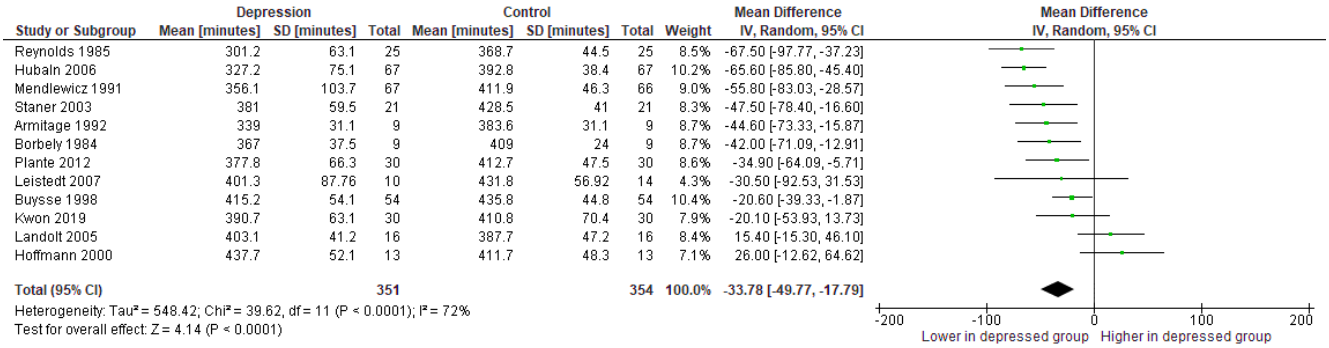
Of the three studies that reported delta power in SWS, frequency definitions of delta varied across studies, therefore were not quantitively comparable (Goldschmeid, 2019 [0.5–3.9 Hz]; Plante, 2012 [1-4.5 Hz]; Leisteidt, 2007 [no definition]). However within the studies, Goldschmied, Cheng, Hoffmann, et al. (2019) reported lower delta power in SWS in the depression group compared to controls (Goldschmeid 2019- control: 427.3 ± 81.0 μV^2, depression: 392.4 ± 62.4 μV^2, $p < 0.01$). In Plante et al. (2012) and Leistedt et al. (2007), delta power in SWS was not different between depression and controls (Plante, 2012- control: 17.3 ± 6.8 μV^2/Hz, depression: 22.7 ± 13.1 μV^2/Hz, p = 0.54; Leistedt, 2007- control: 465.1 ± 144.8 μV^2, depression: 501.3 ± 177.0 μV^2, p = 0.69).

REM density was higher in the depression group than controls by 0.58 REM events per minute (95% CI: 0.16, 1.0, p = 0.007). (Figure 2.13). One study, Kwon et al. (2019), used an alternate definition for REM density and therefore was not directly comparable (see Table 2.1 for definitions). When removing this study, the difference between REM density in the depression and control groups was non-significant (mean difference: 0.66, 95% CI: 0.10, 1.41, p = 0.09) (Figure 2.14).

One study (Plante et al. 2012) reported an arousal index higher in the depression compared to the control group (control: 7.9 ± 4.3 arousals/ hour, depression: 10.6 ± 5.6 arousals/ hour).

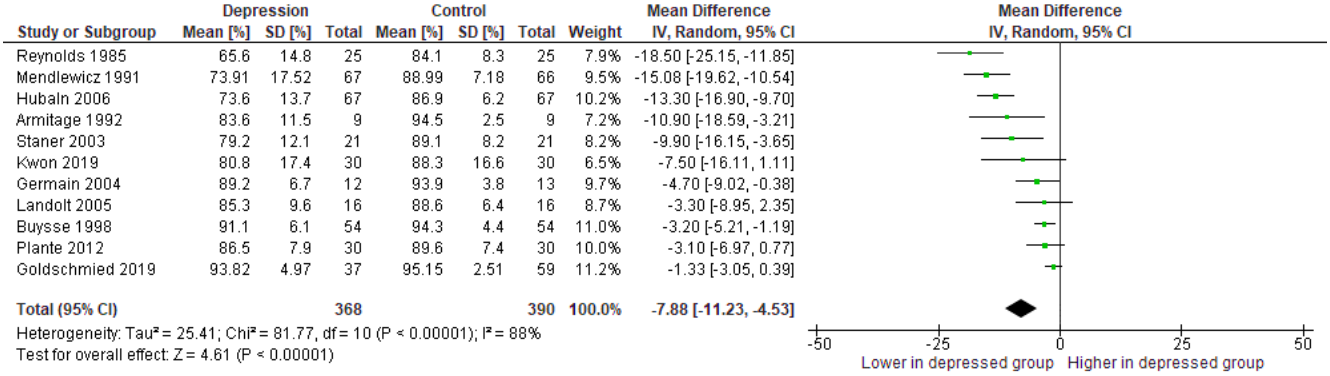
The following variables were not reported any study; minimum oxygen saturation, oxygen desaturation index (ODI), mean desaturation, EEG spectral power in delta, theta, alpha and sigma frequency ranges, number and density of spindles, and K-complexes.

Figure 2.4. Forest plot of total sleep time in adults with depression compared to control participants



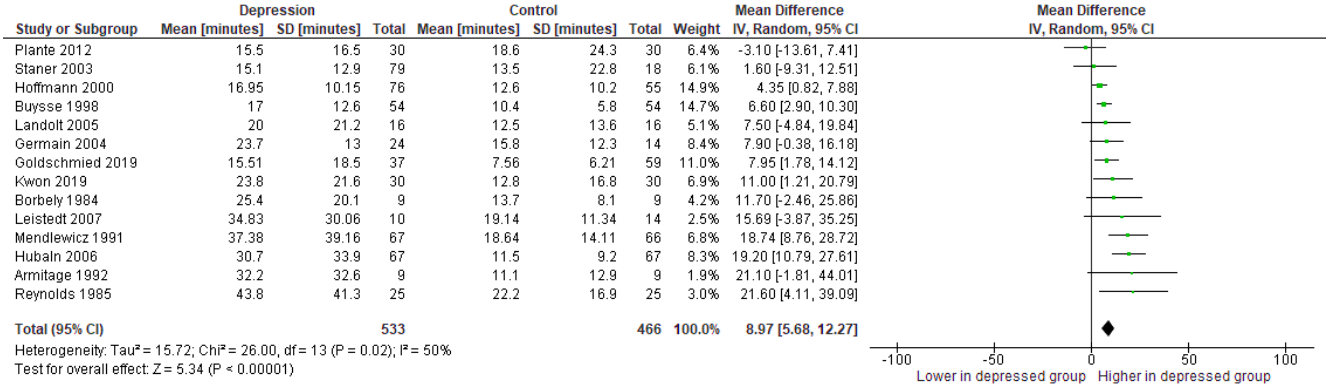
Total sleep time (minutes) was reported by twelve studies. Depressed participants had 33.78 minutes less total sleep time than controls (95% CI 17.79 to 49.77, $p < 0.0001$). Ten studies (83%) reported depressed participants having more TST than controls. There was substantial heterogeneity as represented by an I^2 value of 72%. The standard mean difference was 0.61 (95% CI 0.89 to 0.32, $p < 0.0001$) indicating a medium effect estimate.

Figure 2.5. Forest plot of sleep efficiency in adults with depression compared to control participants



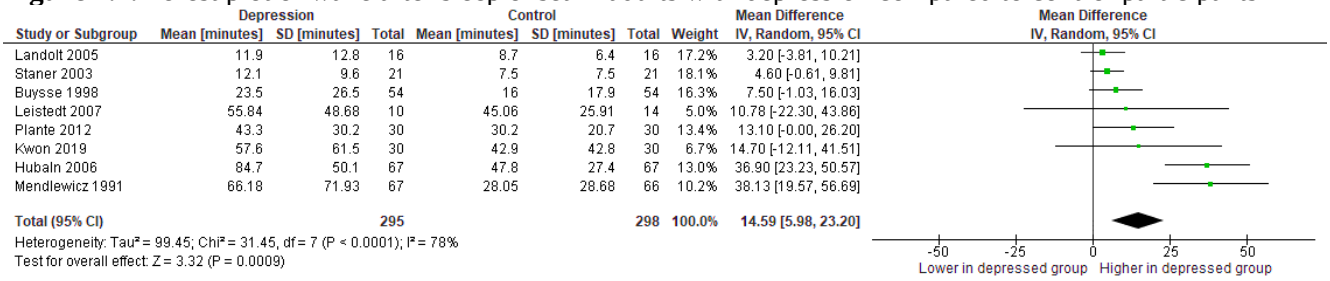
Sleep efficiency (% of total sleep time/time in bed) was reported by eleven studies. Depressed participants had 7.88% lower sleep efficiency compared to controls (95% CI 4.53 to 11.23, $p < 0.0001$). All studies reported lower sleep efficiency in depressed participants compared to controls. There was considerable heterogeneity as represented by an I^2 value of 88%. The standard mean difference was 0.81 (95% CI 1.06 to 0.55, $p = 0.005$) indicating a large effect estimate.

Figure 2.6. Forest plot of sleep onset latency in adults with depression compared to control participants



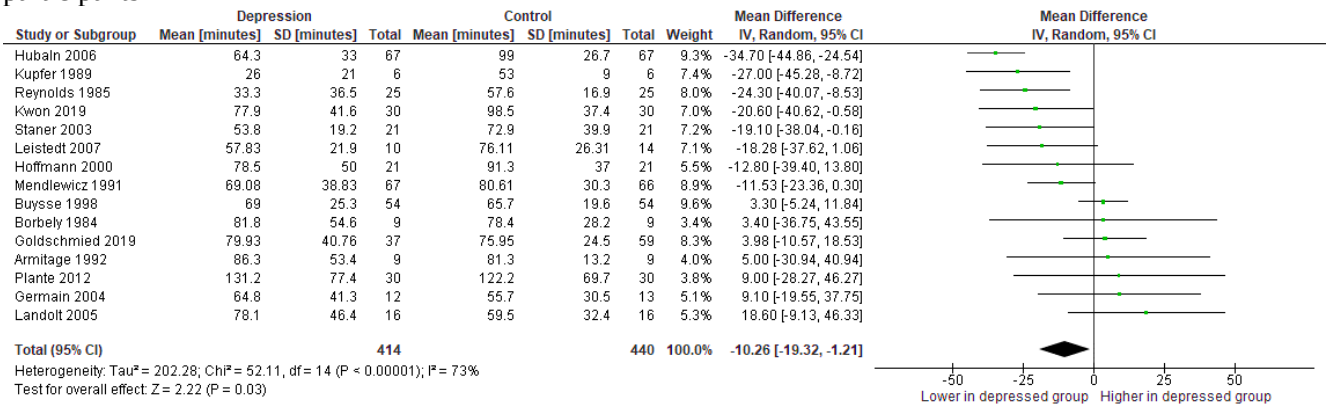
Sleep onset latency (minutes) was reported by fourteen studies. Depressed participants fell asleep 8.97 minutes later than controls (95% CI 5.68 to 12.27, p < 0.0001). Thirteen studies (92%) reported delayed sleep onset latency in depressed compared to control participants. There was moderate heterogeneity as represented by an I^2 value of 50%. The standard mean difference was 0.54 (95% CI 0.40 to 0.67, p < 0.0001) indicating a medium effect estimate.

Figure 2.7. Forest plot of wake after sleep onset in adults with depression compared to control participants



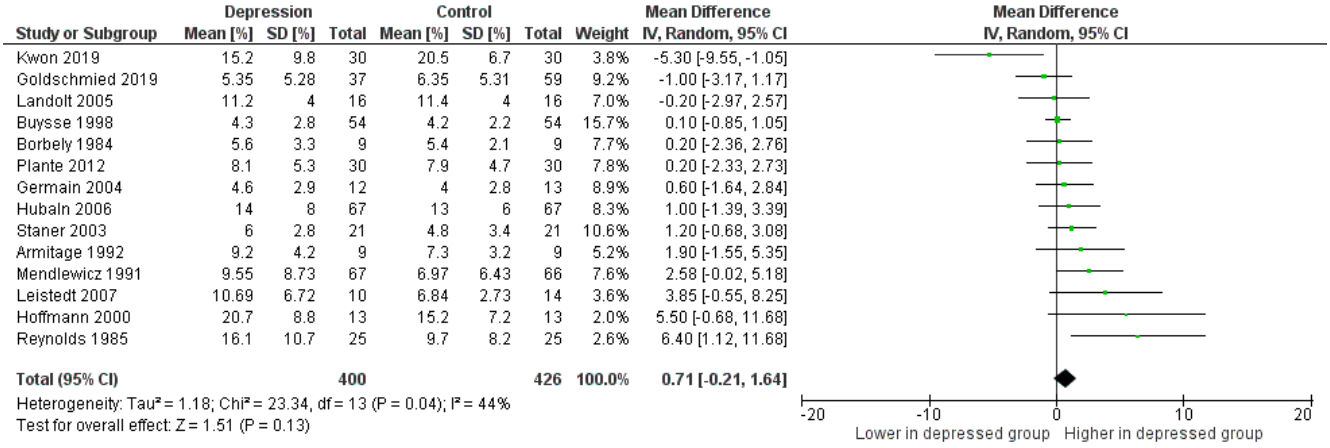
Wake after sleep onset (minutes) was reported by eight studies. Depressed participants had 14.59 minutes more wake after sleep onset than controls (95% CI 5.98 to 23.20, p < 0.0001). All studies reported higher wake after sleep onset in depressed compared to control participants. There was considerable heterogeneity as represented by an I^2 value of 78%. The standard mean difference was 0.55 (95% CI 0.37 to 0.72, p = 0.0009) indicating a medium effect estimate.

Figure 2.8 Forest plot of rapid eye movement (REM) onset latency in adults with depression compared to control participants



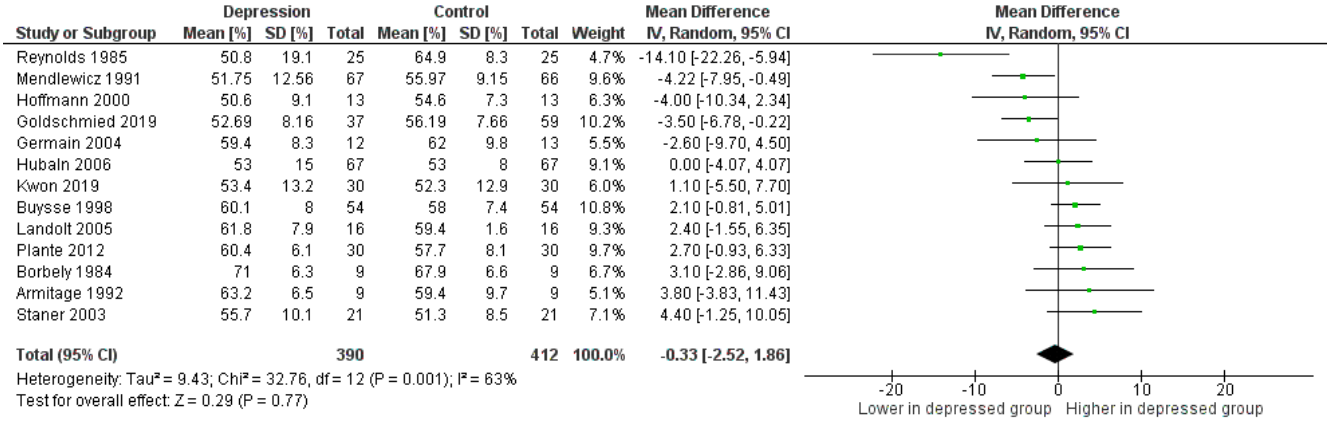
REM onset latency (minutes) was reported by fifteen studies. Depressed participants REM onset was 10.26 minutes earlier than controls (95% CI 1.21 to 19.32 p = 0.03). Seven studies (46%) reported earlier REM onset latency in depressed participants compared to controls. There was substantial heterogeneity as represented by an I^2 value of 73%. The standard mean difference was 0.29 (95% CI 0.01 to 0.56, p = 0.04) indicating a small effect estimate.

Figure 2.9. Forest plot of stage 1 sleep in adults with depression compared to control participants



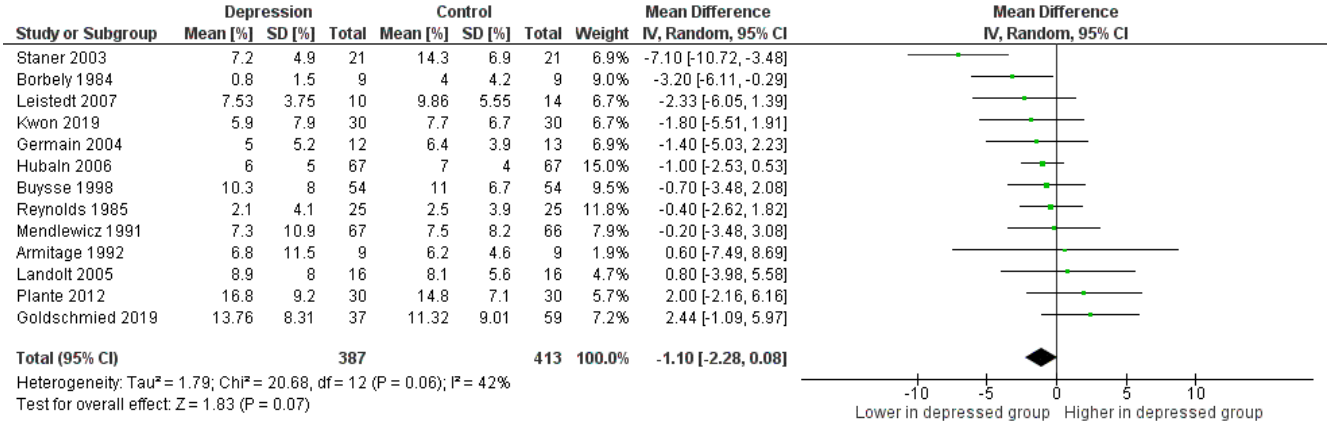
Stage 1 sleep (% of total sleep time) was reported by fourteen studies. There was no difference in stage 1 sleep between depression and controls (depressed participants had 0.71% more stage 1 sleep than controls, 95% CI 0.21 to 1.64, p = 0.13). Eleven studies (78%) reported more stage 1 sleep in depressed compared to control participants. There was moderate heterogeneity as represented by an I^2 value of 44%. The standard mean difference was 0.15 (95% CI 0.03 to 0.34, p = 0.13) indicating a small effect estimate.

Figure 2.10. Forest plot of stage 2 sleep in adults with depression compared to control participants



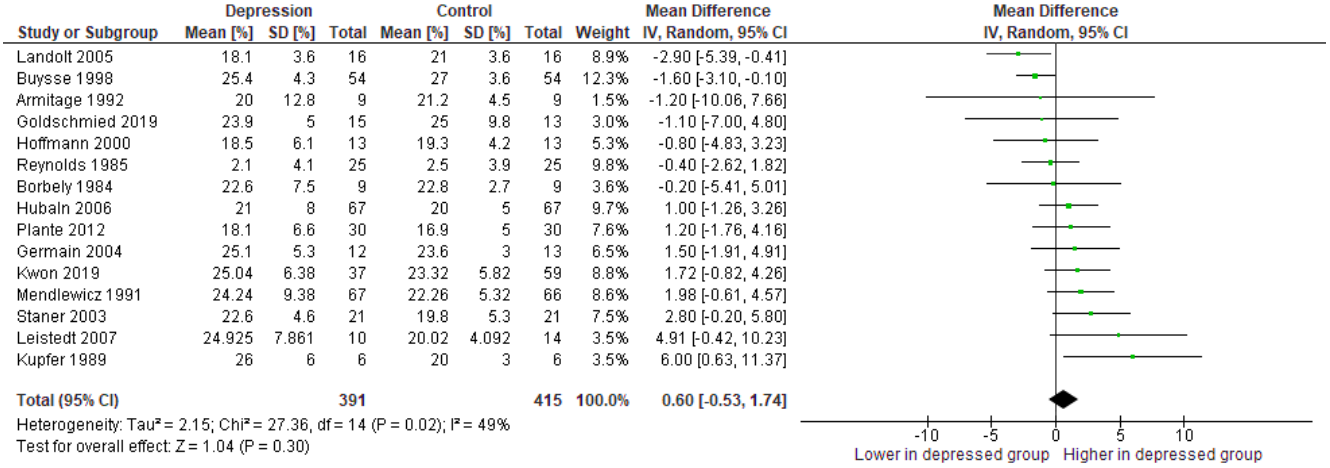
Stage 2 sleep (% of total sleep time) was reported by thirteen studies. There was no difference in stage 2 sleep between depression and controls (depressed participants had 0.33% less stage 2 sleep than controls, 95% CI 2.25 to 1.86, p = 0.77). Seven studies (53%) reported more stage 2 sleep in depressed participants compared to controls. There was substantial heterogeneity as represented by an I^2 value of 63%. The standard mean difference was 0.03 (95% CI 0.27 to 0.20, p = 0.79) indicating a small effect estimate.

Figure 2.11. Forest plot of stage 3 sleep in adults with depression compared to control participants



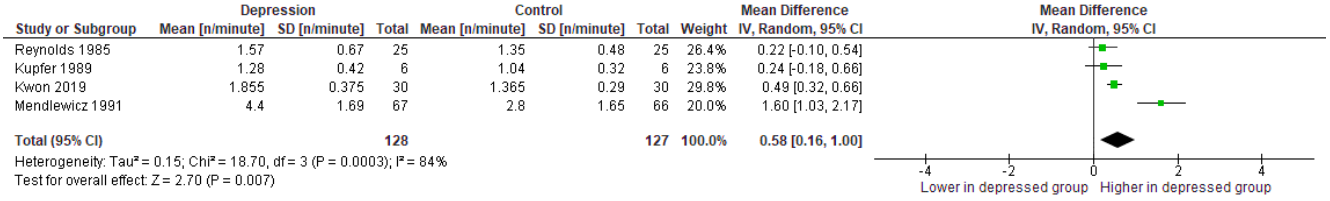
Stage 3 sleep (% of total sleep time) was reported by thirteen studies. There was no difference in stage 3 sleep between depression and controls (depressed participants had 1.1% less stage 3 sleep than controls (95% CI 0.08 to 2.28, p = 0.07). Nine studies (69%) reported less stage 3 sleep in depressed participants compared to controls. There was moderate heterogeneity as represented by an I^2 value of 42%. The standard mean difference was 0.15 (95% CI 0.05 to 0.34, p = 0.14) indicating a small effect estimate.

Figure 2.12 Forest plot of REM sleep in adults with depression compared to control participants



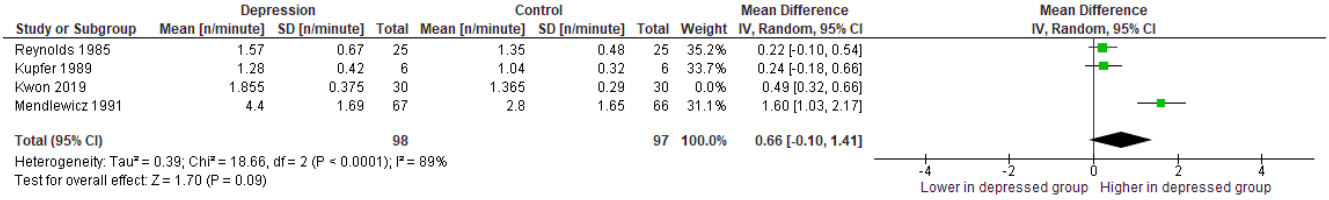
Rapid eye movement sleep (% of total sleep time) was reported by 15 studies. There was no difference in REM sleep between depression and controls (depressed participants had 0.6% more REM sleep than controls (95% CI 0.53 to 1.74, p = 0.30). Eight studies (53%) reported more REM sleep in the depression group compared to controls. There was moderate heterogeneity as represented by an I^2 value of 49%. The standard mean difference was 0.09 (95% CI 0.10 to 0.29, p = 0.36) indicating a small effect estimate.

Figure 2.13. Forest plot of REM density using all definitions in adults with depression compared to control participants



REM density was reported by four studies. Depressed participants had a higher REM density by 0.58 rapid eye movements per minute compared to controls (95% CI 0.16 to 1.0, p = 0.007). There was considerable heterogeneity as represented by an I^2 value of 84%. All studies reported higher REM density in depressed participants compared to controls. The standard mean difference was 0.88 (95% CI 0.43 to 1.34, p = 0.0001) indicating a large effect estimate.

Figure 2.14. Forest plot of REM density using REM activity /time spent in REM sleep definition in adults with depression compared to control participants



REM density using the REM activity /time spent in REM sleep (see characteristics table 2.1 for full definition) was reported by three studies. There was no difference in REM density between older depression and controls (depressed participants had a higher REM density by 0.66 rapid eye movements per minute compared to controls (95% CI 0.10 to 1.41, p = 0.09). There was considerable heterogeneity as represented by an I^2 value of 89%. The standard mean difference was 0.95 (95% CI 0.59 to 1.31, p = 0.0007) indicating a large effect estimate.

2.4.5 Older adults

2.4.5.1 Primary measures

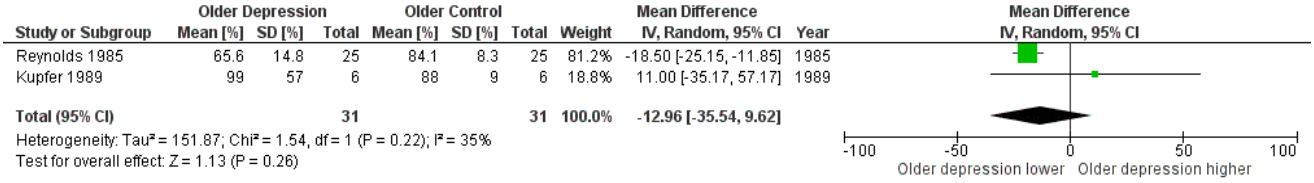
Total sleep time (TST) and SOL were reported by Reynolds et al. (1985) only. Within this study, the depression group had lower TST (older controls: 368.7 ± 46.3, older depression: 301.2 ± 63.1 mins, p = 0.0002) and later SOL (older controls: 22.2 ± 16.9, older depression: 43.8 ± 41.3 mins, p < 0.05) than controls. Sleep efficiency was not significantly different in the older depression group compared to the control group (MD:13.0%, 95% CI:9.6, 35.5 (Figure 2.15). REM onset latency was 25.5 minutes earlier in the older depression group (95% CI: 13.5 to 37.4, p < 0.001). (Figure 2.16).

The older depression group had 6.9% more N1 sleep (95% CI :1.8, 11.9, p = 0.007) and 14.1% more N2 sleep than the controls (95% CI: 6.9, 21.3, p < 0.001) (Figure 2.17 and 2.18). There was no significant difference in REM sleep between the older depression and control groups, and effect estimates were small to none (Figure 2.19). SWS sleep was reported by Reynolds et al. (1985) only and within this study there was no difference in the amount of SWS sleep between older depression and control groups (older controls: 2.5 ± 3.9%, older depression: 2.1 ± 4.1%, p = ns).

2.4.5.2 Secondary sleep outcomes

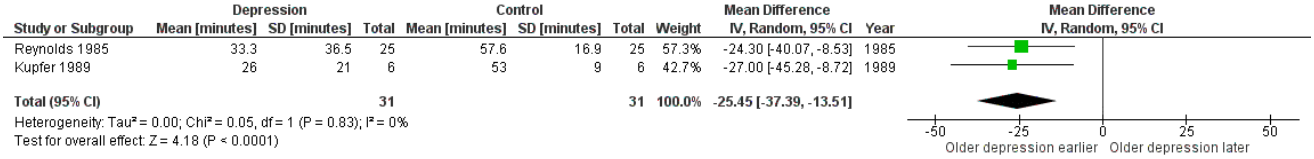
In older adults with depression compared to controls, there was no difference in REM density (MD:0.23/ min, 95% CI: 0.03 to 0.48) (Kupfer et al., 1989; Reynolds et al., 1985)(Figure 2.20).

Figure 2.15 Forest plot of sleep efficiency in older adults with depression compared to control participants



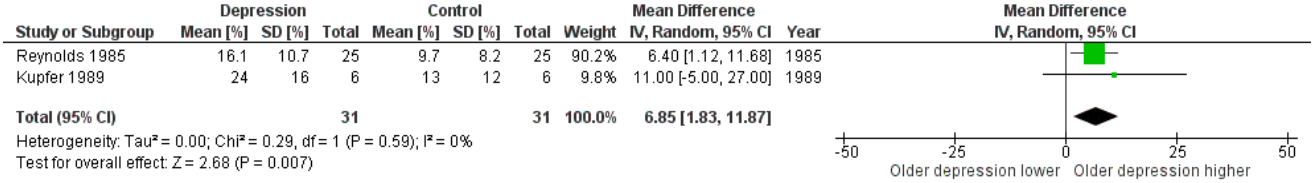
Sleep efficiency (% of total sleep time/time in bed) was reported by two studies. There was no difference in sleep efficiency between older depression and controls (Older depressed participants had 12.96% lower sleep efficiency compared to controls, 95% CI 9.62 to 35.54, p = 0.26). One study (50%) reported less sleep efficiency in depressed participants compared to controls. Heterogeneity was not important in this outcome as represented by an I^2 value of 35%. The standard mean difference was 0.70 (95% CI 1.03 to 2.43, p=0.43) indicating a medium effect estimate.

Figure 2.16 Forest plot of REM onset latency in older adults with depression compared to control participants



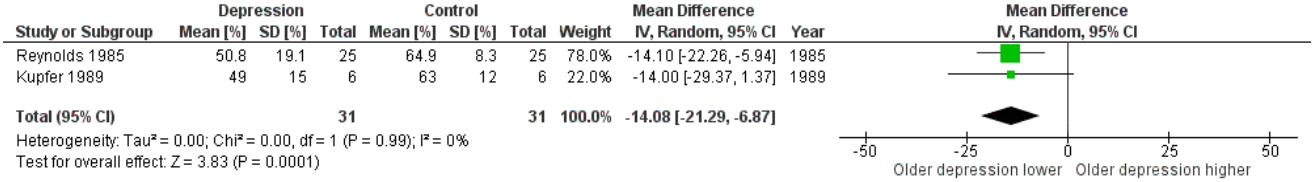
REM onset latency (minutes) was reported by two studies. Depressed participants reached their first REM period 25.45 minutes earlier than controls (95% CI 13.51 to 37.39, p < 0.0001). Heterogeneity was not important in this outcome as represented by an I^2 value of 0%. All studies reported earlier REM onset latency compared to controls. The standard mean difference was 0.95 (95% CI 0.42 to 1.48, p = 0.0005) indicating a large effect estimate.

Figure 2.17 Forest plot of stage 1 sleep in older adults with depression compared to control participants



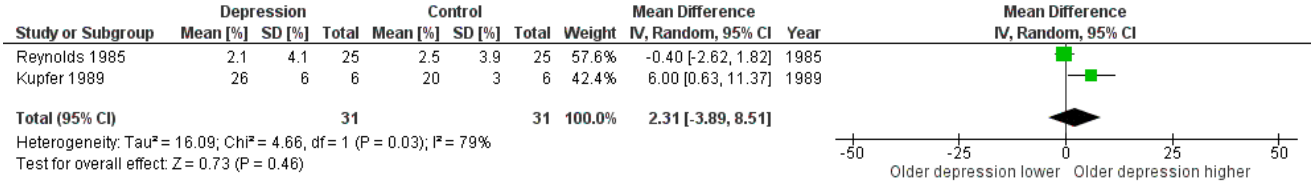
Stage 1 sleep (% of total sleep time) was reported by two studies. Depressed participants had 6.85% more stage 1 sleep than controls, 95% CI 1.83 to 11.87, p = 0.007). All studies reported more stage 1 sleep in depressed compared to control participants. Heterogeneity was not important in this outcome as represented by an I^2 value of 0%. The standard mean difference was 0.67 (95% CI 0.16 to 1.19, p = 0.01) indicating a medium effect estimate.

Figure 2.18 Forest plot of stage 2 sleep in older adults with depression compared to control participants



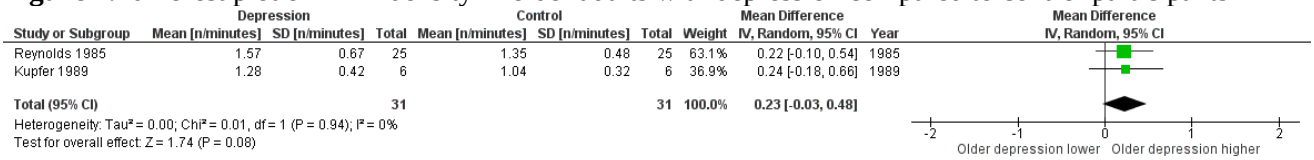
Stage 2 sleep (% of total sleep time) was reported by two studies. Depressed participants had 14.08% more stage 2 sleep than controls (95% CI 6.87 to 21.29, p = 0.0001). Heterogeneity was not important in this outcome as represented by an I^2 value of 0%. All studies reported less stage 2 sleep in depressed compared to control participants. The standard mean difference was 0.94 (95% CI 0.42 to 1.47, p = 0.0005) indicating a large effect estimate.

Figure 2.19 Forest plot of REM sleep in older adults with depression compared to control participants



Rapid eye movement (REM) sleep (% of total sleep time) was reported by two studies. There was no difference in sleep efficiency between older depression and controls (Older depressed participants had 2.31% less REM sleep than controls (95% CI 3.89 to 8.51, p = 0.46). One study (50%) reported more REM sleep in depressed compared to control participants. There was considerable heterogeneity as represented by an I^2 value of 79%. The standard mean difference was 0.40 (95% CI 0.81 to 1.61, p = 0.52) indicating a medium effect estimate.

Figure 2.20 Forest plot of REM density in older adults with depression compared to control participants



REM density (REM activity /time spent in REM sleep) was reported by two studies. There was no difference in REM density between older depression and controls (depressed participants had a higher REM density by 0.23 rapid eye movements per minute compared to controls, 95% CI 0.03 to 0.48, p = 0.08). All studies reported higher REM density in depressed participants compared to controls. Heterogeneity was not important in this outcome as represented by an I^2 value of 0%. The standard mean difference was 0.41 (95% CI 0.09 to 0.92, p = 0.11) indicating a medium effect estimate.

2.6 Discussion

This study is novel in systematically reviewing objective macro- and micro-architecture EEG measures in unipolar depression across younger and older adult groups. Given the impact of sleep on depressive symptoms and cognitive risk, identifying objective EEG disturbances in depression will allow for targeted for sleep intervention. Adults with depression had moderate differences in sleep initiation and continuity, as evidenced by reduced total sleep time, poorer sleep efficiency, delayed sleep onset and more wake after sleep onset. However, adults with depression had no difference in the relative percentage of time spent in any sleep stage compared to controls. REM onset latency was slightly earlier, and REM density was marginally higher in participants with depression compared to controls (Berger & Riemann, 1993; Kupfer, 1976; Lauer et al., 1991). The only microarchitectural variable assessed within this review was delta power in slow-wave sleep, though, because of different filter and frequency definitions, we were unable to quantitively compare this measure across studies. Within the three studies that assessed delta power within slow-wave sleep, there were inconsistent results (Goldschmied, Cheng, Hoffmann, et al., 2019; Leistedt et al., 2007; Plante, Landsness, Peterson, Goldstein, Riedner, et al., 2012). A definitive outcome cannot be interpreted given the unreliability of few studies with relatively small sample sizes. No respiratory sleep measures could be compared within this review.

In the older adults with depression, sleep initiation and continuity measures could not be quantitatively compared, however, within one study there was reduced total sleep time and sleep efficiency, consistent with the results in the total sample of adults with depression (Reynolds et al., 1985). In older adults with depression, there was also more stage 1 sleep and significantly less stage 2 sleep than controls. A greater amount of stage 1 sleep also suggests impaired sleep continuity; however, this difference was modest in older adults with depression. Although no differences were observed in the amount of N3, higher percentage of stage 1 and 2 sleep could represent a shift to lighter sleep in lieu of SWS. The effects of REM onset latency were especially driven by the two studies of older adults with depression, with a larger effect size in the older subgroup. Further, while the current paper supports increases in REM

density in younger adults with depression, this is not true in older adults with depression. This is inconsistent with previous literature in younger adults with depression, therefore REM density may not be a good marker of depression across the lifespan (Berger & Riemann, 1993; Lauer et al., 1991).

2.6.1 Heterogeneity and bias

There was a moderate (SOL, N1, SWS, REM) to considerable (TST, SE, WASO, ROL, N2, REM density) amount of heterogeneity in the sleep measures. A large amount of variation in sleep initiation and continuity measures is not unexpected given the variable methodology between studies using first-night sleep studies and adaption night data (nights 2 and 3) (Lorenzo & Barbanoj, 2002). We also need to consider the effects of both hyposomnia and hypersomnia which are both prevalent in depression but potentially present opposing results in sleep initiation and continuity values (Geoffroy et al., 2018). Across the studies, the minimum sleep affecting antidepressant medication washout was approximately 7-10 days, however, the studies did not specify which medications were being used nor how many participants were taking medications. Previous literature has emphasised the effect of antidepressant medication on sleep architecture and timing (as reviewed in Berger and Riemann (1993) and Wichniak et al. (2017)). Across all studies, two sleep scoring criteria, Rechtschaffen and Kales (1968) (R&K) (k=13) and the American Academy of Sleep Medicine (AASM) 2007 (k=2), were used to score sleep studies (Iber et al., 2007). These criteria differ in defining: total sleep time (>R&K), stage 1 sleep (> AASM), stage 2 sleep (>R&K), slow -wave sleep (> AASM), and wake after sleep onset (>AASM) (Moser et al., 2009) adding further variation to results. REM density results were highly heterogeneous because two different definitions were used across studies, hence, only a subsample could be quantitively compared. Within the two studies reporting on older adults, most variables had a negligible to low amount of heterogeneity (SE, ROL, N1, N2, REM density). However, REM sleep was considerably heterogeneous.

In this meta-analysis, and in the depression literature more broadly, there is not one standard set of criteria used to define major depression. Although this is pragmatic in clinical environments, it is problematic in a research context, rendering it difficult to compare groups and intervention effects

(Snaith, 1993). In this meta-analysis, depression was defined based on accepted assessment criteria that overlap in their symptom item assessments but are not analogous (Beck et al., 1988; Snaith, 1993). The severity of depression in participants in the included studies varies from mild to very severe which may affect the sleep outcomes.

Six of the included studies poorly reported participant selection, with the differential exclusion of cases and controls within certain studies posing a high risk of bias to the study outcomes. Following the risk of bias sensitivity analysis, REM onset latency and REM density were not significantly different between the groups. REM onset latency values in studies using 'healthy sleeping controls' had smaller study effects (both positive and negative) compared to studies that did not have different selection criteria for sleep in control participants. REM density was no longer significantly different between the depression and control groups following the removal of studies selecting 'healthy sleeping' controls. These studies of younger adults had the largest mean difference in REM density (Kwon et al., 2019; Mendlewicz & Kerkhofs, 1991). Both studies of older adults selected 'healthy sleeping' control participants. Therefore, the outcomes of the two studies need to be tentatively considered. Controlling for sleep outcomes in the selection of control participants only poses an issue when assessing differences between groups, as the outcome of sleep is impacted by group selection.

Given the limitations of the studies within this meta-analysis, it is difficult to conclude any specific sleep biomarker of depression, especially when considering depression across age groups. There is difficulty in both the definition of depression, and there have been modifications in how sleep measures are defined over time. Notwithstanding these limitations, the results robustly indicate difficulties with sleep initiation and continuity. When looking across the lifespan, REM onset latency was significantly earlier in older adults with depression compared to controls. However, older adults with depression did not have any difference in REM density compared to controls. Alterations in sleep timing in adults with depression as well as earlier REM onset latency seen in older adults with depression are representative of sleep phase disruption, suggesting that targeting circadian sleep phase may be a useful intervention in this group (Hoyos et al., 2020; Trivedi & Rush, 2000). Although we did observe less stage 2 sleep in

older adults with depression compared to controls, this systematic review and meta-analysis could not gather enough data on SWS in older adults to compare to normal ageing literature, which cites disrupted NREM sleep (Danker-Hopfe et al., 2005).

2.7 Limitations, Future Directions and Conclusions

Limitations of this study include inconsistent diagnostic criteria for defining depression and sleep scoring criteria used across studies. We acknowledge that some articles may not have been identified through our search. Attempts were made to email the study authors in the case that macro- or micro-architecture data was not reported, but no responses were received. We could not perform quantitative analysis on sleep EEG micro-architecture measures and respiratory events due to differing frequency definitions and insufficient data. Further, multiple sleep outcomes explored in this meta-analysis could increase the chances of alpha inflation in multiple comparisons.

Future research would benefit from consistency in defining depression, which is imperative in a research context, as well as consistent definition of sleep spectral analysis frequency ranges. To fully understand sleep biomarkers within depression, it would be useful to further categorise groups based on severity or subgroups with evident hypo- or hypersomnia. In future research, the matching of control participants should include the same level of exclusion of sleep impairment if we are to compare the effect of depression on sleep. This systematic review describes impaired sleep continuity and initiation as the most consistent indication of depression across the lifespan, however, this is not sensitive or specific to the disorder. Although the current work agrees with theories of REM sleep disturbances in depression, there is nuance surrounding older adults with depression as normal ageing processes are incorporated, earlier REM onset latency is predominant and later REM density is not evident, however, the lack of available data makes it difficult to draw concrete conclusions. Further, the quality of case-control matching in studies which support REM density and latency differences in depression is poor. Clinically, this systematic review and meta-analysis reports moderate sleep initiation and continuity issues in depression, as opposed to REM density and REM onset latency markers, providing some evidence for the potential utility of circadian interventions which target sleep phase and drive.

Chapter 3- Assessing Sleep Architecture and Cognition in Older Adults with Depressive Symptoms Attending a Memory Clinic

In Chapter II we showed that older adults with depression had worse sleep initiation and continuity. The meta-analysis highlighted the dearth of literature reporting sleep macro- and micro-architecture in older adults with depression, emphasising the importance of measuring sleep architecture in an older depression cohort. Memory performance has been reliably mechanistically linked to sleep. Given older adults with depression demonstrate poor sleep, we wanted to explore the interactions of sleep and memory in older adults. Further, there have not been any previous studies assessing objective EEG outcomes and their relationship with clinical memory and structural neuropathology outcomes in older adults with depression. This research is pertinent as older adults with depression, and especially those with later onset of depression, have reported neuropsychological impairments.

Chapter III has been submitted to the Journal of Affective Disorders for review.

3.1 Abstract

While depression is intrinsically and bidirectionally linked with both sleep disturbance and cognition, the inter-relationships between sleep, cognition, and brain integrity in older people with depression are undefined. We aimed to identify if older adults with depressive symptoms and those with late-onset (LO) depression have differences in sleep architecture compared to controls and if these sleep differences relate to cognitive performance or neural integrity in related brain areas.

One hundred and seventy-two older adults (mean age 64.3 years) attending a memory clinic underwent a neuropsychological battery of declarative memory and executive function tasks, cerebral magnetic resonance imaging and overnight polysomnography (PSG). A cut-score of $\geq$ and < 6 on the 15-item Geriatric Depression Scale was used to define the depression (n = 66, mean = 9.39) and control (n = 106) groups, respectively. A lifetime history of depression was assessed using Diagnostic and Statistical Manual of Mental Health Disorders- IV (DSM-IV) criteria, and age of illness onset was used to classify individuals as having early (EO, n = 35) or late (LO, n = 23) onset depression (< or $\geq$ 50 years). Primary sleep outcomes included time spent in slow-wave sleep (SWS) and rapid eye movement (REM) sleep, as well as quantitative electroencephalographic (EEG) measures of EEG delta power in non-REM sleep and sleep spindle density (no of spindle events per minute of N2 sleep) from frontal and central brain regions. From structural MRI, we derived hippocampal volume (n = 52) and prefrontal cortex average thickness (n = 36). Pearson's correlations and Fisher's r-to-z transformations and analysis of variance methods were used to compare within and between group differences and assess associations between sleep and neuropsychological and sleep and MRI measures.

The time spent in SWS or REM sleep did not differ between groups. However, sleep onset latency (p = 0.005) and REM onset latency (p = 0.02) were later in the entire depression group compared to controls. There were no group differences in delta power or sleep spindle density. When the early-onset (EO) and LO depression group was compared to controls there were no differences in sleep macro- or micro-architecture after controlling for covariates. Memory and executive function performance did not differ between depression and control groups nor between depression onset subgroups. We observed a differential association between SWS and memory between groups with less SWS associated with

poorer memory (r =.31, p = 0.023) in the depression group, while less SWS was related to better memory in the control group (r = -0.20, p = 0.043; Fishers r-to-z = -3.19). No significant associations were found between delta power, sleep spindles and memory. Neither SWS nor delta power were related to executive function. Hippocampal volume and prefrontal cortex thickness did not differ between depression and control groups or between subgroups and were not related sleep macro- or micro-architecture.

Older participants with depressive symptoms attending a memory clinic showed no deficits in SWS and REM sleep durations but did show delayed sleep and REM onset. For those with depression, less SWS appears to be linked to poorer episodic memory performance. Reduced hippocampal volumes did not mediate this relationship, suggesting a broader distributed neural network may underpin these associations. Further studies are needed to determine if changes in sleep in those with depressive symptoms predict cognitive decline and illness trajectory longitudinally.

3.2 Introduction

Depression is the most common psychiatric disorder in older adults and is associated with cognitive impairment, worse morbidity and mortality (World Health Organization, 2017, see review by Naismith et al., 2012). Deficits in learning and memory, processing speed and executive functioning are common and may be more pronounced in those with illness onset in later life (typically defined as illness onset after 50 or 60 years), termed late-onset (LO) depression compared to early-onset (EO) depression (Hickie & Scott, 1998 and see review by Naismith et al. 2012). Of significance, a body of work has indicated that cognitive deficits in older adults with LO depression, in particular, may be related to underlying cerebrovascular disease (Salloway et al., 1996) evidenced by white matter lesions on neuroimaging (Hickie et al., 1997). Moreover, loss of neural integrity in the hippocampus and prefrontal cortex (PFC), key brain areas related to memory and executive function respectively, are observed in older adults with depression (Elderkin-Thompson et al., 2009; Sawyer et al., 2012; Steffens et al., 2011)

Sleep disturbance is a key feature of major depressive disorder (MDD) across the lifespan (Perlis et al., 1997; Poole & Jackowska, 2018). In older adults specifically, community studies show that self-reported sleep disturbance is linked to both the onset and recurrence of depression (Cho et al., 2008). Studies using actigraphy assessment have shown that sleep disturbance is more pronounced in those with later ages of onset and is associated with cognitive impairment (McKinnon et al., 2019; Naismith et al., 2009; Naismith et al., 2011) and reduced brain functional connectivity even in those with largely remitted symptoms (McKinnon et al., 2018; Naismith et al., 2011).

Research using reference standard polysomnography (PSG) to objectively measure sleep has typically focused on major depression (MD) in younger adults. Meta-analyses have revealed various alterations in sleep macro-architecture including impaired sleep continuity with increased arousals, less time spent in slow-wave sleep (SWS), increased time spent in rapid eye movement (REM) sleep, higher REM density and shortened REM onset latency (Baglioni et al., 2016; Benca et al., 1992; Buysse et al., 1988; Dykierek et al., 1998; Gillin et al., 1981; Lauer et al., 1991; Reynolds et al., 1985). However, the robustness of these sleep macro-architecture measures and their sensitivity and specificity to depression compared to other mental health disorders is contended (Baglioni et al., 2016; Plante et al., 2013). In

studies assessing sleep micro-architecture using quantitative EEG analysis techniques, regional increases in delta power (SWA) in bilateral prefrontal, lateral parietal and occipital brain regions in younger adults with depression compared to controls have been observed (Plante, Landsness, Peterson, Goldstein, Riedner, et al., 2012). However, these increases have not been replicated in other PSG studies of depression, likely due to the reduced EEG channel montages used which limit the ability to detect regional changes in sleep micro-architecture and different definitions of delta frequency (slow-wave activity) (Goldschmied, Cheng, Hoffmann, et al., 2019; Leistedt et al., 2007). Further, one study in younger adults found increased frontal and parietal spindle density in depression compared to control participants (Plante et al., 2013). However, in older adults there are known reductions in frontal sleep spindle density and sigma power (Landolt & Borbély, 2001; Martin et al., 2013). Given the link between overnight changes in cognition and sleep, identifying markers of poor sleep in depression in older samples is key to identifying potential targets for cognitive intervention.

There are no studies exploring quantitative EEG in older adults with depression despite known changes in non-REM (NREM) sleep and observed sleep fragmentation with normal ageing (Conte et al., 2014; Crowley, 2011; Ohayon et al., 2004). In a recent study of older people with lifetime depression, sleep latency and latency to REM was increased relative to controls (Hoyos et al., 2020). Only one known PSG study of 76 older people has examined EO and LO depression groups (defined by depression onset after the age of 60), however, no between-group differences in sleep macro-architecture were found (Buysse et al., 1988). There have been limited studies using objective PSG and no studies using power spectral analysis techniques to examine sleep micro-architecture in older depression samples concerning the characterisation of sleep nor its inter-relationships with cognition and brain integrity.

Limited studies have examined overnight memory paradigms in younger people with depression, using procedural and working memory tasks. Some studies in younger people with depression have reported associations between SWS and sleep spindles and declarative and non-declarative memory (Göder et al., 2011; Nishida et al., 2016), however this is not consistent across the literature (Dresler et al., 2011). Two previous studies in older adults with depression have identified a link between self-reported and actigraphy measures of poor sleep quality and worse declarative memory, however, there have been no

studies using objective EEG measures (Naismith et al., 2009; Naismith et al., 2011). Prior work in healthy ageing samples has revealed that slow waves and sleep spindles, key sleep micro-architecture features, are associated with overnight memory consolidation and executive function (Dijk, 2009; Fernandez & Lüthi, 2020). Synchronisation of slow-wave oscillations and sleep spindles are posited to represent hippocampal and thalamocortical activity associated with the consolidation of memories (Lafortune et al., 2014; Mander et al., 2013; Seeck-Hirschner et al., 2012). Further, executive function has been linked with activation of the prefrontal cortex and an increase in delta power in this area (Anderson & Horne, 2003; Elderkin-Thompson et al., 2009). Hence, it is plausible that sleep processes are also disturbed in older people with depression and may even be linked to underlying cognitive decline or brain degeneration (see review by Naismith et al. (2012)). Further, no studies have assessed neuropsychological outcomes in a clinical setting in relation to sleep micro-architecture in older adults with depression, nor with EO or LO depression subgroups. Therefore, this study sought to better understand how sleep EEG markers differ in older adults with and without depressive symptoms and those with early and later illness onset. We also investigated the relationship between sleep macro-architecture and sleep micro-architecture with memory and executive functioning and key markers of brain integrity relevant to the neurobiology of depression in older people.

First, we assessed differences in PSG-derived sleep macro- and micro-architecture measures between older people with depressive symptoms compared to controls and between LO and EO depression phenotypes. We hypothesised that, compared to controls, participants with depressive symptoms and especially those meeting criteria for LO depression would demonstrate less SWS, more REM sleep, and lower delta EEG power during NREM and fewer sleep spindles. Second, we explored differences in memory and executive function performance between groups and their relationship with sleep macro- and micro-architecture measures. We hypothesised that participants with depressive symptoms and the LO depression group would demonstrate poorer memory and executive function performance compared to controls, and that poorer memory performance would be associated with less SWS, lower delta EEG power and less sleep spindle density, and poorer executive function would relate to less SWS and reduced delta power. Third, as an exploratory aim, we assessed the relationship between magnetic

resonance imaging (MRI)-derived hippocampal and prefrontal cortex (PFC) volumes and SWS, delta EEG power and sleep spindle activity in depression and control groups and EO and LO subgroups.

3.3 Methods

3.3.1 Participants

This study was a retrospective analysis of participants recruited between 2008 and 2019 from the Healthy Brain Ageing Research (HBA) Clinic, Sydney, a specialist early intervention memory and cognition clinic for those experiencing cognitive decline and/or mood symptoms. Inclusion criteria required participants to be aged 50-90 years, fluent in English and to have a referral from a medical practitioner. Exclusion criteria were: a dementia diagnosis; stroke or transient ischaemic attack; head injury with loss of consciousness >30 minutes, history of neurological disease or nonaffective psychiatric illness (e.g. psychosis), intellectual disability, insufficient English for standardised neuropsychological assessment, other medical conditions known to affect cognition (e.g. cancer) and history of substance abuse.

For this sub-study, participants were also excluded if they had: a Mini-Mental State Examination (MMSE) score < 24 (Folstein et al., 1975); no PSG data available; major sleep disorders such as narcolepsy; or, use of sleep affecting medications such as benzodiazepines or tricyclic antidepressants. The use of newer-generation antidepressants was recorded.

This study was approved by the University of Sydney Human Research Ethics Committee (#2012/1873).

3.3.2 Clinical assessment

Using a semi-structured interview, a medical specialist completed a medical, sleep, cognitive and lifestyle history and recorded medication and alcohol use. Body mass index (BMI) was calculated using standard height and weight measurements (weight in kg/ (height in m^2) and for descriptive purposes, the Independent Activities of Daily Living Index and Cumulative Illness Rating Scale - Geriatric version (CIRS-G) were completed to describe daily functioning and medical burden respectively (Folstein et al., 1975; Hindmarch et al., 1998; Miller et al., 1992).

3.3.3 Mood assessment

A trained research psychologist characterised lifetime depression history in all participants using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV SCID) (Bell, 1994) or the Mini-International Neuropsychiatric Interview (M.I.N.I) (Sheehan et al., 1998), and where applicable, also ascertained age of first illness onset. As previously reported in Hickie et al. (2005), we defined EO depression (EO) cases according to an age of onset less than 50 years and LO depression (LO) cases as greater than or equal to 50 years. The self-report Geriatric Depression Scale-15 item (GDS-15) (Yesavage, 1988) was used. Scores range from 0 to 15, with a higher score indicating more depressive symptoms. The GDS-15 has high sensitivity and specificity for detecting major depression in older adult samples (Adams, 2001; Copeland et al., 2004; Hybels et al., 2012; Mitchell & Subramaniam, 2005; Rinaldi et al., 2003). The presence of depression in this study was defined by a cut-score of ≥ 6. Comparison cases (Control) were health-seeking controls presenting to the HBA clinic, defined by a GDS-15 score of <6 and no lifetime or current history of depression as defined by DSM-IV criteria.

3.3.4 Neuropsychological assessment

A standardised neuropsychological battery was administered to all participants by a clinical neuropsychologist. For descriptive purposes, the Mini-Mental State Examination (MMSE) and the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) were collected to measure global cognition and premorbid IQ, respectively. A comprehensive neuropsychological assessment of verbal and visuospatial learning and memory, executive function, processing speed, language and attention was included, as reported previously (Duffy et al., 2015). For the purposes of this study, we focused on memory and executive functioning outcomes, assessed with the following tests:

- Verbal learning and memory: The Weschler Memory Scale-III Logical Memory II subtest (Wechsler, 1997) and the Rey Auditory Verbal Learning Test (Schmidt, 1996). Scores were calculated according to age-adjusted normative data (Senior, 1999; Wechsler, 1997);
- Executive function: The Trail Making Test Part B (Reitan, 1956), the Delis Kaplan Executive Functioning System Color-Word inhibition subtest (Delis et al., 2001) and the Controlled Oral Word Association Test (letters F, A, S) (Benton et al., 1994). Scores were calculated according to age-adjusted normative data (Delis et al., 2001; Tombaugh et al., 1999).

A memory performance composite score was calculated as a mean *z* score from the Weschler Memory Scale -III Logical Memory II subtest, and the Rey Auditory Verbal Learning Test trial 7 (20-minute recall (Rey, 1941; Wechsler, 1997). An executive function performance composite score was calculated using *z* scores from Trail Making Test part B (Tombaugh, 2004), Delis-Kaplan Executive Function System Stroop Inhibition Test (Delis et al., 2001) and Controlled Oral Word Association Test (Tombaugh et al., 1999).

For descriptive purposes, all individuals were classified according to Winblad et al. (2004) criteria for mild cognitive impairment (MCI), as determined by a consensus meeting of two clinical neuropsychologists and a geriatrician. This was determined by subjective cognitive concerns alongside performance on any of the abovementioned tests at <1.5SD below expected levels, relative to the participant's premorbid functioning estimates, and the absence of functional impairment.

3.3.5 Self-report sleep questionnaires

- *Sleep quality*: The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality and sleep habits during the past month. The scores range from 0 to 21, with a cut-off score of ≥ 5 indicating poor sleep (Buysse et al., 1989).
- *Insomnia:* The Insomnia Severity Index (ISI) is a 7-item questionnaire which measures the nature, severity, and impact of insomnia and the night-time and daytime impact of current symptoms of insomnia (over the prior two weeks). Each item uses a 5-point Likert scale to capture a rating (0 = no problem; 4 = very severe problem) which sum to: indicate no insomnia (0 – 7); sub-threshold insomnia (8 – 14); moderate insomnia (15 – 21); and severe insomnia (22 – 28) (Bastien et al., 2001).

3.3.6 Polysomnography (PSG)

All participants underwent a full-night PSG at the Woolcock Institute for Medical Research within four weeks of their clinical and neuropsychological assessment. The sleep study was completed as a part of a clinical pathway. Participants were instructed to sleep at their habitual bedtime and given an 8-hour sleep opportunity. No adaption night was completed. All-night electroencephalography (EEG) was recorded at the scalp positions F3-M2, F4-M1, C3-M2, C4-M2, O1-M2 and O2-M1 with midline electrodes at Fz, Cz, Pz and Oz referenced to an average of the mastoids. Electrooculogram (EOG) eye movements were recorded via electrodes placed one centimetre superior and lateral and one inferior and lateral to the outer canthus of the eyes. EEG channels were sampled at either 200 Hz (Alice 5 Philips, Amsterdam, Netherlands) or 512 Hz (Embla Titanium, Natus, Pleasanton, CA, USA). Sleep studies were manually scored according to the American Academy of Sleep Medicine 2.2 criteria by a trained technician (Berry et al., 2012).

Primary sleep macro-architecture measures included time spent in SWS and rapid eye movement (REM) sleep. Secondary measures were total sleep time (TST), sleep onset latency (SOL) and REM onset latency (ROL), REM density, wake after sleep onset (WASO) and apnea-hypopnea index (AHI, calculated using 3% oxygen desaturation) as a marker of sleep-disordered breathing severity.

The primary sleep micro-architecture measures for frontal and central EEG channels were: sleep spindle density during stage N2 (11- 16 Hz), and delta power during NREM (absolute EEG delta power μV^2 within the range of 0.5-4.5 Hz). As secondary measures, we also calculated fast (13 - 16 Hz per minute) and slow (11 -13 Hz per minute) spindle density.

3.3.7 Quantitative EEG Analysis

3.3.7.1 EEG Artefact Detection

Polysomnographic recordings were exported to EDF format for artefact detection and quantitative EEG analysis. EEG artefacts were identified using a previously validated algorithm in 5-sec epochs (D'Rozario et al., 2013) and contaminated epochs were rejected prior to quantitative EEG analyses.

3.3.7.2 Power Spectral Analysis

Power spectral analysis was conducted on clean EEG data using standard fast Fourier transform on 5-sec EEG segments to compute EEG power at F3-M2, F4-M1, C3-M2 and C4-M1 (Press et al., 1986). EEG data was sampled at a rate of 200 Hz (Alice 5, Amsterdam, Netherlands) or 512Hz (Embla Titanium, Natus, Pleasanton, USA). The mean absolute power within the defined frequency bands of delta (SWA 0.5-4.5 Hz), theta (4.5-8 Hz), alpha (8-12 Hz), sigma (12-15 Hz) and beta (15-32 Hz) were then calculated for each consecutive 30-sec epoch by averaging the absolute power of the six 5-sec epochs that comprised the 30-sec epoch. EEG delta power during NREM sleep (N2 + N3) for the frontal brain region was calculated by averaging data from the F3-M2 and F4-M1 channels, and for the central region by averaging C3-M2 and C4-M1 channels.

3.3.7.3 Sleep Spindle Detection

An automated sleep spindle detection algorithm was used to identify sleep spindle events, described in Lam et al. (2021). The algorithm applied a 128-order band pass finite impulse response filter of 11-16 Hz to the EEG signal. The following spindle metrics in N2 were derived: sleep spindle density (overall spindle events (11 - 16 Hz) per minute of N2 sleep), slow spindle density (spindle events within the 11-13 Hz range per minute in stage 2 sleep), fast sleep spindle density (spindle events within the 13-16 Hz

frequency range per minute of N2 sleep). Frontal and central sleep spindle metrics were calculated by averaging F3-M2 and F4-M1, and by averaging C3-M2 and C4-M1, respectively.

3.3.7.4 REM Density

Using right and left EOG, REM density (no of REM events per minute of REM sleep) were identified using the automatic detection analysis of the Polygraphic Recording Analyzer in PRANA (PhiTools, Strasbourg, France). REM density events were detected by filtering the left and right EOG channels within a 0.3-10 Hz range and were required to meet the following criteria: 0.05-5-sec in duration at 0.01-sec interval between events, >25μV amplitude and >10μV/sec upstate and downstate slope. Automatically detected REM events were visualised checked and manually reviewed by author A.R.

3.3.7 Magnetic resonance imaging (MRI)

A subset of participants underwent MRI within four weeks of the clinical and neuropsychological assessment using a 3-Tesla General Electric (GE) Discovery MR750 scanner (General Electric Healthcare, Milwaukee, WI, USA) with an eight-channel phased array head coil. A 3D-T1-weighted BRAVO Spoiled Gradient-Recalled (SPGR) sequence was used, acquiring 196 sagittal slices (repetition time = 7.2 ms; echo time = 2.8 ms; flip angle = 12; matrix 256×256; 0.9 mm isotropic voxels). Subcortical volumes and cortical thickness was calculated using the Freesurfer software program (ver. 6.0 http://surfer.nmr.mgh.harvard.edu/) recon-all pipeline, as described previously (Fischl & Dale, 2000). Briefly, this pipeline includes motion correction, removal of non-brain tissue, transformation to Talairach space, and intensity normalisation, tessellation of grey and white matter boundaries and topological correction. Following the formation of the cortical representations, the cerebral cortex was parcellated into sulci and gyri. Cortical parcellation was implemented in Freesufer, assigning neuroanatomical labels based on using the Desikan-Killany atlas (Desikan et al., 2006). For subcortical structures, volumetric segmentation and labelling were automatically estimated by FreeSurfer using differences in voxel intensity, and registration to a probabilistic atlas (Fischl et al., 2002).

The prefrontal cortex (PFC) was calculated as the mean thickness of the medial prefrontal cortex and lateral prefrontal cortex. The mean thickness of the medial prefrontal cortex (sum of regions / n of regions) was calculated from the medial orbital frontal, caudal anterior cingulate and rostral anterior cingulate. Mean lateral prefrontal cortex thickness was calculated from the rostral middle frontal, orbital frontal, pars opercularis, pars triangularis and pars orbitals. Bilateral hippocampal volume was extracted and calculated as a percentage of total intracranial volume ([absolute volume ROI / estimated intracranial volume] *100)(Iglesias et al., 2015).

3.3.8 Statistical analysis

Demographic, clinical and sleep data were analysed using the Statistical Package for Social Sciences (SPSS version 24, Armonk, NY: IBM Corp). Skewed sleep variables were log-transformed to create normally distributed data for parametric analysis. Analysis of variance (ANOVA) was used to assess group differences in sleep and cognitive performance between depression and controls as well as age of onset subgroups. ANOVA was used to ascertain group differences in MRI outcomes in depression and control groups and non-parametric Mann Whitney U tests were used for non-parametric comparisons between age of onset depression subgroups. Based on demographic group differences, analysis of covariance (ANCOVA) was also performed on group differences, covarying for antidepressant use and MMSE scores in the depression and control analyses and antidepressant use, age and sex in LO, EO and control analyses. Pearson's correlations were used to assess relationships between sleep and neuropsychological performance and sleep and MRI variables, and Fisher's r-to-z transformation was used to assess any differences in correlation coefficients between depression and control groups.

3.4 Results

3.4.1 Demographics

Of the 172 participants included in this study, 66 participants had current depressive symptoms defined by a GDS-15 score ≥6 (Depression group) (Table 3.1a) and 106 participants had a GDS-15 score <6 and no lifetime history of depression defined by DSM-IV criteria (Control group). Of the 66 participants in the Depression group, a subset of n = 58 had lifetime major depression. The Depression group were further classified as having early-onset depression (EO group, n = 23) and late-onset depression (LO group, n = 35). Eight participants in the Depression group had missing data on the DSM-IV and could not be confirmed as having lifetime depression or be classified into EO or LO depression groups due to data loss (Table 3.1b).

In total, 28 participants were taking newer generation antidepressants including 19 taking selective serotonin reuptake inhibitors (SSRIs) (15 Depression, four Controls), five taking serotonin-norepinephrine reuptake inhibitors (SNRIs) (all Depression group) and four taking noradrenergic and specific serotonergic antidepressants (NASSAs) (two Depression and two Control group). Antidepressant use was significantly higher in the Depression (33%) compared to the Control (5%) group with Controls taking antidepressants for indications other than depression (e.g. chronic pain). The CIRS-G severity score indicated mild medical burden across all groups (Linn et al., 1968).

3.4.1.1 Depression and Control group differences

There was no significant difference between Depression and Control groups in age, education, BMI, alcohol use, CIRS-G score, WTAR or PSQI scores. The number of participants meeting criteria for mild cognitive impairment (MCI) was however, greater in the Depression, compared to Control group, and MMSE scores were significantly higher in the control group (Table 3.1a). Antidepressant use and MMSE scores were controlled for in the analysis of depression and control group differences.

3.4.1.2 Early and Late-onset depression subgroup differences

The EO group was younger and had a higher percentage of females compared to the control and LO groups, and a higher percentage of antidepressant use compared to the LO group (Table 3.1b). The

Control, EO and LO groups did not differ in CIRS-G, BMI, alcohol use, percentage meeting MCI criteria, MMSE, WTAR or PSQI ratings. Antidepressant use, age and sex were controlled for in the analysis of depression onset subgroup differences

3.4.2 Memory and executive function performance: between group differences

Performance on memory and executive function composite scores were not significantly different between the Depression and Control groups. However, when separated by age of onset, the LO group had worse memory performance compared to controls ($p = 0.046$) (Table 3.1b).

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Table 3.1a Demographic and cognitive group differences in depression (n=66) and control (n=106) groups.

Demographic Measure	**Depression n= 66**	**Control n=106**	**Test Statistic**	**Sig.**
Age, years	63.8 (± 7.1)	64.8 (± 6.7)	0.23	0.360
Gender, % female (n)	55.7% (37)	57.6% (61)	0.06	0.805
Body Mass Index	27.6 (± 4.4)	27.0 (± 6.4)	1.27	0.515
Lifetime heavy alcohol use, % (n)	25.0% (16)	15.2% (16)	9.46	0.118
Education, years	13.5 (± 3.1)	14.0 (± 3.0)	0.01	0.330
Mini-Mental State Examination, /30	28.7 (± 1.4)	29.2 (± 1.0)	6.19	0.028*
Mild Cognitive Impairment, % (n)	75% (48)	59% (62)	20.54	0.030*
Weschler Test of Adult Reading, Predicted IQ	104.5 (± 9.9)	105.6 (± 8.8)	0.06	0.438
Cumulative Illness Rating Scale-G, Severity	1.4 (± 0.6)	1.3 (± 0.7)	0.02	0.394
Pittsburgh Sleep Quality Index Score, /21	7.4 (± 3.4)	7.2 (± 3.7)	0.545	0.714
15-item Geriatric Depression Scale, /15	9.4 (± 2.5)	1.7 (± 1.5)	29.35	<0.001*
DSM-IV Major Depression, % (n)	Current, 19.6% (13)	No depression history	N/A	N/A
DSM-IV Major Depression, % (n)	Remitted, 46.9% (31)	No depression history	N/A	N/A
% Antidepressant use (n)	33% (22)	5% (6)	21.44	<0.001*
Cognitive composite *z*-scores				
Memory	0.018 (± 0.99)	0.216 (± 0.96)	0.65	0.201
Executive function	0.009 (± 0.81)	0.211 (± 0.72)	1.20	0.091

Data presented as mean (±SD), except for gender, alcohol use, mild cognitive impairment diagnosis, antidepressant use and antidepressant use type presented as mean percentage (number of participants). Significance presented from independent t test for continuous variables and chi squared test for categorical variables. * P values <0.05. Lifetime heavy alcohol use defined by NHMRC guidelines. Memory performance composite score was calculated as a mean *z* score from the Weschler Memory Scale -III Logical Memory II and Rey Auditory Verbal Learning Test trial 7 (20-minute recall according to age-adjusted normative data). Executive function performance composite score was calculated using z scores from Trail Making Test, D-KEFS Stroop Inhibition Test and Controlled Oral Word Association Test. Legend- DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition.

Table 3.1b Demographic and cognitive group differences in control (n=106) early-onset (n=35) and late-onset (n=23) groups.

Demographic Measure	Control n=106	Early-onset n= 35	Late-onset n= 23	EO vs. LO		Control vs. EO		Control vs. LO	
				Test Statistic	Sig.	Test Statistic	Sig.	Test Statistic	Sig.
Age, years	64.8 (± 6.7)	59.9 (± 6.2)	66.6 (± 6.0)	0.18	<0.001*	0.05	<0.01*	0.47	0.318
Gender, % female (n)	57.6% (61)	71.4% (25)	52.2% (12)	2.23	0.136	3.57	0.059	0.01	0.939
Body Mass Index	27.0 (± 6.4)	27.9 (± 4.4)	28.0 (± 4.2)	0.42	0.980	0.76	0.488	0.75	0.547
Lifetime heavy alcohol use, % (n)	16.7% (20)	22.6% (7)	27.8% (5)	0.61	0.691	2.10	0.447	4.00	0.341
Education, years	14.0 (± 3.0)	14.1 (± 2.4)	13.5 (± 3.5)	3.94	0.426	2.84	0.765	0.71	0.531
Mini-Mental State Examination, /30	29.2 (± 1.0)	29.1 (± 0.9)	28.6 (± 1.2)	2.44	0.161	0.60	0.694	0.74	0.074
Mild Cognitive Impairment, % (n)	60.8% (73)	77.4% (24)	72.2% (13)	0.61	0.439	19.88	0.066	5.87	0.342
Weschler Test of Adult Reading Predicted IQ	105.6 (± 8.8)	104.2 (± 9.6)	102.6 (± 24.0)	1.99	0.731	0.27	0.758	2.30	0.517
Cumulative Illness Rating Scale Severity /56	1.3 (±0.6)	1.3 (± 0.5)	1.4 (± 0.8)	2.10	0.337	1.52	0.985	0.40	0.283
Pittsburgh Sleep Quality Index Score, /21	7.2 (± 3.7)	7.1 (± 3.2)	7.7 (± 3.4)	0.01	0.441	1.30	0.765	0.94	0.581
15-item Geriatric Depression Scale, /15	1.7 (± 1.5)	9.8 (±2.7)	9.3 (± 2.5)	0.01	0.487	21.55	<0.001*	21.34	<0.001*
DSM-IV Major Depression, % (n)	No depression history	Current, 34.2% (12) Remitted, 65.7% (23)	Current, 47.8% (11) Remitted, 52.2% (12)	N/A					
% Antidepressant use	5% (6)	45.7% (16)	30.4% (7)	0.64	0.425	29.65	<0.001*	16.24	<0.001*
Cognitive composite *z*-scores									
Memory	0.191 (± 0.99)	0.212 (± 0.84)	- 0.315 (± 1.00)	0.57	0.059	0.33	0.913	0.98	0.046*
Executive function	0.186 (± 0.73)	-0.020 (± 0.83)	0.059 (± 0.78)	0.21	0.741	1.14	0.175	0.92	0.498

Data presented as mean (±SD), except for gender, alcohol use, mild cognitive impairment diagnosis, antidepressant use and antidepressant use type presented as mean percentage (number of participants). Significance presented from independent t test for continuous variables and chi squared test for categorical variables. * P values <0.05. Lifetime heavy alcohol use defined by NHMRC guidelines. Memory performance composite score was calculated as a mean *z* score from the Weschler Memory Scale -III Logical Memory II and Rey Auditory Verbal Learning Test trial 7 (20-minute recall according to age-adjusted normative data. Executive function performance composite score was calculated using *z* scores from Trail Making Test, D-KEFS Stroop Inhibition Test and Controlled Oral Word Association Test. Legend- EO: early-onset depression, LO: late-onset depression, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition.

3.4.3 Sleep macro-architecture: between group differences

No differences were observed in REM sleep duration between the Depression and Control groups or the EO and LO subgroups and Controls (Table 3.2a and 3.2b). SWS duration was not different between Depression and Control groups. The LO group had shorter SWS duration than the EO group and Controls (Controls: 74.2 ± 36, EO: 85.8 ± 41.4 mins, LO: 57.1 ± 41.5 mins, p = 0.038), however, this did not remain significant after adjusting for age, sex, and antidepressant use (p = 0.112). There were no significant between groups differences in the duration of sleep stages when compared as percentages of TST (data not shown).

Sleep onset latency was longer by 8 ± 1.3 mins (p = 0.005, adjusted for antidepressant use p = 0.005) and REM onset latency was longer by 24.5 ± 1.3 mins (p = 0.012, adjusted for antidepressant use p = 0.020), in the Depression group relative to the Control group. There were no differences in sleep onset and REM onset latencies between the depression subgroups and Controls. Other secondary sleep measures of TST, WASO, AHI and REM density were not different between Depression and Control groups nor between the EO and LO subgroups and Controls (Table 2a and 2b). However, the percentage of participants with AHI≥15 was higher in the LO group compared to EO and Controls after controlling for covariates (Control: 32.5%, EO: 35.5%, LO: 44.4%, p = 0.002).

Table 3.2a Sleep macro-architecture and respiratory group differences between control (n=106) and depression (n=66) groups.

	Depression (n=66)	**Controls (n=106)**	**ANOVA**		**ANCOVA**	
			F	**Sig.**	**F**	**Sig.**
Total Sleep Time (TST), min	348.3 (± 70.8)	353.2 (± 60.8)	0.01	0.955	0.40	0.673
Sleep Onset Latency (SOL), min	25.2 (± 21.2)	17.8 (± 19.9)	8.19	0.005*	5.53	0.005*
REM Onset Latency (ROL), min	135.0 (± 62.3)	110.6 (± 61.0)	6.54	0.012*	4.00	0.020*
Wake After Sleep Onset (WASO), min	80.2 (± 47.6)	76.1 (± 44.9)	0.11	0.741	1.40	0.249
Rapid Eye Movement Sleep (REM), min	66.9 (± 30.8)	67.8 (± 27.3)	0.12	0.912	0.17	0.838
Non-Rapid Eye Movement Sleep, min	249.1 (± 52.6)	259.8 (± 53.4)	0.85	0.358	0.35	0.354
Stage 1 Sleep, min	27.5 (± 17.8)	22.2 (± 17.1)	3.31	0.710	1.25	0.291
Stage 2 Sleep, min	173.1 (± 54.2)	181.4 (± 51.4)	0.62	0.433	1.94	0.148
Slow-wave Sleep (SWS), min	75.8 (± 46.1)	74.2 (± 36.6)	0.18	0.680	0.54	0.387
REM density, n per min	0.62 (± 0.7)	0.83 (± 1.5)	0.55	0.459	0.53	0.591
Apnea Hypopnea Index, n/ hour	16.6 (± 16.7)	15.0 (± 15.7)	0.11	0.740	3.66	0.610
Participants with AHI≥15, % (n)	40.6% (26)	30.5% (32)	0.47	0.495	2.30	0.074

Data presented as mean (±SD) except for participants with AHI ≥15 which is presented as % (number of participants). Significance presented from ANOVA not adjusted for control variables. # ANCOVA between groups controlled for MMSE and antidepressants in depression and control groups. * P values <0.05. Legend- AHI: apnea hypopnea index; NREM sleep (N1 + N2 + N3).

Table 3.2b Sleep macro-architectural and respiratory group differences between control (n=106) early-onset (n=35) and late-onset (n=23) groups.

	Controls (n=106)	**Early-onset (n=35)**	**Late-onset (n=23)**	**ANOVA**		**ANCOVA**	
				F	**Sig.**	**F**	**Sig.**
Total Sleep Time (TST), min	353.2 (± 60.8)	365.5 (± 67.3)	324.7 (± 82.4)	2.57	0.079	1.69	0.188
Sleep Onset Latency (SOL), min	17.8 (± 19.9)	27.0 (± 25.0)	20.6 (± 15.3)	2.31	0.103	0.90	0.407
REM Onset Latency (ROL), min	110.6 (± 61)	130.9 (± 61.4)	144.6 (± 69.3)	2.86	0.060	2.79	0.065
Wake After Sleep Onset (WASO), min	76.1 (± 44.9)	70.3 (± 43.2)	91.5 (± 51.7)	1.33	0.266	1.61	0.201
Rapid Eye Movement Sleep (REM), min	67.8 (± 27.3)	72.5 (± 32.0)	65.0 (± 32.9)	0.44	0.644	0.70	0.498
Non-Rapid Eye Movement Sleep, min	259.8 (± 53.4)	262.0 (± 19.2)	236.2 (± 59.8)	1.74	0.178	1.02	0.364
Stage 1 Sleep, min	22.2 (± 17.1)	27.3 (± 19.4)	23.6 (± 12.3)	0.84	0.433	1.07	0.347
Stage 2 Sleep, min	181.4 (± 51.4)	176.2 (± 53.8)	179.1 (± 63.0)	0.09	0.910	0.66	0.518
Slow-wave Sleep (SWS), min	74.2 (± 36.6)	85.8 (± 41.4)	57.1 (± 41.5)	3.34	0.038*	2.22	0.112
REM density, n per min	0.83 (± 1.5)	0.45 (± 0.55)	1.20 (± 1.85)	1.03	0.361	0.27	0.764
Apnea Hypopnea Index, n/ hour	15.0 (± 15.7)	16.5 (± 18.5)	15.7 (± 14.6)	0.48	0.621	0.84	0.436
Participants with AHI≥15, % (n)	32.5% (39)	35.5% (11)	44.4% (8)	0.13	0.640	0.01	0.002*

Data presented as mean (±SD) except for participants with AHI ≥15 which is presented as % (number of participants. Significance presented from ANOVA not adjusted for control variables. # ANCOVA between groups controlled for antidepressants, age and sex in control, early-onset and late-onset groups. * P values <0.05.

3.4.4 Sleep micro-architecture: between group differences

There were no significant differences in frontal or central sleep spindles, fast or slow spindles or delta power during NREM sleep between the Depression and Control group nor between the EO and LO groups (Table 3.3a and 3.3b).

Table 3.3a. Micro-architectural group differences between depression (n=66) and control (n=106) groups

		Depression (n=66)	Controls (n=106)	ANOVA		ANCOVA	
				F	Sig.	F	Sig.
Frontal	N2 sleep spindle density, n/min	0.99 (±0.7)	1.19 (±0.8)	1.14	0.157	1.49	0.230
	N2 fast spindle density, n/min	0.10 (±0.1)	0.14 (±0.1)	0.04	0.115	1.36	0.261
	N2 slow spindle density, n/min	0.79 (±0.6)	0.95 (±0.7)	0.73	0.174	1.11	0.332
	NREM Delta (0.5-4.5Hz)	273.4 (±148.7)	264.6 (±131.6)	0.01	0.871	0.68	0.509
Central	N2 sleep spindle density, n/min	1.13 (±0.8)	1.13 (±0.8)	0.03	0.824	0.68	0.507
	N2 fast spindle density, n/min	0.49 (±0.5)	0.60 (±0.6)	0.34	0.270	1.24	0.292
	N2 slow spindle density, n/min	0.49 (±0.4)	0.55 (±0.4)	0.12	0.348	0.70	0.497
	NREM Delta (0.5-4.5Hz)	263.5 (±154.4)	272.0 (±161.9)	0.01	0.661	0.34	0.710

Data presented as mean (±SD). Significance presented from ANOVA not adjusted for control variables. # ANCOVA between groups controlling for MMSE and antidepressants. * P values <0.05.

Table 3.3b. Sleep micro-architecture differences between control (n=106) and control, early-onset (n=35) and late-onset (n=23) groups

					ANOVA		ANCOVA	
		Controls (n=106)	**Early-onset (n=35)**	**Late-onset (n=23)**	**F**	**Sig.**	**F**	**Sig.**
Frontal	N2 sleep spindle density, n/min	1.19 (±0.8)	1.05 (±0.8)	0.86 (±0.4)	1.00	0.416	0.79	0.485
	N2 fast spindle density, n/min	0.14 (±0.1)	0.11 (±0.1)	0.10 (±0.1)	0.01	0.626	0.03	0.338
	N2 slow spindle density, n/min	0.95 (±0.7)	0.86 (±0.6)	0.70 (±0.4)	0.49	0.539	0.30	0.681
	NREM Delta (0.5-4.5Hz)	264.6 (±131.6)	317.8 (±153.7)	263.0 (±154.3)	0.15	0.246	0.05	0.564
Central	N2 sleep spindle density, n/min	1.13 (±0.8)	1.25 (±1.3)	0.93 (±0.6)	0.85	0.519	0.03	0.969
	N2 fast spindle density, n/min	0.60 (±0.6)	0.61 (±0.6)	0.42 (±0.3)	0.30	0.587	0.03	0.935
	N2 slow spindle density, n/min	0.55 (±0.4)	0.64 (±0.4)	0.40 (±0.3)	0.48	0.162	0.32	0.284
	NREM Delta (0.5-4.5Hz)	272.0 (±161.9)	325.0 (±161.0)	232.9 (±170.9)	0.33	0.065	0.13	0.309

Data presented as mean (±SD). Significance presented from ANOVA not adjusted for control variables. # ANCOVA between groups controlling for antidepressants, age and sex in control, early-onset and late-onset groups. * P values <0.05.

3.4.5 Associations between sleep and memory

Within the Depression group, there was a significant positive association between time spent in SWS and composite memory scores and a negative association within the Control group (Control: r = -0.22, p = 0.030, Depression: r = 0.34, p = 0.009) (Table 3.4). When comparing the Depression and Control groups, there was a significant, differential association between time spent in SWS and composite memory scores (Fishers r to z, *z* = -3.4, p = 0.001) (Figure 3.1). There was no significant association within or between Depression and Control groups in frontal or central delta power or sleep spindle density and composite memory scores.

There were no significant differences within or between the EO and LO Depression subgroups and Controls in correlations between memory and time spent in SWS, frontal or central delta power or sleep spindle density.

3.4.6 Associations between sleep and executive functioning

Correlations between time spent in SWS and executive function were not statistically significant within or between Depression and Control groups (Table 3.4). Frontal delta power was associated with executive function within the Control group (r = 0.26, p = 0.036) but not within the Depression group.

Correlations between SWS and executive function were not statistically different within or between the LO depression group and Controls. Frontal delta power and executive function correlation coefficients were not different within or between the EO and LO groups and Controls.

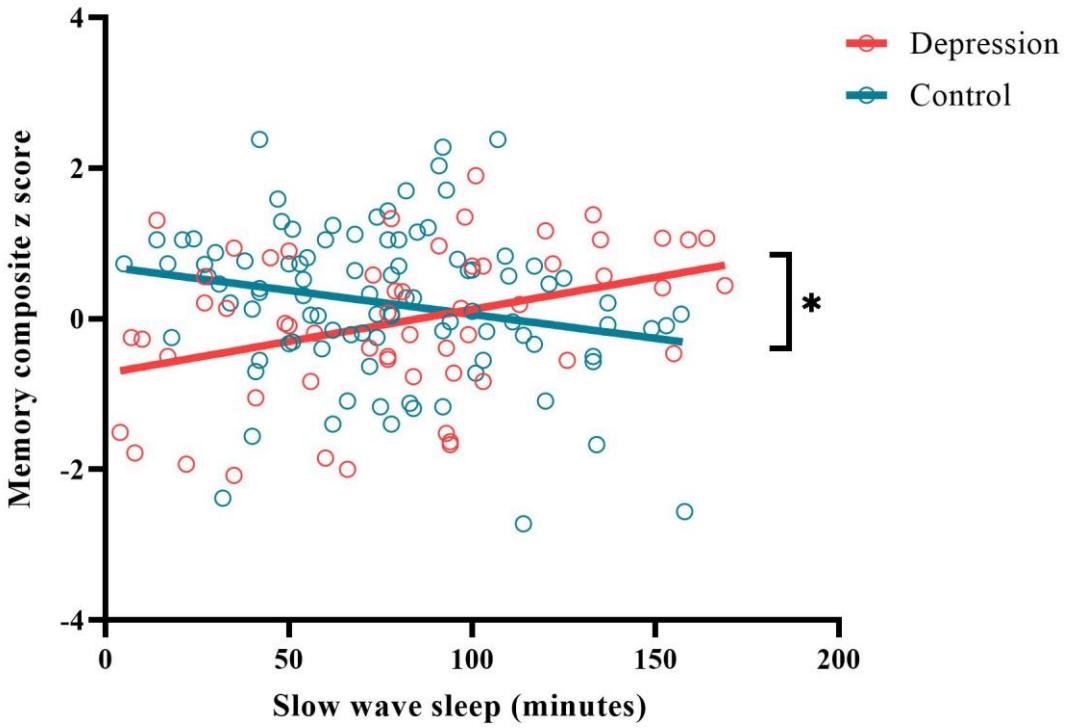
Within the Control group only, higher frontal (r = 0.25, p = 0.038) and central sleep spindle density (r = 0.23, p = 0.038) were associated with better executive function performance.

Table 3.4 Correlations between memory and executive function composite scores and primary NREM macro- and micro-architecture

			Memory				Executive Function			
			Control	**Depression**	**EO**	**LO**	**Control**	**Depression**	**EO**	**LO**
Slow-wave sleep (min)		**r**	-0.219*	0.338**	0.331	0.272	0.071	0.155	0.098	-0.094
		p	0.030	0.009	0.079	0.327	0.486	0.240	0.612	0.738
Frontal	**Spindle density N2**	**r**	0.090	-0.041	-0.254	0.068	0.247*	0.226	0.224	-0.139
		p	0.454	0.775	0.220	0.833	0.038	0.115	0.283	0.667
	NREM Delta (0.5-4.5Hz)	**r**	-0.026	0.106	0.020	0.061	0.261*	0.113	0.021	0.104
		p	0.834	0.515	0.941	0.852	0.036	0.489	0.938	0.749
Central	**Spindle density N2**	**r**	0.137	0.019	-0.296	0.096	0.226*	0.007	-0.232	-0.004
		p	0.212	0.886	0.170	0.754	0.038	0.957	0.287	0.989
	NREM Delta (0.5-4.5Hz)	**r**	0.034	0.142	0.082	0.295	0.209	0.109	0.119	0.078
		p	0.766	0.331	0.717	0.327	0.062	0.456	0.598	0.799

Pearson's correlation coefficient presented as r and significance presented as p. * $p<0.05$, ** $p<0.01$. Correlation used log transformed NREM delta power. Memory and executive function composite z scores were used. Legend- EO: early-onset depression, LO: late-onset depression.

Figure 3.1 Correlation between slow-wave sleep and memory composite *z*-scores



Depression and control group outcomes of memory performance versus SWS (min). Red dots indicate depression participants. Blue dots indicate control participants. Fishers r-to-z transformation was performed to compare associations between memory and SWS and memory ($z = 3.41$, $p = 0.001$), * p values <0.05

3.4.7 Magnetic resonance imaging subgroup and associations with sleep

For the MRI subset, there were 34 participants in the Depression group and 62 in the Control group. All MRI subset participants had hippocampal data (Table 3.5). For the PFC, 50 of the 62 Controls and 30 of the 34 participants with Depression had data. The MRI subset did not differ from the larger sample in age (Control: 65.4 ± 6.1, Depression: 62.9 ± 7.8) or sex (Control: 58% Female, Depression: 56%: Female). The Depression group with MRI had a significantly higher AHI (20.3) than the entire sample.

No differences in hippocampal volume or PFC average thickness were observed within and between Depression and Control groups, (Table 3.5). For both the Control and Depression groups, SWS and sleep spindles were not correlated with hippocampal or PFC volumes. Within the Control group, greater delta power was associated with larger hippocampal volume ($r = 0.36$, $p = 0.018$) (Table 3.6).

Table 3.5 Neuroimaging group differences between depression, control and Mann-Whitney U outcomes between control, early-onset and late-onset depression groups

	Depression		Control		ANOVA		Early-onset		Late-onset		EO vs. LO		Control vs. EO		Control vs. LO	
	N	**Mean (±SD)**	**N**	**Mean (±SD)**	**F**	**Sig.**	**N**	**Mean (±SD)**	**N**	**Mean (±SD)**	**Z**	**Sig.**	**Z**	**Sig**	**Z**	**Sig.**
Hippocampus volume, %[#]	30	0.0097 (±0.01)	56	0.0096 (±0.01)	0.85	0.771	18	0.0100 (±0.01)	8	0.0100 (±0.01)	0.90	0.913	-0.21	0.836	-0.22	0.828
Prefrontal cortex average, thickness, mm^3	22	2.47 (±0.09)	35	2.48 (±0.08)	0.08	0.780	18	2.49 (±0.09)	4	2.42 (±0.09)	0.45	0.471	-0.67	0.501	-0.29	0.766

Data presented as mean (±SD). [#]Hippocampus volume as % of total cranial volume. Results presented from ANOVA for depression and control groups and Mann-Whitney U tests for early-onset and late-onset depression groups. * P values <0.05. Legend- EO: early-onset depression, LO: late-onset depression.

Table 3.6 Correlations of hippocampal volume and prefrontal cortex thickness with slow-wave sleep, frontal NREM delta (0.5-4.5Hz) and sleep spindle density (N2) in depression and control groups

		Hippocampus volume (mm3)[#]				**Prefrontal cortex average thickness**			
		Control	**Depression**	**z**	**p**	**Control**	**Depression**	**z**	**p**
SWS (min)	**r**	0.208	0.210			0.093	0.170		
	p	0.111	0.234	-0.009	0.993	0.523	0.368	-0.323	0.746
	n	60	34			49	30		
Frontal NREM Delta (0.5-4.5Hz)	**r**	0.355	-0.113			0.250	0.240		
	p	0.018*	0.634	1.680	0.093	0.333	0.166	0.033	0.974
	n	44	20			17	35		
Frontal Spindle density N2	**r**	-0.079	-0.151			-0.121	0.006		
	p	0.595	0.433	0.295	0.768	0.554	0.970	-0.473	0.636
	n	47	29			26	37		

[#]Hippocampus volume as % of total cranial volume. Results presented from ANOVA for depression and control groups. Fishers r-to-z transformation was performed to compare associations between sleep and MRI outcomes. * P values <0.05.

3.5 Discussion

This novel study examined whether there were differences in sleep macro- and micro-architecture in older adults with depressive symptoms, generally, and in those with EO and LO depression, specifically. It also explored memory and executive function, hippocampal and prefrontal cortex integrity, and their relationship with sleep. Contrary to our hypothesis, older adults with depressive symptoms and those meeting criteria for LO depression did not have reduced SWS and increased REM sleep duration. However, the depression group did show prolonged latencies to sleep onset and REM sleep onset relative to controls though these alterations to sleep timings were not evident in the late-onset subgroup. More detailed analysis of sleep using quantitative EEG approaches showed no differences in delta power during NREM or sleep spindles during N2 sleep between the depression group and health-seeking controls. There were no differences in executive function between groups, however those with LO depression had worse memory performance relative to controls.

In older adults with depressive symptoms, longer SWS duration was related to better memory in the depression group and conversely, was related to worse memory in the control group. Despite worse memory performance in the LO group, there were no associations between memory and sleep within this group. In the control group, higher delta power during NREM in the frontal brain region and higher sleep spindle density in frontal and central were associated with better executive function. This study also examined hippocampal volume and thickness of the PFC in a subsample with no differences observed between the depression and control groups. Though SWS and sleep spindles showed no relationship to the hippocampal volume or PFC in any group, higher delta power during NREM sleep was associated with greater hippocampal volume in the control group.

Our study did not show differences in the amount of time spent in SWS and REM sleep in this sample of older adults with depressive symptoms. This contrasts with prior meta-analyses in younger adults with affective disorders which reported increased REM sleep and decreased SWS (Baglioni et al. (2016) and Benca et al. (1992)). Inconsistent results between studies may be explained by the difference in the age of participants, with the meta-analysis assessing all age groups including children, as opposed to older adults in the current study. Consistent with our findings, other studies in more similar cohorts of

middle aged and older adults with and without depression showed no differences in sleep macro-architecture (Kupfer et al., 1989; Landolt & Gillin, 2005; Reynolds et al., 1985). In addition to a younger sample, the above referenced meta-analyses included all types of affective disorders and therefore differs from our sample of older adults with unipolar depressive symptoms. Furthermore, our memory clinic outpatient sample had low levels of depressive symptoms, and this is a key consideration when comparing our findings to those in people with depression who had been recruited predominantly from mental health settings.

We did observe delayed latency to sleep onset and REM onset periods in the depression group and this is consistent as sleep timing disturbances are common in depression (Armitage et al., 1992; Reynolds et al., 1985). Both groups also had a short total sleep time, potentially an effect of the sleep laboratory environment. Delayed sleep and REM onset may be indicative of delayed circadian phase as previously noted in older adults with depression (Hoyos et al., 2020). This contrasts with observations in younger adults with depression who showed decreased REM onset latency (Dykierek et al., 1998; Giles et al., 1987; Lauer et al., 1991; Pillai et al., 2011). Interestingly, increased REM onset latency has been observed in older adults with MCI (D'Rozario et al., 2020). In the current sample, there was a higher proportion of participants meeting criteria for MCI in the depression group compared to the control group. This cognitive impairment may reflect underlying cerebrovascular disease as is typical in older samples with depression histories (Jayaweera et al., 2015) or may even signify the presence of underlying neurodegenerative processes in this older depression sample.

Contrary to our hypothesis, we also did not observe any differences in delta power during NREM sleep in the depression onset subgroups relative to controls. This is in contrast to a high-density EEG study, by Plante, Landsness, Peterson, Goldstein, Riedner, et al. (2012), which found increased frontal, parietal and occipital differences in delta power between young adults with depression and controls. However, it is concordant with other studies in young to middle-aged adults with depression, which showed no differences in delta power using a reduced EEG channel montage which is potentially not sensitive enough to capture regional differences in delta power (Goldschmied, Cheng, Hoffmann, et al., 2019; Leistedt et al., 2007). Similar to our findings, one study comparing EO and LO depression did not detect

any significant differences in delta power in NREM between groups (Buysse et al., 1988). The reported reduction in delta power with normal ageing may also affect the magnitude of difference between older participants with depression and controls (Sprecher et al., 2016).

We did not observe any differences in sleep spindle density between the depression and control groups. Prior studies have observed varied results when assessing sleep spindle density in those with depression. In younger adults, Plante et al. (2013) found increased frontal spindles in females with depression but either no difference or decreased sleep spindles in men with depression. Sleep spindle density is also reduced in normal ageing and is posited to represent potential interruptions in thalamocortical networks, potentially accounting for our contrasting result (Sprecher et al., 2016).

Few studies have previously examined how alterations in sleep relate to cognitive functioning in older people with depressive symptoms. In this study, we aimed to determine the inter-relationships between sleep and memory and executive functions in older adults with depressive symptoms generally and EO and LO depression subgroups specifically. Aligned with our hypotheses, we found that SWS and memory were related, but we observed a differential association between groups whereby poorer memory was associated with lower SWS in the depression group and conversely, with more SWS in the control group. Neither SWS, nor delta power were linked to hippocampal volumes in our depression sample, implying that hippocampal compromise is unlikely to mediate the relationship between SWS and memory, however, our small sample size may limit the interpretation of the findings. Two previous studies in younger adults with depression also found a positive association between SWS duration and declarative and non-declarative memory (Göder et al., 2011; Nishida et al., 2016). However, these studies utilised pharmacological intervention and sleep-dependent memory tasks (i.e., tasks of overnight memory consolidation), and are therefore not directly comparable as our study measured sleep and daytime memory over a longer period of time. Indeed, our prior work (Lam et al., 2021) assessed the relationship between sleep-dependent memory and daytime memory and showed a moderate correlation between the two, suggesting they measure related but distinct constructs. Also, it is noted that our sample differs from other studies in that all participants were health-seeking and were, thus, a clinical sample. Further, the negative association between memory performance and SWS is unexpected

but may be related to the presence of MCI in this group. Indeed, 75% of depression group and 59% of controls were classified as meeting criteria for MCI which has been associated with both changes in SWS and memory deficits, therefore, may suggest an association between sleep and memory outcomes (D'Atri et al., 2021).

Though shorter SWS duration was related to poorer memory in the depression group, we observed no associations between memory and the sleep EEG micro-architecture measures of SWA (delta power) and sleep spindles which are thought to play a key role in memory. Prior mechanistic observations of sleep spindle and SWA function have been based on overnight memory consolidation paradigms in healthy adults, therefore these markers may be more indicative of overnight brain plasticity and less representative of long-term changes, as with daytime testing in this study (Fernandez & Lüthi, 2020; Miyamoto et al., 2017). Though there is some evidence to support a multidimensional relationship between sleep disturbance, neuropsychological deficits, and depressive symptoms (Cho et al., 2008; Naismith et al., 2012; Rosenström et al., 2012). Longitudinal studies using neuroimaging and quantitative EEG techniques are required to further delineate these complex inter-relationships.

Better executive function was correlated with higher frontal delta power and frontal and central sleep spindles in the control group. Prior research in healthy adults has associated prefrontal cortex grey-matter atrophy and reduced PFC executive function with reduced NREM delta power (Anderson & Horne, 2003; Dang-Vu et al., 2008; Mander et al., 2013; Maquet et al., 1997) and thalamocortical and hippocampal functional connection with sleep spindle events and delta power (Diekelmann & Born, 2010; Fernandez & Lüthi, 2020; Klinzing et al., 2019). However, we did not find any associations between delta power and PFC volumes in our depression group. Sleep spindle density has been positively associated with executive function in healthy adults (Guadagni et al., 2021), however, there is a dearth of literature on adults with depression. Sleep micro-architecture events, such as delta power and sleep spindles, are functionally related to specific brain regions but may not be as adversely affected by neuropathology in older adults with depressive symptoms.

This work highlights delays in sleep initiation in older adults with depression, therefore, treatments targeting circadian misalignment, such as phase-delay treatment with melatonin or light may be relevant

in older adults with depression (Cole et al., 2002; Mundey et al., 2005). This research also indicates that SWS may play a role in memory performance in older adults with depression which may be targeted by sleep interventions using auditory stimulation to enhance SWS (see review by Harrington and Cairney (2021)).

3.6 Limitations, Conclusions, and Future Directions

This study was limited by the restricted range of depression severity of the participants presenting at the memory clinic, therefore, assessing a sample with more severe depressive symptoms may reveal additional sleep deficits. This sample was also complex because participants were formally referred for assessment as they had emerging cognitive and or mood concerns. Hence, while the two groups were well matched in health-seeking behaviour, age, gender, education, history of alcohol use and premorbid IQ, the control group potentially had subthreshold underlying cognitive difficulties, and indeed both groups may have concomitant underlying neurodegenerative disease. Comorbidities in older adults present a challenge when trying to understand the interrelationships between sleep and cognitive outcomes. However, these comorbidities are prevalent in older representative populations, therefore the outcomes of this study may be more applicable to a general population. This study was potentially underpowered to detect group differences, especially between EO and LO depression and control subgroups. Therefore, further studies with larger samples are needed to test these relationships with optimal power. Further, sleep micro-architecture was performed by an automated algorithm which can be limited by signal quality and algorithm accuracy.

Experimental studies have shown the importance of sleep for mood, memory, and executive function, but there is a dearth of clinical studies attempting to delineate these inter-relationships particularly in older adults with depression. Further imaging and physiology work examining functional brain networks, neuro-metabolites or white matter connectivity may reveal that disruptions within these neural systems play a key role in sleep disturbance in depression. Indeed, as noted, those with later ages of illness onset often have more extensive white matter lesions indicative of cerebrovascular disease (Hickie et al., 1997). While we examined the volume of key brain regions implicated in depression

pathophysiology, further studies examining how white matter lesions may underpin sleep-wake disturbance are warranted.

Alongside these scientific discoveries, it is essential to understand how treatments targeting either depression symptoms or sleep affect sleep architecture, as well as cognition, and importantly how these may slow cognitive decline or depression persistence and/or course. Clinical and research assessment of older individuals with cognitive or mood concerns should also address sleep issues, given a prior body of work showing poorer longitudinal symptom course, cognitive decline, treatment resistance and progression to dementia in older adults with depression (see review by Naismith et al. (2012)).

Chapter 4- A High-density EEG Investigation of Sleep Disturbance and Overnight Emotional Memory Processes in Older Adults with Depression

Chapter III demonstrated differences in sleep initiation in older adults with depression compared to controls, providing more robust support for circadian-related alterations in Chapter II. In older adults with depression in a clinical setting, we observed a positive association between SWS duration and clinical memory performance. Given the importance of emotion in mood-congruency we were interested in exploring aspects of emotional memory which is pertinent to depressive disorders. Emotional memory biases have been reported in young adults with depression and are thought to contribute to maladaptive depressive schemas. Further, emotional memory processing has been mechanistically linked to sleep and its associated arousal systems. We decided to take a sleep-dependent memory design approach to the study, as this is the paradigm which has been used in the literature to establish the connection between sleep EEG markers and memory. High density EEG was also used to pinpoint more precise, regional neural correlates in this population.

4.1 Abstract

Maladaptive cognitive schemas present in depression have been linked with biases in negative information recollection. Older adults with depression have a high incidence of sleep disturbance which has been posited to be mechanistically involved in ineffective emotional memory consolidation, however, no studies have assessed these associations in adults with mental health issues. Therefore this study aimed to investigate differences in measures of overnight emotional memory, sleep macro-architecture and micro-architecture in older adults with and without depression and evaluate the relationship between emotional memory recollection, self-report valence and arousal processing and neurophysiological markers of arousal during REM and NREM sleep.

Older adults (> 50 years) with and without depression underwent overnight polysomnography with high-density electroencephalography (EEG). The International Affective Picture System with concurrent subjective arousal and valence rating and the Cognitive Affective Verbal Learning Task were completed before and after sleep. Group comparisons of demographic, emotional memory, sleep macro-architecture and EEG-derived global markers of arousal during REM (gamma and alpha power) and NREM (alpha and sigma and delta power) were assessed using t-tests and non-parametric chi-squares and Mann-Whitney U tests. Regional EEG arousal markers during REM and NREM were compared using unpaired t-tests and corrected for multiple comparisons using threshold-free cluster enhancement. Spearman's rho correlations and linear regressions were used to assess relationships between sleep macro- and micro-architecture and emotional memory recollection, valence and arousal scores.

Twenty-two older adults (Depression: n = 12, Control: n=10) with a mean age of 63.7 ± 6.5 years completed the study. Older adults with depression did not demonstrate differences in emotional image or word recognition overnight compared to controls. In response to negative images, valence scores were more negative ($p = 0.005$), and arousal scores were higher in the morning relative to the evening ($p = 0.027$) in the depression group, but not in the control group. The depression group spent less time in slow-wave sleep ($p = 0.028$) and had lower global delta power during NREM ($p = 0.030$). Regional analysis revealed lower delta power during NREM in the frontal, parietal and occipital brain regions in

the depression group (ps. < 0.046). No robust associations between overnight memory consolidation, valence or arousal and REM or NREM sleep were observed.

Older adults with depression demonstrate specific negative information biases and an inability to reduce subjective arousal responses to negative information overnight. Reduced global and regional delta power in NREM (N2 and N3) sleep in older adults with depression indicates dysfunction in homeostatic sleep drive. However, there were no direct relationships between NREM and REM arousal and emotional memory recollection, valence, or arousal measures. Indicating that disruption of slow wave frequencies may not be mechanistically involved in maladaptive emotional memory processing. Nevertheless, overnight negative information biases in this group suggest important sleep related mechanisms may play a role in the processing of emotion in depression.

4.2 Introduction

Major depression has been associated with biased recall of negative information compared to positive and neutral information (Bogie et al., 2019; Gaddy & Ingram, 2014; Hamilton & Gotlib, 2008; LeMoult & Gotlib, 2019). The preferential recall of negative information has been associated with an increased likelihood of developing or maintaining depressive symptoms and maladaptive cognitive schemas (Cooney et al., 2010; Everaert et al., 2012; Joormann & Gotlib, 2010). Successful encoding and retrieval of information, and arousal and valence processing of emotional information relies on amygdala and hippocampal networks, which have been shown to lose structural integrity in older adults with depression (Burke et al., 2011; Hickie et al., 2005; Leal et al., 2017). In healthy adults increased activity in amygdala-hippocampal networks during sleep has been linked with the processing of emotional information (as reviewed in Walker and Van Der Helm (2009)).

Poor sleep, especially poor continuity and timing, is inherently linked to depression across the lifespan (Boivin, 2000; Monteleone et al., 2011; Poole & Jackowska, 2018). Specifically, poor sleep continuity is indicated by lower total sleep time, lower sleep efficiency, higher EEG arousal index, more time spent awake after sleep onset and altered sleep timing includes delayed sleep onset and later onset to REM sleep (Boivin, 2000; Monteleone et al., 2011; Poole & Jackowska, 2018). Normal sleep has been linked to the favourable reprocessing of emotional information (reviewed in Walker and Van Der Helm (2009)). Studies in healthy adults have often focused on research models which separate the emotional memory processing contributions of rapid eye movement (REM) sleep and slow-wave sleep (SWS) (Wagner et al., 2002; Wagner et al., 2001; Wiesner et al., 2015). However, mechanisms during both REM and SWS likely contribute to this process. REM sleep has been linked to amygdala and hippocampal reactivation as well as reductions in noradrenergic activity, which is thought to support the brain plasticity needed to process both the valence and arousal aspects of emotional information (Van Der Helm et al., 2011). The reduction of amygdala activity during REM sleep is related to the reduction of the amygdala mediated arousal response to emotional stimuli the following morning (Van Der Helm et al., 2011). REM arousals, measured as higher gamma EEG activity, and selective REM sleep deprivation were associated with higher emotional reactivity or arousal to emotional information

in healthy young adults (Rosales-Lagarde et al., 2012; Van Der Helm et al., 2011), and conversely REM-rich sleep enhanced memory for emotional information (Wagner et al., 2001; Wiesner et al., 2015). Based on this research, it is possible that higher levels of arousal during sleep in people with mental health issues may contribute to poor emotional information processing (Riemann et al., 2012; Van Der Helm & Walker, 2011). One recent study assessed overnight changes in amygdala activity in response to negative information in children and young adults with anxiety and found a blunted ability to reduce amygdala reactivity and arousal in response to negative information (Sollenberger et al., 2023). Nevertheless, there is limited research assessing sleep-dependent emotional memory consolidation in depression samples or in older adults with depression who are at risk of neurodegeneration in related brain areas (Sebastian Köhler et al., 2010; Sheline et al., 2008; Tadayonnejad & Ajilore, 2014).

The prefrontal cortex (PFC) and its activation during non-REM sleep has also been associated with the ability to regulate responses to emotional information (as reviewed in Walker and Van Der Helm (2009)). The PFC is thought to inhibit amygdala activation during sleep, mediating the maladaptive processing of memories (Van Der Helm & Walker, 2011; Walker & Van Der Helm, 2009). It is posited that the disruption of this interaction between the PFC and amygdala may also contribute to emotional disorders such as depression (Van Der Helm & Walker, 2011). NREM sleep is somewhat understudied in relation to emotional memory, even though slow-wave oscillations and sleep spindles have been established as EEG markers of thalamocortical activation and are tightly associated with memory consolidation (Cairney et al., 2014; Muehlroth et al., 2019). One study using a nap paradigm in healthy young adults found that slow-wave sleep (SWS) duration and sleep spindle count were related to better recognition of negative stimuli with targeted memory reactivation, however this study did not measure overnight sleep (Cairney et al., 2014). Whereas a second study in healthy adults found SWS did not selectively improve recollection of negative information compared to positive and neutral information (Denis et al., 2020). Reductions in delta EEG power have also been reliably observed in normal ageing, and studies of slow-wave sleep dynamics have observed reductions in delta power in the first half of the night in depressed participants compared to controls (Armitage, 1995; Ferrarelli & Tononi, 2020;

Landolt & Borbély, 2001). Although, again, there are no studies in older depressed adults despite the reported changes to NREM sleep macro- and micro-architecture in these populations.

Few studies have assessed the relationship between emotional memory and sleep in young adult participants with subthreshold or mild depression, comparing REM-rich to NREM-rich sleep, however results are inconsistent (McNamara et al., 2010, Harrington et al., 2018b, Harrington et al., 2018a). No studies have assessed the effect of sleep disturbance in older adults with depression using arousal markers in REM and NREM sleep, two distinct but temporally related sleep stages associated with emotional memory consolidation. Further, no studies have assessed arousal measures in an emotional memory paradigm using quantitative high-density EEG (hdEEG) methodology which allows for the exploration of regional brain activity during sleep.

By measuring emotional memory recollection and self-reported arousal and valence in a sleep-dependent memory paradigm with PSG and hdEEG, this research aimed to provide insight into the mechanistic understanding of the effect of arousal in overnight consolidation of emotional memory in older adults with depression. Based on findings from Chapter II we aimed to quantify measures of poor sleep timing, continuity, and EEG arousal in sleep macro-architecture and global and regional micro-architecture. We also aimed to understand if EEG arousal measures during REM and NREM related to aspects of emotional memory recollection, and self-report valence and arousal. If sleep abnormalities in older adults with depression are related to the ability to process emotional information, it may provide potential sleep targets for functional improvement to emotional information processing and contribute to a broader understanding of sleep functions and depression pathophysiology.

In older adults with and without depression we aimed to investigate between group differences in 1) emotional memory (change in overnight recollection, valence, and arousal), 2) sleep macro-architecture and 3) sleep micro-architecture using high-density EEG. We hypothesised that the depression group compared to controls, would demonstrate:

1) Worse overnight emotional memory recognition
    a. Better recall of negative emotional images and words compared to neutral and positive.
    b. A sustained self-rated negative image arousal and valence level at morning post-sleep retrieval relative to pre-sleep evening retrieval.
2) Altered sleep macro-architecture
    a. Worse sleep initiation as indicated by delayed sleep onset latency (SOL), shorter latency to REM.
    b. Worse sleep continuity as indicated by less total sleep time (TST), lower sleep efficiency (SE), more wake after sleep onset (WASO)
    c. Higher overnight arousal during sleep as indicated by higher REM and NREM arousal index
3) Altered overnight EEG arousal in sleep micro-architecture
    a. Higher overnight arousal during REM sleep as indicated by; higher gamma (25-40Hz) and, alpha (8-12Hz) EEG power during
    b. Higher overnight arousal during NREM sleep as indicated by; lower delta (1-4.5Hz) and sigma power (spindle frequency activity 12-15Hz) and higher alpha power (8-12Hz) during NREM sleep

Secondly, the study aimed to investigate associations in the depression group between emotional memory (valence, arousal) from the International Affective Picture System (IAPS) task for negative images and REM arousal metrics; global REM gamma and alpha activity and REM EEG arousal index. We hypothesised that a sustained valence and arousal, indicative of poor emotion reactivity processing, in the morning compared to the evening would correlate with higher global REM arousal metrics.

Lastly, we aimed to investigate associations between emotional memory recognition for negative images from the IAPS task and NREM arousal metrics; global NREM delta, alpha and sigma power and NREM EEG arousal index. We hypothesised that worse negative image recognition in the depressed group would correlate with lower global delta power in NREM, lower sigma power and higher alpha power and NREM arousal index.

4.3 Methods

4.3.1 Participant recruitment and screening

Participants were recruited via the Healthy Brain Ageing Clinic (HBA) program, the Woolcock Institute volunteer database and community advertisements between December 2021 and December 2022. As a part of the HBA program, participants underwent full medical, mood and neuropsychiatric assessment, assessed by a neuropsychologist and geriatrician. Participants recruited via other pathways were administered an abridged version of the neuropsychological assessment. The neuropsychological battery included; Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001), Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996; Senior, 1999), Trail Making Test (TMT) (Reitan, 1956; Tombaugh, 2004), D-KEFS Stroop Colour and Text Test (Benton et al., 1994; Delis et al., 2001) and Controlled Oral Word Association Test (COWAT) (Tombaugh et al., 1999). To screen for sleep apnea, a Nonin WristOx 2 oximetry device (Nonin Medical, Inc. Plymouth, Minnesota, USA) was by participants, at home, for 3 nights. Insomnia severity was measured using the Insomnia Severity Index (Bastien et al., 2001).

4.3.2 Exclusion criteria

All participants were 50- 90 years of age and fluent in English. Participants were excluded if they were identified as having; a diagnosis of Alzheimer's disease or mild cognitive impairment or a Mini-Mental State Examination (MMSE) score of < 24, any neurological disorder, mental health disorders other than major depression or anxiety, suicidality, substance abuse or any serious medical condition. Participants were excluded if they had a history of head trauma with associated loss of consciousness more than 30

minutes or a major cerebrovascular event. Current shift workers and people who have travelled overseas within the last two weeks were also excluded. Antidepressant and sedative medications, except for selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors, were excluded. Other sleep affecting medications were not taken within two months of the sleep study.

Participants were excluded from the study if they had two or more tasks in the neuropsychological battery with age scaled scores <1.5 standard deviations below their premorbid intelligence z score on the Wechsler Test of Adult Reading (WTAR).

Those with severe sleep apnea were excluded as defined by a previous polysomnography (PSG) within 1 year or by an overnight desaturation index >20 (using 4% desaturation criteria) measured using a WristOx device. Severe insomnia was excluded by a cut-off score ≥ 21 in the Insomnia Severity Index (Bastien et al., 2001). Those with any other diagnosis of a primary sleep disorder were excluded.

4.3.3 Depression and control group definition

Participants completed the Geriatric Depression Scale 15-item (GDS-15) (Yesavage, 1988). The Depression group was defined by a cut-score of ≥ 6 on the GDS-15. To determine a lifetime history of depression, a trained researcher performed the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) Mini-International Neuropsychiatric Interview (M.I.N.I). The control group had a GDS-15 score < 6 and no history of major depression as defined by the DSM-IV M.I.N.I (Bell, 1994; Sheehan et al., 1998). Case and control participants were age matched within 2 years.

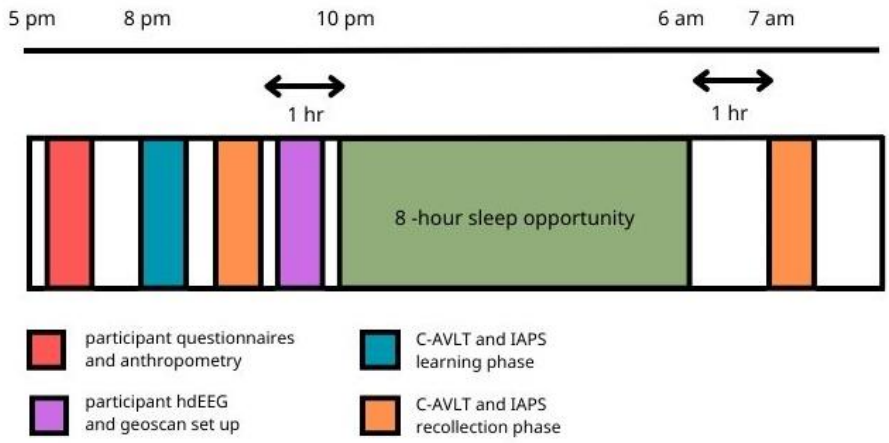
Medical history, current medications, lifestyle factors such as exercise, smoking and alcohol consumption and education information was also collected for screening, demographic, and analytic purposes.

4.3.4 Study protocol

Participants arrived at approximately 5.00 pm and, following consent, completed anthropometric measurements (height, weight, blood pressure) and a series of self-reported sleep and mood questionnaires (Figure 4.1). Participants began the emotional memory tasks approximately two hours

before bedtime finishing approximately an hour before bedtime. Bedtimes were within one hour of their habitual self- reported bedtime. Participants underwent overnight polysomnography with high-density EEG and following an 8-hour sleep opportunity, morning emotional memory task phases commenced one hour after waking.

Figure 4.1 Study protocol timeline



Study timeline shows approximate times for participants based on a habitual sleep time of 10pm. Key: hdEEG – high-density electroencephalography, C-AVLT- Cognitive Affective Verbal Learning Task, IAPS- International Affective Picture System.

Sleep and mood questionnaires included:

- Pittsburgh Sleep Quality Index (PSQI) – assesses sleep quality and sleep habits during the previous month (Buysse et al., 1989).
- Morningness-Eveningness Questionnaire – measures sleep preference and self-reported chronotype, how one functions in the morning and the evening (Horne & Östberg, 1976).
- Epworth Sleepiness Scale – measures subjective ratings of daytime sleepiness (Johns, 1991).
- Flinders Fatigue Scale – assesses symptoms of fatigue in the previous two weeks (Gradisar et al., 2007).
- Hospital Anxiety and Depression Scale (HADS) – measures anxiety and depression symptoms in the week prior (Zigmond & Snaith, 1983).

4.3.4.1 Emotional Memory Tasks

Two emotional memory tasks, the International Affective Picture System and Cognitive-Affective Verbal Learning Test, were administered. The International Affective Picture System (IAPS) is a series of emotional images that were used in a computerised overnight memory remember-know paradigm (Dunn, 2004; Lang et al., 1997). Eighty-one images from the IAPS stimulus (27 each of positive, negative and neutral) were selected based on valence and arousal clustering values developed by Constantinescu et al. (2017). Fifty-two images (13 each of positive, negative and neutral) were also selected for each recognition stage with similar clustering valence and arousal values to the target images. Based on research from Constantinescu et al. (2017), all arousal scores for positive and negative images were selected within the range of 4-6, whereas neutral stimuli had arousal scores <3.5. Negative valence scores were <3, positive valence scores were >7 and neutral valence scores ranged from 4.8-5.3.

Participants were exposed to the 81 target images in a learning phase in a, presented for 2 seconds each in a random order. After a 30-minute delay, participants underwent a recognition task to identify 81 target images from 52 foil images, again presented in a random order. Following each image, participants were asked, “Have you seen this image before?” and were instructed to indicate one of the responses “know”, “remember” or “no”. Following an eight-hour sleeping opportunity, and one hour to overcome sleep inertia, participants completed a secondary recognition phase with alternate foil images. Subjective arousal and valence ratings were captured with each image in all learning and recognition phases using the affective slider (Betella & Verschure, 2016). The scale scores were converted to a value between zero and one. Recognition accuracy of the target images was calculated by dividing the percentage of correct know responses by the total amount of relative target images. The valence scores were averaged at each learning and recognition phase for positive, negative, and neutral images, with a score closer to one indicating a more positive score and zero more negative score. The subjective arousal scores were also averaged at each learning and recognition phase for positive, negative, and neutral images with a score closer to one indicating a higher arousal and zero lower arousal. Change in evening to morning scores were calculated by subtracting the absolute evening score from the morning score.

An emotional word list, the Cognitive-Affective Verbal Learning Test (C-AVLT) was used in a modified format (Considine et al., 2017). This task involves the participant learning 16 affective words read out to them in five learning trials, followed by a distractor list and a short delay free recall. The long delay free recall phase was conducted in the evening after 20 minutes and then again in the morning one hour after waking. A recognition list of 48 words, which included the 16 target words, was completed in the morning. Raw scores were calculated for each recall phase for total recall as well as positive, negative, and neutral stimuli. The valence factor, a score of valence bias, was also calculated as per the methodology described in Considine et al. (2017). The change in evening to morning scores were calculated by subtracting the absolute evening score from the morning score.

4.3.4.2 Polysomnography

All participants were in bed within an hour of their habitual bedtime and were provided an 8-hour sleep opportunity. Polysomnography with high-density electroencephalography (hdEEG) data was collected using 256-channel caps (HydroCel Geodesic Sensor Net 130 LTM) and acquired on a NetAmps 400 system using NetStation software (MagstimEGI, Eugene, OR). Other included physiological measures were electrooculography, chin and leg electromyography, nasal and oral airflow, abdominal and thoracic respiratory movement, and finger-pulse oximetry. Sleep studies were manually scored according to the American Academy of Sleep Medicine 2.2 criteria by a trained technician (Berry et al., 2012).

4.3.5 EEG processing

The hdEEG data was processed using Fieldtrip (http://fieldtriptoolbox.org), EEGLAB (http://www.sccn.ucsd.edu/eeglab/) and the Faster Toolbox (Nolan et al., 2010). Following raw hdEEG data import, a Hamming-windowed finite input response bandpass filter was applied between 0.1 and 60Hz (transition bandwidth: 0.2 Hz), and a notch filter at 50 Hz was applied to remove line-noise. Artefact rejection and identification of poor-quality channels was done through manual visual quality checking. Artefactual time segments were removed, poor-quality channels were interpolated, and all channels not located above a cranial bone i.e., cheek and neck areas, were removed (resulting in N=178

EEG channels). Finally, the EEG signals were re-referenced to the average signal of all good quality channels and segmented to separate files for all sleep stages.

4.3.6 Power-spectral analysis

Power spectral analysis was performed using the P-welch method on 6-second Hamming-windows with a 50% overlap (resulting in a frequency resolution of 0.122 Hz). EEG spectral bands were defined as low-delta: 0.5-1 Hz, delta: 1-4.5 Hz, theta: 4.5-8 Hz, alpha: 8-12 Hz, sigma: 12-15 Hz, beta: 15-25 Hz and gamma: 25-40 Hz. The resulting spectrograms for each sleep stage were inspected and channel-wise statistical outliers in the delta and beta frequency band with threshold values above 3 standard deviations were identified. These channels were interpolated, and the spectrograms were recomputed.

To normalise the power-spectrum, the power in each frequency band was divided by the total power summed across frequency bands and averaged across channels. In addition to channel-wise spectral power, global spectral power was calculated as the average across channels within each frequency band. An issue with cross-frequency normalized power is that group differences in one frequency band can be influenced by aggregated group differences in the other frequency bands. In order to validate results, a separate post-hoc analysis was performed using normalized power relative to total power within frequency bands and across channels, reported in appendix supplementary Figure 6.5.

4.3.7 Statistics

Demographic, emotional memory recognition phases, sleep macro-architecture and global sleep spectral power group data was compared using independent t-test, non-parametric chi-square and Mann-Whitney U tests where appropriate. In both C-AVLT and IAPS tasks, 2-way repeated measure ANOVA was used to calculate the group differences in evening to morning scores.

Regional spectral power between-group differences were caluclated at each channel using a two-sample unpaired t-test. Regional data was corrected for multiple comparisons using the threshold-free cluster enhancement (TFCE) significant threshold at p value <0.05. The correction was performed with 10000 permutations (Winkler et al., 2014). An unpaired t-test covarying for SWS duration was performed on

the NREM regional spectral power to understand the contribution of SWS duration on this group difference. Spearman's rho non-parametric correlations were performed on arousal index measures and IAPS emotional memory scores. Simple linear regression was performed to test the predictive value of REM and NREM global frequency outcomes and depression on IAPS emotional memory performance and score. Sensitivity analyses were conducted for antidepressant medication use for all sleep EEG analysis and results are reported when there was a significant change from the initial analysis.

4.4 Results

4.4.1 Participant Characteristics

One hundred and thirty-two participants were screened, and 22 participants completed the study (n = 12 depression and n = 10 controls) (for exclusion reasons see appendix supplementary Table 6.2). There were no group differences between depression and control groups in age, gender, education level, MMSE scores, and Premorbid WTAR FSIQ scores (Table 4.1). The depression group, on average, had a mild depression severity (GDS-15 = 8.3 ± 2.5) with 25% of the depressed participants also meeting DSM-IV criteria for current depression. Selective serotonin reuptake inhibitors were the only antidepressant medication being taken by two participants with depression and one control participant (for an indication other than depression).

Subjective assessments of insomnia (Insomnia Severity Index), sleep quality (Pittsburgh Sleep Quality Index) and sleepiness (Epworth Sleepiness Scale) were well matched between the groups (Table 4.1). However, the Flinders Fatigue Scale score was higher in the depression group compared to controls (Control: 7.0 ± 4.5, Depression: 12.3 ± 4.0, $p = 0.009$). Sleep apnea severity measures including the apnea hypopnea index and oxygen desaturation index from PSG were not significantly different between groups (Table 4.1).

Table 4.1 Participant Characteristics

	Depression (n=12)	**Control (n=10)**	**Test statistic**	**Sig.**
	Mean ±SD	**Mean ±SD**		
Age (years)	63.1 ±6.3	64.6 ±7.1	0.83	0.600
Gender (% Female) [a]	92%	70%	1.72	0.190
Geriatric Depression Scale-15 (score/15)	8.3 ±2.5	1.5 ±1.3	3.77	<0.001*
DSM-IV Major unipolar depression (% current) [a]	25%	N/A	N/A	N/A
Hamilton Anxiety Depression Scale-Anxiety (score/21)	9.2 ±4.3	6.3 ±2.8	3.20	0.082
Education (years)	15.0 ±3.7	14.7 ±2.7	0.31	0.836
Mini Mental State Examination (score /30)	29.0 ±1.3	29.6 ±0.8	1.37	0.237
Premorbid IQ (Weschler's Test of Adult Reading FSIQ)	103.8 ±9.4	102.9 ±9.9	0.03	0.823
Insomnia Severity Index (score /28)	10.8 ±5.1	7.2 ±4.9	0.10	0.106
Pittsburgh Sleep Quality Index (score /21)	8.4 ±2.9	6.1 ±3.3	0.20	0.096
Flinders Fatigue Scale (score /31)	12.3 ±4.0	7.0 ±4.5	0.13	0.009*
Epworth Sleepiness Scale (score /24)	7.8 ±4.3	6.2 ±4.5	0.05	0.416
Apnea Hypopnea Index (events/hour)	13.2 ±8.4	8.0 ±5.1	4.52	0.094
3% Oxygen Desaturation Index (events/hour)	6.8 ±6.1	5.3 ±3.8	2.43	0.479
Medication (SSRI only)	16% (n=2)	10% (n=1)	N/A	N/A

Data presented as mean± SD where applicable. * $p<0.05$. Independent t-test was applied unless stated otherwise, test statistic F. [a] Non-parametric chi-squared tests were performed, test statistic χ^2. Apnea Hypopnea Index and Oxygen Desaturation Index reported from polysomnography. Due to data loss Epworth Sleepiness Scale n=9 for control group and Oxygen Desaturation Index n=9 for control group.

4.4.4 Emotional memory: between group differences

4.4.4.1 International Affective Picture System Task

4.4.4.1.1 Recognition accuracy

Due to insufficient completion of the IAPS task, data were excluded from the analysis for one depression and one control participant (n = 20, control n=9, depression n=11). In the IAPS task recognition accuracy of all images (negative, positive, and neutral) was not different between depression and control groups at any of the recognition phases nor in overnight change (Table 4.2a and 4.2b). There were also no between group differences when recognition accuracy was assessed separately for negative, positive, or neutral images in the morning and evening or overnight (Table 4.2a, Figure 4.1a).

4.4.4.1.2 Negative images: valence and arousal

In relation to valence, the depression group had a more positive response to negative images at all learning (Control: 0.09 ± 0.05, Depression: 0.21 ± 0.09, p = 0.007), evening recognition (Control: 0.11 ± 0.05, Depression: 0.41 ± 0.09, p=.004) and morning recognition phases compared to controls (Control: 0.13 ± 0.08, Depression: 0.23 ± 0.09, p = 0.020). The overnight change in valence scores for negative images from evening to morning was lower (more negative) in the depression group and higher (more positive) in the control group (Control: 0.01 ± 0.05, Depression: -0.02 ± 0.05, F (1,18) = 10.23, p = 0.005) (Figure 4.2b).

The depression group had lower self-rated arousal scores for negative images in the learning phase (Control: 0.76 ± 0.12, Depression: 0.69 ± 0.07, p = 0.0038) and evening recognition phase (Control: 0.78 ± 0.09, Depression: 0.67 ± 0.09, p = 0.012). The overnight change in arousal scores for negative images from evening to morning was different between the groups with higher morning arousal in the depression group and no change in the control group (Control: 0.00 ± 0.06, Depression: 0.02 ± 0.06, F (1,18) = 5.82, p = 0.027) (Figure 4.2c).

4.4.4.1.3 Positive images: valence and arousal

The depression group had a more negative response to positive images compared to the control group at the learning (Control: 0.80 ± 0.06, Depression: 0.69 ± 0.09, p= 0.020) and evening recognition phase (Control: 0.75 ± 0.07, Depression: 0.65 ± 0.09, p = 0.012), but not in the morning. The overnight change in valence scores for positive images significantly differed between the groups with the depression group maintaining similar scores and the control group scoring positive images lower (more negative) from evening to morning (Control: -0.02 ± 0.06, Depression 0.00 ± 0.05, F (1,18) = 6.87, p = 0.017).

Arousal scores for positive images were not different between the groups at any recognition phase nor in overnight change.

4.4.4.1.4 Neutral images: valence and arousal

Valence and arousal scores were not different between depression and control groups at any of the recognition phases, nor in overnight change (Table 4.2a).

Table 4.2a International Affective Picture System Task Recognition Accuracy, Valence, and Arousal Scores (n=20)

	Recognition accuracy (%)				Mann-Whitney U	Valence				Mann-Whitney U	Arousal				Mann-Whitney U
	Depression (n=11)		Control (n=9)		Sig.	Depression (n=11)		Control (n=9)		Sig.	Depression (n=11)		Control (n=9)		Sig.
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Learning															
Positive stimulus			N/A			0.69	0.09	0.80	0.06	0.020*	0.57	0.14	0.56	0.18	0.766
Negative stimulus						0.21	0.09	0.09	0.05	0.007*	0.69	0.07	0.76	0.12	0.038*
Neutral stimulus						0.46	0.03	0.46	0.03	1.000	0.48	0.09	0.50	0.08	0.603
Evening Recognition	91.9	6.6	91.7	8.2	0.766										
Positive stimulus	89.7	8.6	90.8	11.2	0.603	0.65	0.09	0.75	0.07	0.012*	0.56	0.12	0.55	0.15	0.941
Negative stimulus	92.4	8.7	91.4	8.1	0.766	0.24	0.09	0.11	0.05	0.004*	0.67	0.09	0.78	0.09	0.012*
Neutral stimulus	93.7	5.2	93.0	7.7	0.941	0.51	0.01	0.51	0.04	0.412	0.48	0.09	0.46	0.07	0.261
Morning Recognition	91.9	6.6	91.7	8.2	0.766										
Positive stimulus	90.2	10.3	91.8	8.0	0.882	0.65	0.10	0.73	0.05	0.095	0.56	0.11	0.52	0.15	0.603
Negative stimulus	89.0	14.2	93.4	5.8	0.941	0.23	0.09	0.13	0.08	0.020*	0.69	0.07	0.78	0.13	0.095
Neutral stimulus	87.5	16.9	89.7	10.6	0.824	0.50	0.02	0.52	0.03	0.152	0.47	0.09	0.48	0.05	0.882

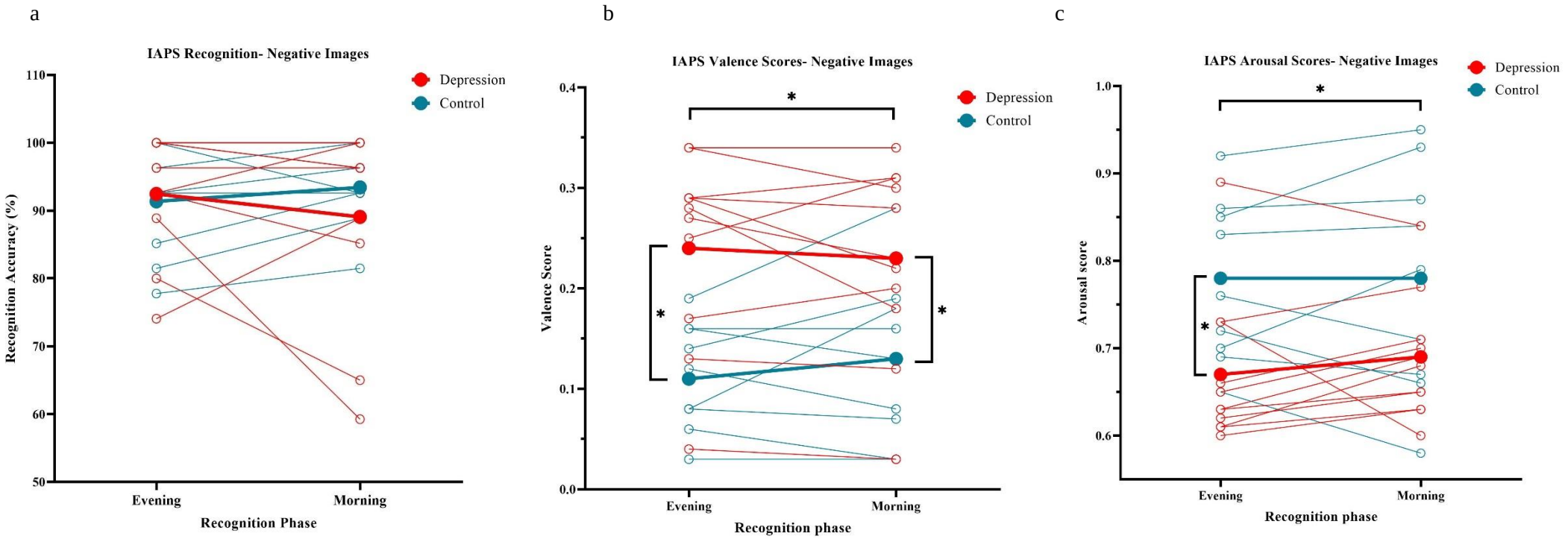
Data presented as mean± SD where applicable. * $p<0.05$. The valence score represents the average emotional self-rating with a score closer to 1 indicating a more positive score and 0 more negative score. The arousal score represents the average arousal self-rating with a score closer to 1 indicating a higher arousal and 0 lower arousal. Mann-Whitney U test were applied to calculate group differences in recognition accuracy, valence, and arousal scores.

Table 4.2b International Affective Picture System Task Change in Evening to Morning Recognition Accuracy, Valence, and Arousal Scores (n=20)

	Recognition accuracy (%)				RM ANOVA		Valence				RM ANOVA		Arousal				RM ANOVA	
	Depression (n=12)		Control (n=10)		F	Sig.	Depression (n=11)		Control (n=9)		F	Sig.	Depression (n=11)		Control (n=9)		F	Sig.
	Mean	SD	Mean	SD			Mean	SD	Mean	SD			Mean	SD	Mean	SD		
Δ evening to morning	23.1	25.2	18.1	16.9	0.11	0.739												
Δ positive	0.5	9.8	0.97	6.2	0.11	0.741	0.00	0.05	-0.02	0.06	6.87	0.017*	0.00	0.05	-0.02	0.05	0.17	0.684
Δ negative	-3.4	11.6	2.1	4.6	0.17	0.687	-0.02	0.05	0.01	0.05	10.23	0.005*	0.02	0.06	0.00	0.06	5.82	0.027*
Δ neutral	-6.2	14.1	-3.3	7.0	0.03	0.867	-0.01	0.02	0.01	0.02	0.74	0.400	-0.01	0.03	0.02	0.05	0.02	0.895

Data presented as mean± SD where applicable. * $p<0.05$. Change in evening to morning scores were calculated by subtracting the absolute evening score from the morning score. The valence score represents the average emotional self-rating with a score closer to 1 indicating a more positive score and 0 more negative score. The arousal score represents the average arousal self-rating with a score closer to 1 indicating a higher arousal and 0 lower arousal. A 2-way repeated measures ANOVA was used to calculate the group differences in evening to morning scores.

Figure 4.2 Evening and morning recognition accuracy, valence, and arousal scores for negative images on the IAPS task (n=20)



Individual subject values are represented by hollow circles, red (depression) and blue (control). Mean group scores are represented by filled circles. Significant group differences at each recognition phase and across phases represented by * <0.05. a) Recognition accuracy caluclated as a percentage of hits compared to the total amount of negative images at evening and morning recognition phase. b) Higher valence values represent more positive valence scores. Valence scores of negative images were significantly different between depression and control groups at the evening and morning phases. Change in overnight scores was also different between depression and control groups. c) Higher arousal values represent a higher arousal score. Arousal scores of negative images were significantly different between groups at evening recognition phase. Change in overnight arousal scores was significantly different between the groups.

4.4.4.2 Cognitive-Affective Verbal Learning Test

In the C-AVLT task total word recall was not different between groups at the short or long delay recall during the evening or the morning recall (Table 4.3a). However, the depression group had better recall of negative words at both the short delay recall phase (Control: 37.5 ± 21.2, Depression: 66.7 ± 26.8, p = 0.011) and morning recall phases (Control: 40.0±26.9, Depression: 70.8 ± 35.1, p = 0.034). Positive and neutral word recall were not different between groups at any of the recall phases. The change in overnight total word recall or recall of negative, positive, or neutral words was not significantly different for between the groups (Table 4.3b).

Valence factor scores, a measure of valence bias, were significantly different at the short delay recall phase with the depression group showing a bias toward more negative words compared to the controls who had more positive valence factor scores (Control: 1.0 ± 4.3, Depression: -1.7 ± 3.2, p = 0.017). Valence factor scores during the evening long recall, the morning recall and the overnight change did not differ between the groups (Table 4.3b).

Table 4.3a Cognitive-Affective Verbal Learning Task Raw Scores and Valence Factor Scores (n=21)

	Recognition accuracy (%)				Test Statistic	Valence Factor				Test Statistic
	Depression (n=12)		Control (n=10)		Sig.	Depression (n=12)		Control (n=10)		Sig.
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Learning List A 1-5	72.4	12.7	64.1	10.5	0.117					
Short delay free recall	73.4	17.1	61.3	11.3	0.060	-1.7	3.2	1.0	4.3	0.017*
Positive stimulus	56.3	32.2	50.0	20.4	0.587					
Negative stimulus	66.7	26.8	37.5	21.2	0.011*					
Neutral stimulus	88.5	16.4	82.5	22.2	0.472					
Evening Long delay free recall	74.5	20.4	68.1	14.8	0.413	-0.4	4.6	1.4	4.3	0.464
Positive stimulus	64.6	37.6	55.6	24.3	0.638					
Negative stimulus	66.7	34.3	47.2	29.2	0.187					
Neutral stimulus	91.7	8.4	88.9	15.9	0.483					
Morning Long delay free recall	71.9	22.1	58.1	19.6	0.141	-1.1	5.6	0.5	4.4	0.346
Positive stimulus	60.4	40.5	47.5	21.9	0.355					
Negative stimulus	70.8	35.1	40.0	26.9	0.034*					
Neutral stimulus	92.7	14.6	86.3	23.2	0.445					

Data presented as mean± SD where applicable. * $p<0.05$. The valence factor (VF) represents the emotional bias with a more positive VF indicating a better recollection of positive words. Independent t-tests were applied to the learning and recall scores and Mann-Whitney U test was applied to the valence scores due to non-normal data distribution.

Table 4.3b Cognitive-Affective Verbal Learning Task Change in Evening to Morning Raw Score and Valence Factor (n=21)

	Change in recognition accuracy (%)				RM ANOVA		Valence Factor				RM ANOVA	
	Depression (n=12)		Control (n=10)		F	Sig.	Depression (n=12)		Control (n=10)		F	Sig.
	Mean	SD	Mean	SD			Mean	SD	Mean	SD		
Δ evening and morning	-2.6	1.7	-9.9	4.7	1.62	0.218	-3.7	6.1	-3.0	4.8	0.59	0.450
Δ positive	-4.2	2.9	-8.1	-2.4	0.46	0.504						
Δ negative	4.2	0.8	-7.2	-2.3	3.26	0.087						
Δ neutral	1.0	6.2	-2.6	7.3	0.64	0.433						

Data presented as mean± SD where applicable. * $p<0.05$. Change in evening to morning scores were calculated by subtracting the absolute evening score from the morning score. The valence factor represents the emotional bias with a more positive VF indicating a better recollection of positive words. A 2-way repeated measures ANOVA was used to calculate the group differences in evening to morning raw and valence factor scores.

4.4.5 Sleep macro-architecture: between group differences

The Depression group had less slow-wave sleep (duration and percentage) than controls (Control: 46.2 ± 11%, Depression: 34.6 ± 11.9%, p = 0.028) but did not differ on measures of sleep initiation (sleep onset latency, REM onset latency), sleep continuity (total sleep time, sleep efficiency, wake after sleep onset) or overnight EEG arousal indices, see Table 4.4. Results remained unchanged after running a sensitivity analysis removing participants taking antidepressants and those with apnea hypopnea indices over 30.

Table 4.4 Macro-architecture differences between depression and control groups

	Depression (n=12) **Mean ±SD**	**Control (n=10)** **Mean ±SD**	**Test statistic**	**Sig.**
Time in Bed	471.5 ±28.0	473.2 ±46.7	2.43	0.917
Total sleep time (minutes % of TIB)	383.6 ±44.1	385.5 ±42.5	0.01	0.923
Sleep efficiency (% of TIB) [a]	81.6 ±9.8	81.6 ±6.0	0.39	0.710
Sleep onset latency (minutes) [a]	18.8 ±19.9	12.8 ±8.7	0.26	0.603
Wake after sleep onset (minutes)	68.5 ±33.5	75.0 ±37.1	0.91	0.673
REM onset latency (minutes)	126.0 ±53.0	96.0 ±45.6	0.98	0.175
Arousal index	33.9 ±13.0	26.5 ±7.0	3.39	0.123
REM arousal index	31.1 ±8.6	27.8 ±10.6	1.00	0.428
NREM arousal index	29.7 ±14.4	21.8 ±6.7	5.20	0.109
Stage 1 sleep (% of TST)	15.5 ±10.3	11.0 ±7.1	1.27	0.254
Stage 1 sleep (minutes)	57.8 ± 33.6	41.7 ±25.9	0.70	0.231
Stage 2 sleep (% of TST)	29.4 ± 7.9	23.29 ±6.2	0.24	0.062
Stage 2 sleep (minutes)	113.4 ±35.5	89.3 ±23.6	0.47	0.081
Slow-wave sleep (% of TST)	34.6 ±11.9	46.2 ±11	0.10	0.028*
Slow-wave sleep (minutes)	134.1 ±49.4	178.8 ±49.9	0.03	0.048*
REM sleep (% of TST)	20.4 ±5.1	19.4 ±4.1	0.14	0.619
REM sleep (minutes)	78.3 ±22	75.5 ±20.1	0.06	0.768
NREM sleep (% of TST)	79.5% ±5.13%	80.6 ±4.1	0.14	0.774
NREM sleep (minutes)	305.3 ±40.4	309.9 ±31.4	0.78	0.619

Data presented as mean± SD where applicable. * $p<0.05$. Independent t-test was applied unless stated otherwise, test statistic F. [a] Non-parametric Mann-Whitney U were performed on non-parametric data, test statistic Z.

4.4.6 High-density EEG arousal measures: between group differences

4.4.6.1 REM sleep

4.4.6.2.1 Global EEG REM arousal measures

During REM sleep, normalised global gamma or alpha EEG power was not different between the depression and control groups (Table 4.5).

4.4.6.2.2 Regional EEG REM arousal measures

During REM sleep, there were no significant regional differences in gamma or alpha power across all channels between depression and control groups (Figure 4.3). For a full list of regional channel statistics see appendix supplementary Table 6.3-6.4. Full reporting of all REM spectral power frequency bands group differences is available in appendix supplementary Figure 6.3. Post-hoc exploration of regional REM gamma and alpha frequency contributions spatially across the brain were performed. Differences in REM gamma activity alterations were observed, results reported in appendix supplementary Figure 6.5.

4.4.6.2 NREM sleep

4.4.6.2.3 Global EEG NREM arousal measures

During NREM, normalised global delta power was lower in the depression group (Control: 0.424 ± 0.03, Depression: 0.370 ± 0.060, $p = 0.030$) with no differences in sigma and alpha power. Results were unchanged following a sensitivity analysis removing participants taking antidepressants.

4.4.6.2.3 Regional EEG NREM arousal measures

All spectral power channel group differences that were observed were significant at the uncorrected level. We did not find any significant differences after multiple comparison corrections using TFCE. The depression group, relative to the controls, demonstrated less NREM delta power predominantly in the frontal lobes but also in five channels across the parietal and occipital lobes (channel n = 19, mean difference/ mean β contrast = 0.08, uncorrected ps. < 0.046) (Figure 4.4). NREM sigma and alpha frequencies showed no statistically significant difference in regional channels between depression and

control groups. For a full list of regional channel statistics see appendix supplementary Table 6.3-6.4. Other NREM spectral power frequency group differences are reported in appendix Supplementary Figure 6.4. Post-hoc exploration of regional NREM delta, sigma, and alpha frequency contributions spatially across the brain were performed. NREM delta, sigma and alpha power differences were observed with results reported in appendix supplementary Figure 6.5.

Table 4.5 Global EEG power differences in REM and NREM (N2 and N3) between depression and control groups (n=22)

	EEG frequency band	Depression (n=12) Mean ±SD	Control (n=10) Mean ±SD	Test statistic	Sig.
REM	global normalised gamma power	0.036 ±0.048	0.027 ±0.016	0.33	0.742
	global normalised alpha power	0.071 ±0.028	0.076 ±0.033	0.97	0.688
NREM (n2 and n3)	global normalised delta power	0.370 ±0.060	0.424 ±0.037	1.59	0.030*
	global normalised sigma power	0.020 ±0.011	0.020 ±0.007	1.31	0.927
	global normalised alpha power	0.045 ±0.018	0.050 ±0.018	0.08	0.552

Data presented as mean± SD where applicable. Values presented in μV^2. * $p<0.05$. Non-parametric Mann-Whitney U test was performed on global normalised gamma power, test statistic Z. Independent t-test was performed on all other variables, test statistic F. Frequency bands were defined as gamma power (25-40Hz), alpha power (8-12Hz), sigma power (12-15 Hz) and delta power (1-4.5 Hz).

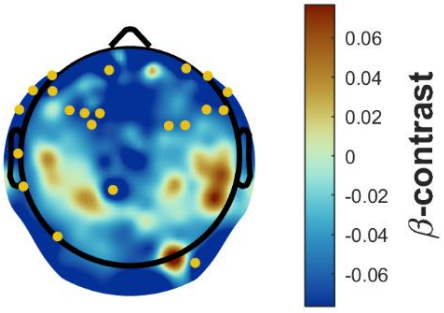
Figure 4.3 Topographic plots of β contrast alpha and gamma spectral frequency differences during REM between depression and control groups normalized across all frequencies

REM alpha power (8-12Hz) REM gamma power (25-40Hz)

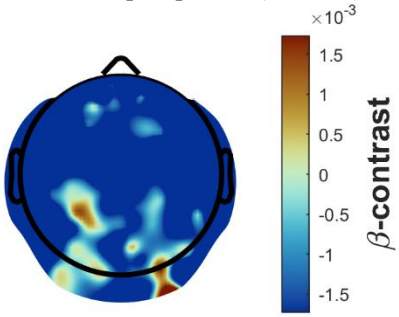
Topographical head plots present the mean power of all REM periods normalised against total power summed across frequency bands and channels. Red indicates β contrast values are higher in the depression group, whereas blue values are lower in the depression group compared to controls. No channels were significant following threshold-free cluster enhancement.

Figure 4.4 Topographic plots of β contrast delta, alpha and sigma spectral frequency differences during NREM (N2 and N3) between depression and control groups normalized across all frequencies

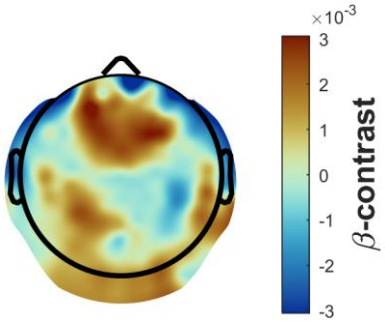
NREM delta power (1-4.5 Hz)



NREM alpha power (8-12Hz)



NREM sigma power (12-15 Hz)



Topographical head plots present the mean power of all N2 and N3 periods normalised against total power summed across frequency bands and channels. Red indicates β contrast values are higher in the depression group, whereas blue values are lower in the depression group compared to controls. Yellow channel markers represent channels with significant uncorrected values $p<0.05$. No channels were significant following threshold-free cluster enhancement.

4.4.6.3 Associations between EEG arousal measures and emotional memory

4.4.6.3.1 REM arousal measures

Simple linear regression was used to test if global REM EEG arousal measures and depression significantly predicted a change in overnight valence and arousal response to negative stimuli on the IAPS task. Due to insufficient completion of the IAPS task one depression and one control participant had their data excluded from the analysis (n = 20, control n=9, depression n=11). C-AVLT scores were not correlated to sleep measures due to lack of variation in data points in overnight change results.

Global REM gamma power and depression did not predict an overnight change in arousal (R^2 = 0.026, F (2,17) = 0.226, p = 0.800) or valence responses to negative stimuli (R^2 = 0.088, F (2, 17) = 0.825, p = 0.455) (Figure 4.5). Similarly, global REM alpha power and depression did not predict an overnight change in arousal (R^2 = 0.041, F (2, 17) = 0.359, p = 0.704) or valence responses to negative stimuli (R^2 = 0.122, F (2, 17) = 1.183, p = 0.330).

Pearson's correlations were performed to identify associations between REM arousal index and aspects of emotional memory. There was no association between overnight change in negative image arousal nor valence scores and REM arousal index within the depression group (arousals r = -0.552, p = 0.063, valence r = 0.212, p = 0.556).

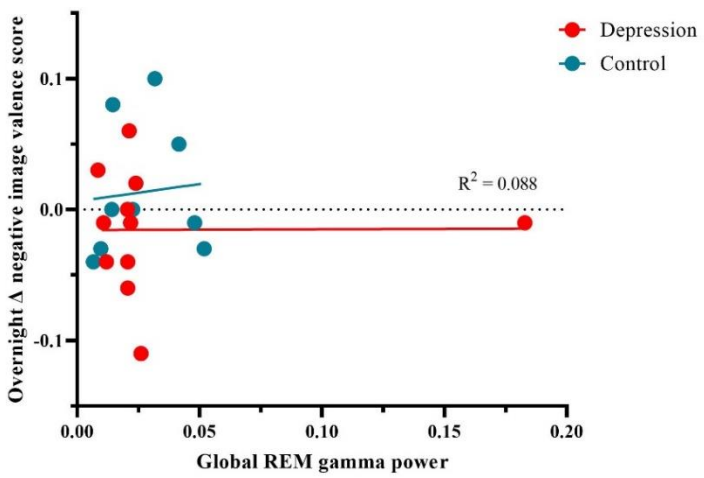
4.4.6.3.2 NREM arousal measures

Simple linear regression was used to test if global NREM EEG arousal measures and depression group significantly predicted a change in overnight recognition of negative images on the IAPS task. Due to insufficient completion of the IAPS task one depression and one control participant had their data excluded from the analysis (n = 20, control n=9, depression n=11). Global NREM delta power and depression did not significantly predict overnight recognition of negative images (R^2 = 0.089, F (2, 17) = 0.835, p = 0.451) (Figure 4.6). NREM sigma and depression did significantly negatively predicted overnight change in negative image recognition (R^2 = 0.453, F (2, 17) = 7.044, p = 0.006), however, when removing an outlier from the depression group this relationship became non-significant (R^2 = 0.181, F (2, 16) = 1.764, p = 0.203). Global NREM alpha and depression did not significantly predict overnight negative image recognition (R^2 = 0.154, F (2, 17) = 1.553, p = 0.240).

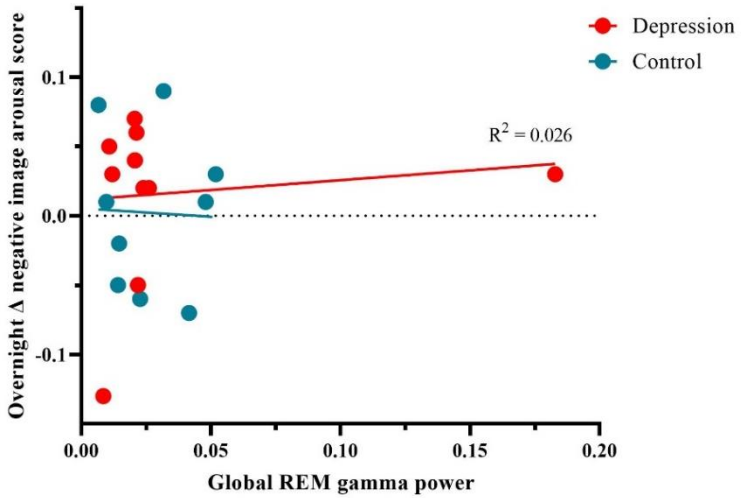
There were no significant associations between NREM arousal index and total negative overnight memory recognition on the IAPS task (r = 0.145, p = 0.652).

Figure 4.5 Scatterplot of linear regression relationship between normalised REM gamma and alpha power and overnight negative image valence and arousal scores (n=20)

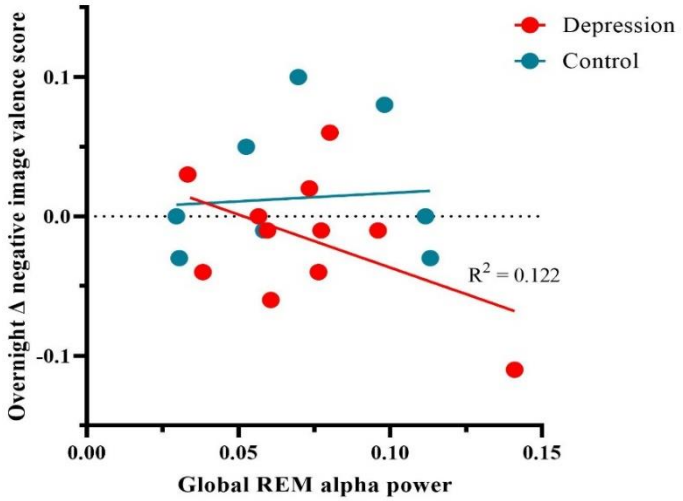
a



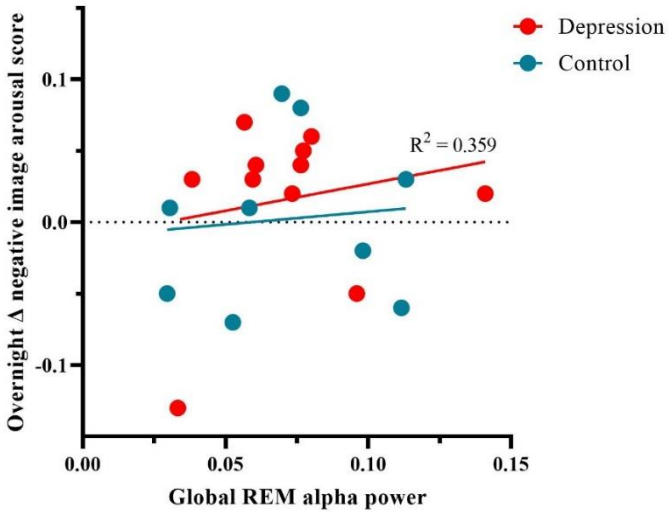
b



c



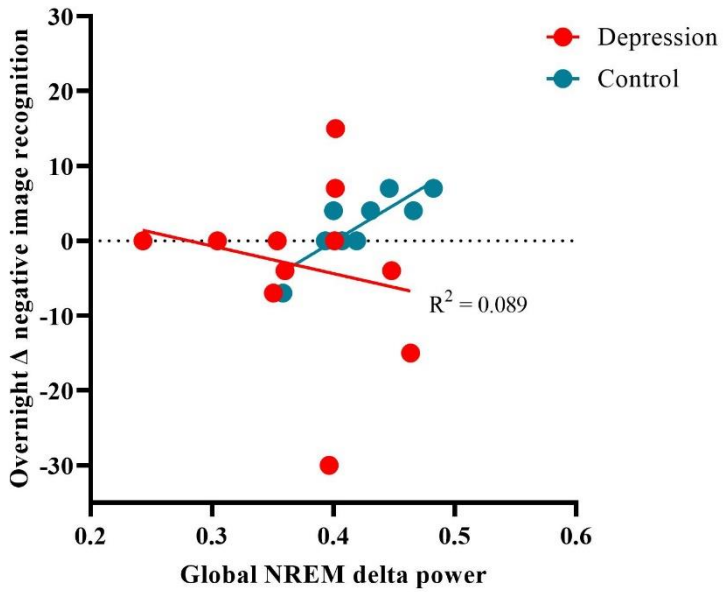
d



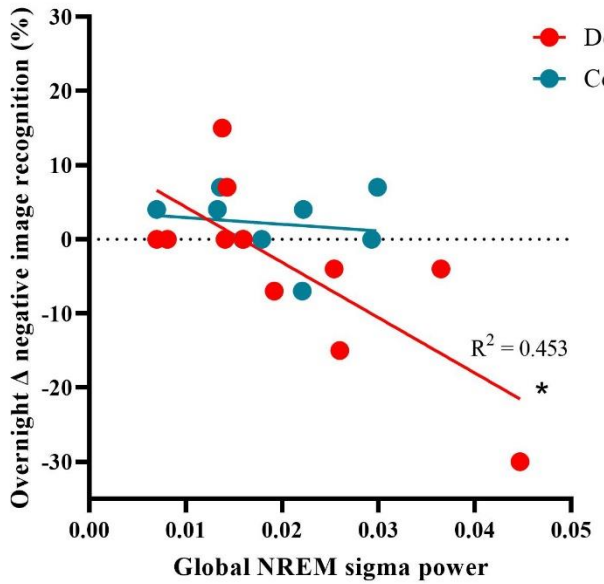
Figures a-d represent individual average normalised REM gamma and alpha power values in comparison the overnight negative image valence and arousal scores. Red circles are representative of depression individual scores and blue circles represent controls. R square linear regression values represent the change in arousal or valence measures predicted by REM gamma or alpha power and depression.

Figure 4.6 Scatterplot of linear regression relationship between normalised NREM delta, sigma and alpha power and overnight negative image recognition (n=20)

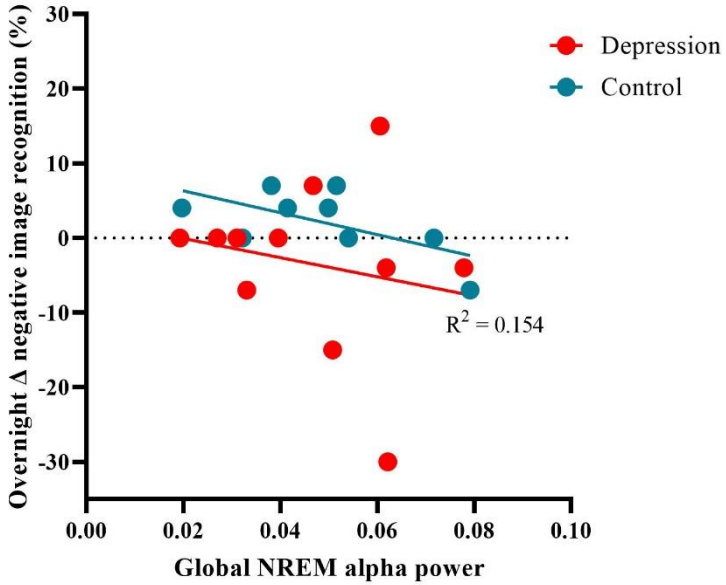
a



b



c



Figures a-c represent individual average normalised NREM delta, sigma, and alpha power values in comparison the overnight negative image recognition performance (%). Red circles are representative of depression individual scores and blue circles represent controls. R square linear regression values represent the recognition performance predicted by NREM delta, sigma and alpha power and depression. An outlier in the depression group produced significant association between NREM sigma power and negative image recognition, however, once removed association became non-significant.

4.5 Discussion

Concordant with our hypothesis, the depression group demonstrated higher arousal scores in response to negative images in the morning relative to the evening, compared to the controls, who showed no change. Further, when assessed overnight, participants with depression had a more negative response to negative images in the morning, whereas controls did not show this change. However, contrary to our hypothesis, there were no group differences in overnight memory recognition. The depression group spent less time in slow-wave sleep and had a trend of lower NREM global and regional frontal, parietal and occipital delta EEG power compared to controls. No group differences were observed in REM arousal measures and neither NREM nor REM arousal measures showed significant associations with emotional memory.

We observed emotional memory biases towards negative information within valence scores in the depression group, but we did not find better recollection of negative information compared to positive and neutral information across all tasks, as previously found in mood congruency studies of younger adults with depression (Gaddy & Ingram, 2014; Hamilton & Gotlib, 2008). Overnight, negative images were rated more negatively, and arousal scores increased in the depression group, differentially from controls. These findings indicate potential impairments in overnight emotion processing in older adults with depression. Studies that support the mood-congruency theory, suggest that people with depression display biases in implicit memory recollection, rather than explicit memory, which is congruent with our results (Bradley et al., 1995; Ellwart et al., 2003). This study found differences in negative image valence and arousal processing overnight, however, there was no associations with increased physiological arousal of EEG markers.

The depression group did not demonstrate altered sleep measures of sleep initiation and continuity, inconsistent with previous literature and Chapter II (Monteleone et al., 2011; Poole & Jackowska, 2018). However, total sleep time was short in both groups, possibly due to the sleep laboratory environment and the 8-hour sleep opportunity. We observed less SWS in the depression group compared to the controls, and evidence of lower global and regional delta power. Both groups had proportionally more SWS and less stage 2 sleep than expected in older adults (Ohayon et al., 2004). It

has been posited that SWA (delta power) in major depression plays a different role in sleep homeostasis compared to healthy adults (Goldschmied, Cheng, Armitage, et al., 2019). Studies measuring slow wave dynamics over the course of NREM cycles have found that adults with depression have lower overall delta power and a greater reduction of delta power over the night, which is consistent with a change in sleep propensity in this group (Borbély et al., 1984; Goldschmied, Cheng, Armitage, et al., 2019). A high density EEG study noted the opposite, with increased frontal and parietal delta power in younger adults with major depression compared to controls (Plante, Landsness, Peterson, Goldstein, Riedner, et al., 2012). Notably, older healthy adults demonstrate an age-dependent reduction in delta power associated with neural atrophy in related brain areas (Mander et al., 2013), however, older adults with depression in this study have further reductions in delta power than older adults without depression, indicating additional deficits. Despite prior work implicating PFC activation during NREM sleep with amygdala activation and emotional memory recollection, we did not observe any associations between NREM delta power and emotional memory performance, suggesting SWA may not be important for overnight emotional memory consolidation in older adults with depression (Van Der Helm & Walker, 2011; Walker & Van Der Helm, 2009).

When comparing global and regional REM gamma and alpha power there were no differences between depression and controls. Gamma activity in REM sleep has been posited to represent increased coherence in cortical regions associated with arousal and increases in noradrenergic and amygdala activity (Cavelli et al., 2015; Van Der Helm et al., 2011). However, we could not establish any associations between observed change in overnight valence arousal scores and gamma power as have previously reported in healthy adults (Van Der Helm et al., 2011) and insomnia samples (Wassing et al., 2016). Our findings demonstrate that REM EEG arousal is not greater in older adults with depression and that other mechanisms may be responsible for deficits in emotional memory valence and arousal processing.

Higher global NREM sigma power was associated with worse negative image recognition in the depressed group; however, this effect was driven by one participant, and therefore, this finding was not robust. Our results are contrary to work in healthy adults showing that more sleep spindles was related

to better negative stimuli recognition compared to neutral, with cued targeted memory activation (Cairney et al., 2014). NREM and REM arousal measures were not predictive of overnight change in emotional memory recognition, valence, or arousal processing, suggesting sleep fragmentation and arousal in older adults with depression may not be mechanistically related to poor emotional memory processing. However, our exploratory findings need to be confirmed in future larger studies.

4.6 Strengths, Limitations, Further Direction and Conclusions

This study is novel in assessing group differences and associations between emotional memory and objective high-density EEG measures, in an older depressed sample compared to controls. The study is strengthened by its use of depression and control participants screened for cognitive impairment and matched at an individual level for age and at a group level for education, premorbid IQ, sleep apnea severity, and insomnia severity.

Despite a well-characterised cohort, the current study was limited by its small sample size. Future research should employ larger samples to confirm our findings. The depression severity of our sample, on average, was mild, therefore potentially not capturing the full spectrum of effects of severe depression pathology on both sleep and emotional memory. It should also be acknowledged that other medical history and medication use may have had effects on sleep, despite performing sensitivity analyses for antidepressant use and sleep apnea. Some ceiling effects were also observed in the emotional memory tasks, indicating further studies should consider the difficulty of tasks whilst accounting for participant burden. The scoring of sleep studies was not able to be blinded, potentially impacting sleep measures. We adopted a conservative statistical approach to control for multiple comparisons when analysing the regional EEG data. Though between group differences in regional delta power were observed at the uncorrected level, our results should be considered preliminary and future larger studies are required to confirm our findings.

Specific overnight impacts on valence and arousal processing in response to negative information in our depression group indicate that sleep processes may be involved in the maintenance of depressive schemas. However, further research is required to elucidate the potential mechanisms behind these

processes. Future studies would benefit from using additional objective physiological arousal measurements such as pupillometry or functional MRI during emotional memory tasks.

The findings of this study indicate that deficits in SWS and reduction in delta power during NREM are evident in older adults with depression, beyond changes observed in healthy older adults and may indicate sleep homeostatic dysfunction. Further studies should aim to assess slow wave dynamics in older adults with depression to identify potential treatment targets. Reduced SWS duration and trends of global and regional reductions in delta power imply that therapeutic targets for the homeostatic sleep drive such as sleep deprivation therapies or interventions to boost slow-wave sleep may be useful in older adults with depression. EEG markers of arousal during REM and NREM sleep were not robustly associated with overnight emotional memory processing. Clinically, overnight alterations in negative information processing suggests that improving sleep in people with depression may impact mood congruency.

Chapter 5- Discussion and Conclusions

5.2 Summary and Aims

Sleep disturbance is bi-directionally related to depression, presenting as both a symptom of depression and preceding the onset of depressive symptoms (Boivin, 2000; Monteleone et al., 2011; Poole & Jackowska, 2018). Despite well-established associations, the exact nature of sleep disturbance in depression is poorly defined (Cho et al., 2008; Lee et al., 2013). In younger adults, research has attempted to identify sensitive and specific EEG biomarkers for depression (Baglioni et al., 2016; Benca et al., 1992). However, there remains debate as to the specificity of these markers for depression, compared to other psychological disorders. Further, older adults are often not included in studies of investigating sleep in depression despite acknowledged changes to sleep timing and NREM sleep with ageing (Conte et al., 2014; Crowley, 2011; Mitchell & Subramaniam, 2005; Ohayon et al., 2004)

Older adults with depression not only present with sleep disturbances but also with more severe memory impairments than controls (Thomas et al., 2009). Depression in older adults is linked to more marked neural cerebrovascular changes than older adults without depression, especially in those with later depression onset (Aizenstein et al., 2016). The benefits of sleep for memory consolidation processes in healthy adults are well established (Diekelmann & Born, 2010). However, studies investigating associations between objective sleep measures and memory in older adults with depression are limited (Diekelmann & Born, 2010). Some studies in older adults with depression have assessed the relationship between self-reported sleep quality and objective sleep quality, measured by actigraphy, in relation to memory outcomes. However, there have been no studies that have objectively measured sleep using polysomnography in this population (Naismith et al., 2009; Naismith et al., 2011; Sutter et al., 2012). Identifying sleep physiological markers of depression across age groups may provide therapeutic targets for this population at risk of the consequences of poor sleep (Mitchell & Subramaniam, 2005).

Emotional memory processing biases in depression have previously been observed with an inclination toward negative information being pertinent in maintaining depressive schemas (Bogie et al., 2019; Callahan et al., 2016; LeMoult & Gotlib, 2019). Research exploring the mechanistic underpinnings of sleep-dependent emotional memory processing posit that connections between the amygdala and prefrontal cortex (PFC) drive these processes in healthy adults (reviewed in Walker and Van Der Helm

(2009)). Studies examining the potential role of REM and NREM sleep in the consolidation of emotional memories state that high levels of fragmentation and arousal during sleep may interrupt emotion processing may explain the processing biases of emotional information in mental health disorders such as depression (Cairney et al., 2014; Riemann et al., 2012; Rosales-Lagarde et al., 2012; Wagner et al., 2001; Wiesner et al., 2015). Yet, there have been no studies assessing the relationship between sleep markers of arousal and overnight emotional memory in depression.

Therefore, the overarching aims of this thesis were to:

1) Characterise objective sleep macro- and micro-architecture measures in adults and older adults with depression by conducting a systematic review and meta-analysis of the literature (Chapter II):

2) Identify whether sleep architecture differs in older adults with depression and late-onset depression compared to older adults without depression and explore relationship with performance on neuropsychological tasks (Chapter III):

3) Compare overnight emotional memory and EEG arousal measures during NREM and REM sleep using high-density EEG between older adults with depression and controls (Chapter IV):

4) Investigate the relationships between specific components of emotional memory and NREM and REM sleep arousal measures in older adults with depression (Chapter IV).

5.2.1 Chapter II

Chapter II reports the findings of a systematic review and meta-analysis in depression studies that used polysomnography to objectively measure sleep macro- and micro-architecture. Our study showed that adults with depression had poor sleep initiation and continuity indicated by less total sleep time and sleep efficiency, prolonged sleep onset, and more time spent awake after sleep onset compared with controls. REM onset latency was earlier in those with depression, but this effect was driven by older adults with depression. Older adults with depression had more stage 1 sleep and less stage 2 sleep indicating impaired sleep continuity. Increased REM density was evident in younger adults with

depression but not in older adults with depression. In this study, we were unable to quantitatively compare sleep micro-architecture measures between the groups due to the limited studies and inconsistent EEG analysis approaches. Sensitive sleep biomarkers in depression are highly desirable as targets for potential therapeutics. This study suggests that objective measures of poor sleep initiation and continuity are the most robust markers of depression across the lifespan. Overall, this work provides important insights into trait sleep markers in depression, especially in older age.

5.2.2 Chapter III

Due to the limited availability of published studies reporting sleep micro-architecture (EEG) measures identified in the prior systematic review, in Chapter III we aimed to address this gap by studying older adults with depressive symptoms and those with late-onset depression. We also sought to understand the relationship between sleep macro- and micro-architecture, neuropsychological performance, and brain integrity. Older adults with depressive symptoms and those with late-onset depression did not differ in our primary sleep variables of interest. However, the depression group had delayed sleep onset and REM onset latencies compared to controls. In the depression group, those with poorer memory had less SWS, and conversely, the control group showed an opposite association. Our NREM sleep micro-architecture measures of interest (sleep spindles and delta EEG power) were not associated with memory performance on the neuropsychological task. This study highlights the importance of assessing sleep as a contributing factor to neuropsychological function, especially in older adults with depression who are at risk for both sleep and neuropsychological deficits.

5.2.3 Chapter IV

The prospective study undertaken in Chapter IV aimed to investigate overnight emotional memory and measures of arousal during NREM and REM sleep measured using high-density EEG in older adults with depression. The study also aimed to understand the relationships between aspects of emotional memory processing and REM and NREM sleep arousal measures.

In relation to emotional memory, older adults with depression had a more negative valence rating and higher subjective arousal scores in response to negative information in the morning compared to the evening. The depression group also spent less time in slow-wave sleep than the control group. High-density EEG analysis revealed deficits in global NREM delta power in the depression group and in regional delta power in frontal, parietal and occipital brain regions. There were no robust associations between NREM or REM sleep EEG arousal measures and emotional memory outcomes in the depression group.

Older adults with depression displayed preferences for negative information and an inability to reduce arousal responses to negative information overnight. These findings suggest emotional information valence and arousal processing are differentially affected during sleep in older adults with depression. The reduction of global and regional delta power during NREM suggests altered sleep homeostasis in older adults with depression which could be targeted by future interventions to increase slow wave sleep.

5.3 Key contributions of this thesis

This is the first body of work to investigate sleep disturbance and associated memory impairments in older adults with depression, an understudied population. This thesis contributed to the characterisation of objective sleep EEG differences in older adults with depression compared to controls and provided insights into the limitations in sensitivity and specificity of previously identified sleep-related markers of depression. A crucial outcome of this study redirects the focus of future research to address sleep timing and continuity issues in depression. Altered sleep timing and continuity are not specific to depressive disorders compared to other mental health conditions but they are the most robust and consistent sleep-related changes in depression observed across the adult lifespan and therefore provide ideal targets for sleep interventions in this population.

Using novel approaches, this research attempted to elucidate associations between cognitive performance on clinical neuropsychological tasks and objective measures of sleep macro- and micro-architecture in an older depression population. The findings of the retrospective study included in this

thesis (Chapter III) echoed the results of the meta-analysis by showing abnormal sleep timing in older adults with depression. This thesis also emphasised a significant relationship between the amount of slow-wave sleep and clinical memory performance, supporting previous mechanistic understanding of the role of slow-wave sleep in memory processes. These findings underscore the importance of addressing sleep disturbances in the treatment of depression and suggest that interventions aimed at improving slow-wave sleep could have a beneficial effect on cognitive functioning.

This thesis was the first to assess overnight emotional memory recollection, arousal, and valence and to use high-density EEG to measure regional differences in sleep micro-architecture in older adults with depression. Further, this study was novel in comparing aspects of emotional memory to both REM and NREM sleep arousal measures in older adults with depression. The final data chapter suggests that older adults with depression have specific impairments in subjective overnight negative information valence and arousal processing, inferring sleep may be important in emotion processing. This finding has implications for the understanding of the role of sleep in the maintenance of depressive schemas. Contrary to the previous chapters, this study did not find evidence of disturbed sleep continuity or maintenance, potentially due to the small sample size and mild depression severity. However, the study demonstrates deficits in delta power (slow wave activity) during NREM sleep in the depression group compared to controls, suggesting dysfunction of the sleep homeostasis process in older adults with depression.

5.3 Strengths and Limitations

This thesis is one of the first bodies of work to objectively assess sleep macro- and micro-architecture in older adults with depression. Participants were comprehensively phenotyped in terms of their cognition, an aspect often overlooked in studies of older populations. The participants recruited through the Healthy Brain Ageing clinic presented with subjective cognitive complaints, which, while making it difficult to interpret the outcomes of sleep and cognition, are more representative of an older population. This thesis also adopted multimodal techniques including reference standard measurement

of sleep with in-lab polysomnography, comprehensive regional analysis of sleep micro-architecture using 256 channel high-density EEG as well as MRI to measure brain structure.

The meta-analysis of objective sleep EEG micro-architecture in Chapter II was limited in its assessment of older adults with depression as only two published studies were available. Although this is the largest pooled sample of older adults with depression, the limited sample size requires the results to be interpreted with caution. Further, in the meta-analysis, there were multiple depression criteria used across the studies to select the cases, making it difficult to ascertain the severity of depression within the total sample and limiting the generalisability of the findings across the severity scale. Similarly, the use of two different sleep scoring criteria used across studies could impact the macro-architecture measures due to variation in stage N1, N3 and REM sleep and wake after sleep onset between AASM and R & K scoring criteria (Moser et al., 2009). Furthermore, meta-analyses are subject to potential publication bias as the data is derived from published studies which potentially favour more positive outcomes.

The studies undertaken in both empirical chapters had relatively small sample sizes. Due to the exploratory nature of this research, power calculations were not performed for these studies, therefore, the ability to detect between-group differences is limited in the sleep and cognitive measures assessed, particularly in, early-onset and late-onset depression subgroups in Chapter III. Future studies that include a larger number of participants and are adequately powered are required to confirm the findings presented in this thesis.

Depression severity can interact with both memory and sleep disturbance. Chapters III and IV assessed only participants with mild depression severity, and it is possible that more marked changes in sleep macro- and micro-architecture as well as emotional memory are present in those with more severe depression. In the prospective sleep and emotional memory study, we did not conduct a screening polysomnography to confirm the presence of sleep disorders such as sleep apnea. However, we did implement screening procedures including questionnaires and wrist oximetry but acknowledge the potential confounding effects of co-existing sleep disorders. Moreover, given the high prevalence of related comorbidities and medication use in depression and in older adults we also acknowledge the

challenges in balancing the selection of a sample free of confounders and one that is representative of the population studied.

Lastly, given the cross-sectional, observational design of these studies, it is difficult to ascertain the long-term effects of depression on both sleep and memory and the causative factors within these associations or the temporality of effects. Future longitudinal and interventional studies are required to fully elucidate the impact of depression on sleep and memory in older adults.

5.4 Clinical Significance and Future Directions

This thesis provides several avenues for future work in the field of sleep and depression in ageing that require multimodal, multifaceted approaches to pursue. Importantly, it is still unclear what causes depression and what neuropathological mechanisms are involved. Despite initial work attempting to define and characterise sleep-related disturbances within depression, it remains unclear how depression impacts sleep and if the same mechanisms that cause depressive symptoms also affect sleep. Further research is required to elucidate the interaction of neurodegenerative processes in older adults with depression and the effect on sleep. Pinpointing the mechanisms of sleep disturbance in depression may aid the development of targeted interventions to improve both sleep and depression symptoms.

Findings from our meta-analysis suggest that targeting sleep timing and continuity using sleep phase delay interventions such as melatonin or light therapy in people with depression may be warranted (Cole et al., 2002; Mundey et al., 2005). Further, the deficits in NREM delta power in older adults with depression supports the future testing of interventions to increase slow wave sleep such as acoustic stimulation or non-invasive brain electrical stimulation. From a clinical perspective, this work also underscores the importance of objectively measuring sleep in older adults who present with depression, to mediate any contribution of sleep disturbance to symptom severity.

From a methodological perspective, this thesis highlighted the paucity of work examining sleep micro-architecture in depression as well as inconsistencies in the standardisation of the quantitative EEG analysis techniques employed, the sleep EEG metrics reported, and the frequency range definitions used. Consensus of a standardised approach for the analysis and reporting of sleep micro-architecture

variables in the field are thus crucial for future research efforts. Furthermore, multimodal neuroimaging techniques such as functional MRI in combination with high-density EEG technology would allow for more comprehensive characterisation of the pathology present in older adults with depression, to understand regional areas of sleep EEG deficits and identify potential targets for therapeutic interventions.

In this thesis, moderate associations between clinical assessments of memory and sleep in older adults with depression were observed. However, questions remain in understanding if the neuropathology that drives depression also affects memory and sleep, or if sleep disturbance uniquely affects the ability to form and maintain long-term memories independent of depressive state. Though there is some evidence for the relationships between sleep, memory and depression, the interaction between these factors has been poorly defined in older adults with depression, a population who are at higher risk of neuropsychological deficits. Our findings of a positive relationship between slow-wave sleep and memory performance in older adults with depression further supports the testing of targeted interventions such as overnight selective auditory stimulation, which has shown beneficial effects on overnight memory processing in healthy adults (Harrington & Cairney, 2021).

Our finding that older adults with depression were less able to process the emotional aspects of valence and reduce arousal produced specifically by negative information, during sleep, has clinical significance. This observation highlights the link between sleep and emotional processing difficulties in depression which may impact the development and maintenance of maladaptive depressive schemas. It emphasises the need to address sleep issues in people who present clinically with depressive symptoms. However, further research is needed to understand whether the ability to process emotional information is dependent on specific sleep mechanisms. It is also unclear whether disrupted sleep independently worsens emotional processing or if it is an inherent feature of the depressive state. Addressing these questions will require experimental sleep manipulation and intervention studies which employ multimodal brain imaging and comprehensive neurophysiological measures. This future research will provide insights into the bidirectional relationships between sleep and depression and test

the effects of targeted sleep interventions to enhance memory and emotional processing with the goal of ultimately improving the quality of life of older adults living with depression.

6- Appendix

6.1 Meta-Analysis Search Terms

Search dates 6th July 2020, 23rd November 2021

Embase

(depress* OR late-life depression OR depression in older adults OR major depression OR major depressive disorder* OR depressive symptoms OR affective disorder*) AND sleep AND (brain activity OR EEG OR power spectral analysis OR electroencephalogra* OR PSG OR polysomnogra*)

PubMed

(depress* OR late-life depress* OR depression in older adults OR major depression OR major depressive disorder* OR depressive symptoms OR affective disorder*) AND sleep AND (brain activity OR EEG OR power spectral analysis OR electroencephalogra* OR PSG or polysomnogra*)[All fields]

SCOPUS

TITLE-ABS-KEY ((depress* OR late-life depress* OR depression in older adults OR major depression OR major depressive disorder* OR depressive symptoms OR affective disorder*) AND sleep AND ("brain activity" OR eeg OR "power spectral analysis" OR electroencephalogra* OR psg OR polysomnogra*)

Web of Science

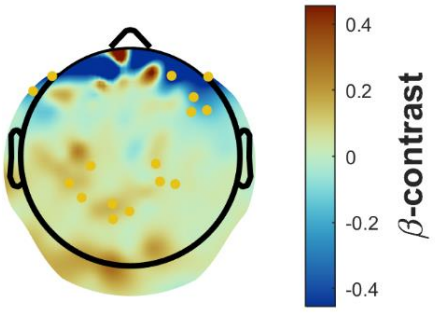
(TS=("brain activity" OR EEG OR "power spectral analysis" OR electroencephalogra* OR PSG or polysomnogra*)OR TI=("brain activity" OR EEG OR "power spectral analysis" OR electroencephalogra* OR PSG or polysomnogra*)) AND (TS=sleep OR TI=sleep) AND (TS=(depress* OR “late-life depress*” OR “depression in older adults” OR “major depression” OR “major depressive disorder*” OR “depressive symptoms” OR “affective disorder*”) OR TI=(depress* OR “late-life depress*” OR “depression in older adults” OR “major depression” OR “major depressive disorder*” OR “depressive symptoms” OR “affective disorder*”))

Supplementary Table 6.2 Reasons for participant exclusion at screening

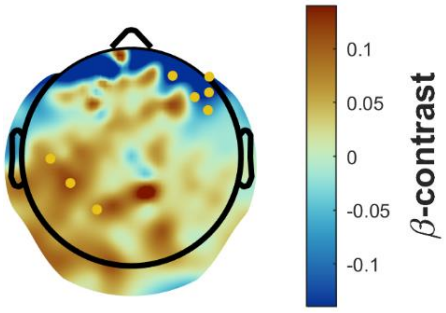
Reason for exclusion	**Number of excluded participants**
Medication	13
Other medical condition	7
Other sleep disorder	32
Other neuropsychological	2
Other neuropsychiatric	4
Does not fit depression or control criteria	26
Unable to complete protocol	6
Not interested/ lost to follow-up	20
Total	110

Supplementary Figure 6.3 Topographic plots of secondary β contrast spectral frequency differences during REM between depression and control groups normalized across all frequencies

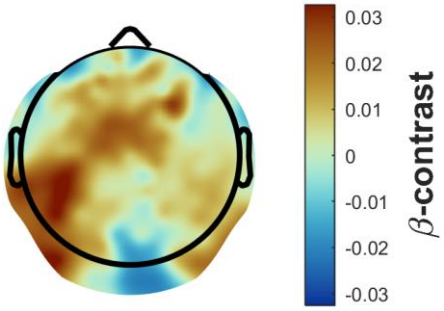
REM low-delta power (0.5-1 Hz)



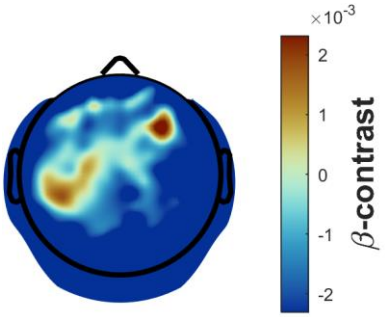
REM delta power (1-4.5 Hz)



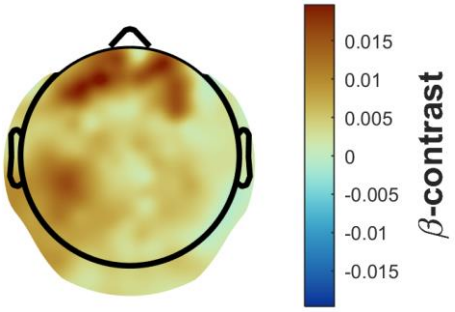
REM theta power (4.5-8 Hz)



REM sigma power (12-15 Hz)



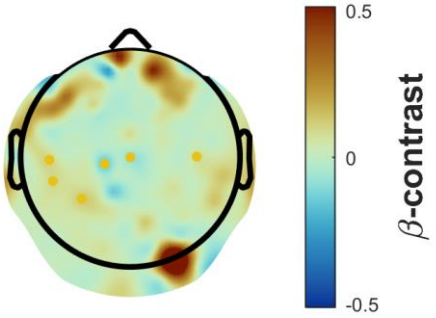
REM beta power (15-25 Hz)



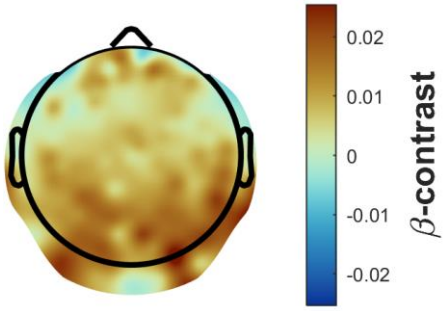
Topographical head plots present the mean power of all REM periods normalised against total power summed across frequency bands and channels. Red indicates β contrast values are higher in the depression group, whereas blue values are lower in the depression group compared to controls. Yellow channel markers represent channels with significant uncorrected values $p<0.05$. No channels were significant following threshold-free cluster enhancement. There was less REM low-delta (n = 7, mean difference = 0.41, uncorrected ps. <0.050) and delta power (n = 5, mean difference = -0.20, uncorrected ps. <0.047) in the depression group compared to controls in the frontal regions (Figure 4.3). There was more REM low-delta across bilateral parietal regions (n = 9, mean difference = 0.09, uncorrected ps. < 0.047) and more REM delta power in the left parietal region in depression group compared to controls (n = 3, mean difference = 0.09, uncorrected ps. <0.049). There were no regional differences in beta, sigma, and theta frequencies between groups.

Supplementary Figure 6.4 Topographic plots of secondary β contrast spectral frequency differences during NREM (N2 and N3) between depression and control groups normalized across all frequencies

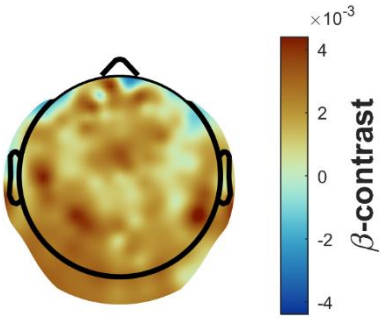
NREM low-delta power (0.5-1 Hz)



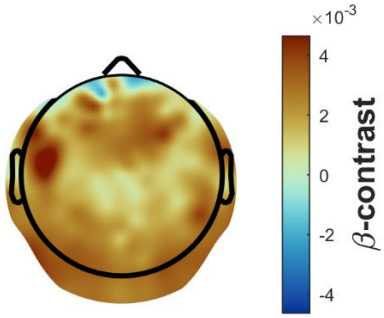
NREM theta power (4.5-8 Hz)



REM beta power (15-25 Hz)



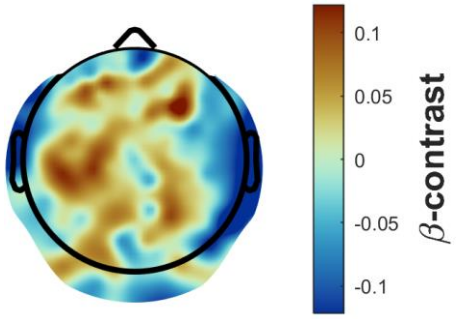
NREM gamma power (25-40Hz)



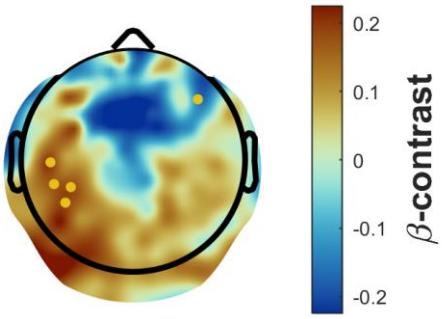
Topographical head plots present the mean power of all N2 and N3 periods normalised against total power summed across frequency bands and channels. Red indicates β contrast values are higher in the depression group, whereas blue values are lower in the depression group compared to controls. Yellow channel markers represent channels with significant uncorrected values $p<0.05$. No channels were significant following threshold-free cluster enhancement. Regional differences were observed with more NREM low-delta evident in the depression group in right and left parietal regions ($n = 4$, mean difference = 0.10, uncorrected ps. < 0.046) but less low-delta observed in the central parietal region ($n = 2$, mean = 0.13, uncorrected ps. < 0.050). There were no regional differences between depression and control groups in gamma, beta, or theta frequencies between depression and control groups. A t-test was run on regional NREM group differences covarying for SWS duration. Following this analysis, regional delta power group differences were nullified in parietal regions and the number of significantly lower frontal channels was reduced ($n = 5$, mean difference = 0.12, uncorrected ps. < 0.048).

Supplementary Figure 6.5 Topographic plots of selected β contrast spectral frequency differences during REM and NREM (N2 and N3) between depression and control groups normalised within frequencies

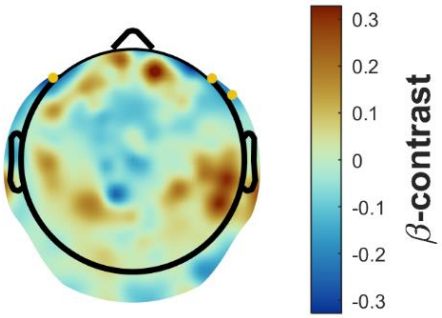
REM alpha power (8-12Hz)



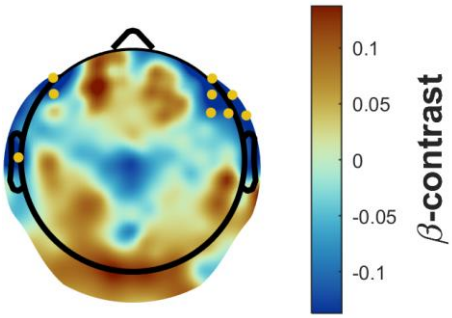
REM gamma power (25-40Hz)



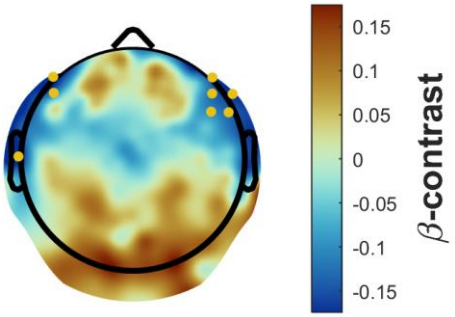
NREM delta power (1-4.5 Hz)



NREM alpha power (8-12Hz)



NREM sigma power (12-15 Hz)



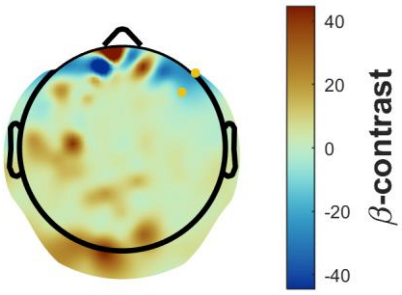
Topographical head plots present the mean power of selected REM and NREM (N2 and N3) periods normalised against total power summed within frequency bands and channels. Red indicates β contrast values are higher in the depression group, whereas blue values are lower in the depression group compared to controls. Yellow channel markers represent channels with significant uncorrected values $p<0.05$. No channels were significant following threshold-free cluster enhancement.

REM gamma activity was higher in the left parietal region compared to other areas of the brain in the depression compared to controls (channel n = 4, mean difference = 0.19, uncorrected ps. < 0.046). One channel in the right frontal region had a lower amount of gamma relative to the rest of the brain in the depression group compared to the controls (channel n = 1, mean difference = 0.17, uncorrected p = 0.045). There was no difference in regional distribution of alpha power between the depression and control group.

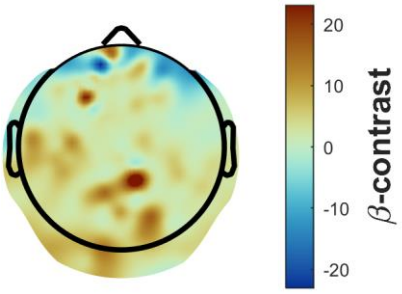
NREM delta power (channel n = 3, mean difference = 0.24, uncorrected ps.< 0.041), sigma power (channel n = 9, mean difference = 0.17, uncorrected ps.< 0.041) and alpha power (channel n = 8, mean difference= 0.17, uncorrected ps. < 0.0208) were relatively lower in depressed participants compared to the controls in the right and left frontal regions relative to the rest of the brain.

Supplementary Figure 6.6 Topographic plots of absolute spectral frequency differences during REM between depression and control groups

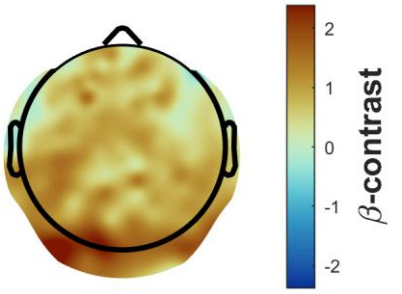
REM low-delta power (0.5-1 Hz)



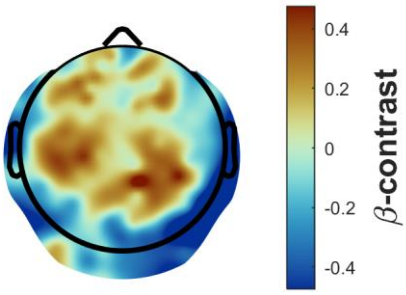
REM delta power (1-4.5 Hz)



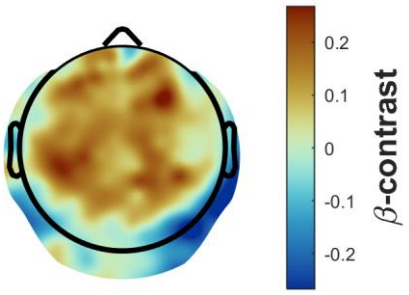
REM theta power (4.5-8 Hz)



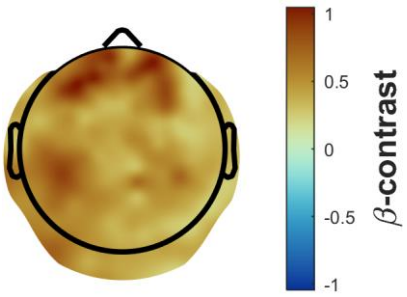
REM alpha power (8-12Hz)



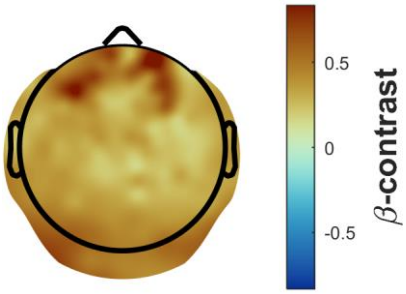
REM sigma power (12-15 Hz)



REM beta power (15-25 Hz)



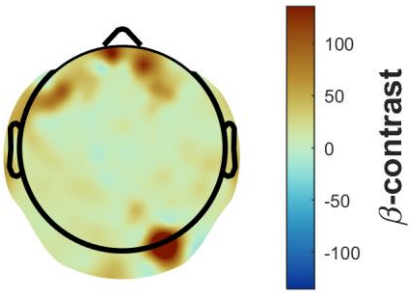
REM gamma power (25-40Hz)



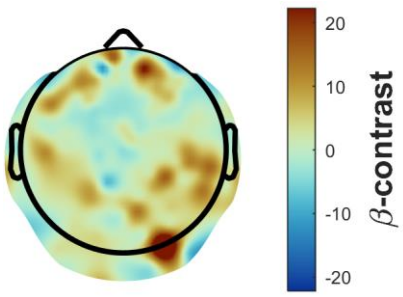
Topographical head plots present the absolute mean power of REM periods normalised against total power summed across frequency bands, and channels. Red indicates β contrast values are higher in the depression group, whereas blue values are lower in the depression group compared to controls. Yellow channel markers represent channels with significant uncorrected values $p<0.05$. No channels were significant following threshold-free cluster enhancement.

Supplementary Figure 6.7 Topographic plots of absolute spectral frequency differences during NREM between depression and control groups

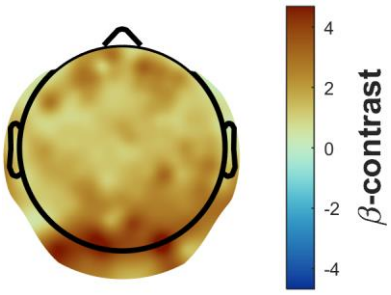
NREM low-delta power (0.5-1 Hz)



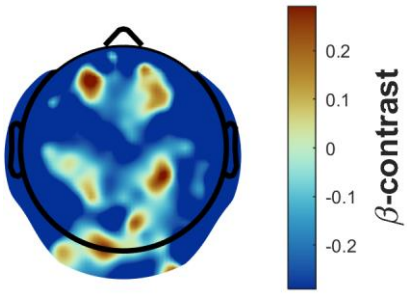
NREM delta power (1-4.5 Hz)



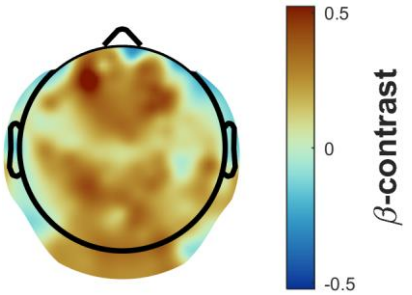
NREM theta power (4.5-8 Hz)



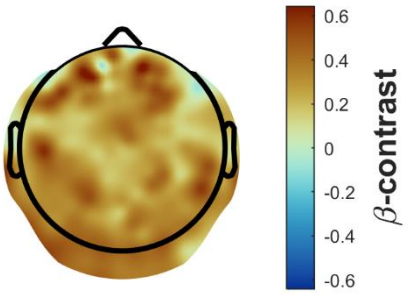
NREM alpha power (8-12Hz)



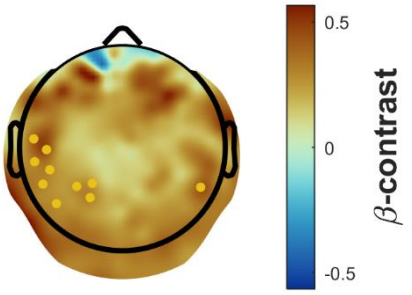
NREM sigma power (12-15 Hz)



NREM beta power (15-25 Hz)



NREM gamma power (25-40Hz)



Topographical head plots present the absolute mean power of NREM (N2 and N3) periods normalised against total power summed across frequency bands and channels. Red indicates β contrast values are higher in the depression group, whereas blue values are lower in the depression group compared to controls. Yellow channel markers represent channels with significant uncorrected values $p<0.05$. No channels were significant following threshold-free cluster enhancement.

Supplementary Table 6.3 List of significant uncorrected channels within REM frequencies normalised across channels (supplementary Figure 6.4)

Channel label	β contrast	T statistic	uncorrected p	TFCE p
REM low-delta				
1	-0.6553	-2.91	0.008	0.413
122	0.0526	2.45	0.009	0.210
54	-0.5836	-2.52	0.021	0.668
130	0.0281	2.03	0.027	0.224
175	-0.2996	-2.00	0.032	0.431
169	-0.1866	-1.93	0.033	0.435
84	0.0556	2.08	0.035	0.194
75	0.1393	1.96	0.038	0.197
99	0.0865	1.98	0.039	0.198
123	0.0873	1.96	0.040	0.228
60	0.0934	2.10	0.041	0.198
11	-0.7818	-2.18	0.043	0.468
94	0.0874	1.74	0.044	0.213
93	0.1593	1.47	0.047	0.265
170	-0.1073	-1.96	0.048	0.432
61	-0.275	-1.82	0.050	0.707
REM delta				
1	-0.3424	-2.96	0.007	0.268
75	0.1251	2.14	0.015	0.338
174	-0.1705	-2.46	0.022	0.279
175	-0.1242	-2.14	0.043	0.295
92	0.0816	2.05	0.046	0.374
11	-0.2992	-2.13	0.047	0.303
70	0.073	1.72	0.048	0.358
169	-0.0758	-2.07	0.049	0.299

Supplementary Table 6.4 List of significant uncorrected channels within NREM frequencies normalised across channels (Figure 4.4)

Channel label	β contrast	T statistic	uncorrected p	TFCE p
NREM low-delta				
84	0.1297	2.47	0.017	0.612
148	0.0756	1.90	0.036	0.993
178	-0.0854	-1.95	0.039	0.917
70	0.1132	1.93	0.045	0.662
74	0.0897	2.00	0.046	0.657
53	-0.1769	-1.23	0.050	0.895
NREM delta				
173	0.0129	-3.03	0.006	0.110
1	-0.1065	-2.94	0.007	0.110
49	0.0805	-2.92	0.009	0.125
168	0.0295	-2.66	0.009	0.113
67	0.0518	-2.75	0.012	0.125
72	-0.065	-2.77	0.013	0.125
54	-0.1786	-2.59	0.017	0.130
169	0.0036	-2.57	0.017	0.115
10	-0.0901	-2.46	0.017	0.117
41	-0.0033	-2.40	0.017	0.129
165	0.012	-2.45	0.021	0.128
81	0.0396	-2.47	0.022	0.288
164	-0.0146	-2.39	0.027	0.129
30	-0.049	-2.38	0.028	0.129
61	-0.0161	-2.25	0.036	0.132
86	-0.1578	-1.52	0.039	0.240
133	0.0614	-2.17	0.040	0.548
55	-0.0703	-2.18	0.040	0.134
42	-0.0301	-2.17	0.042	0.135
33	-0.2809	-1.96	0.043	0.150
96	-0.0077	-2.11	0.046	0.295

Supplementary Table 6.5 List of significant uncorrected channels within REM and NREM frequencies normalised within channels (supplementary figure 6.7)

Channel label	β contrast	T statistic	uncorrected p	TFCE p
REM gamma				
75	0.1859	2.14	0.029	0.276
83	0.1897	2.09	0.036	0.279
74	0.1716	2.14	0.037	0.275
175	-0.1705	-2.13	0.045	0.461
70	0.2124	2.08	0.046	0.279
NREM delta				
1	-0.2284	-2.71	0.012	0.849
173	-0.1814	-2.53	0.019	0.858
54	-0.308	-2.12	0.041	0.911
NREM alpha				
72	-0.232	-3.35	0.000	0.683
1	-0.1768	-2.98	0.004	0.430
168	-0.1399	-2.69	0.013	0.443
174	-0.1367	-2.74	0.014	0.439
54	-0.2191	-2.64	0.015	0.738
55	-0.1482	-2.54	0.018	0.743
169	-0.108	-2.54	0.020	0.465
173	-0.1808	-2.46	0.021	0.480
NREM sigma				
1	-0.2381	-3.19	0.003	0.560
168	-0.1152	-3.26	0.003	0.536
173	-0.1986	-2.75	0.012	0.582
174	-0.1809	-2.75	0.012	0.582
169	-0.1232	-2.65	0.012	0.600
55	-0.1435	-2.55	0.017	0.945
72	-0.1936	-2.30	0.030	0.967
167	-0.1758	-2.26	0.034	0.732
54	-0.2011	-2.10	0.041	0.966

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