Sleep dependent memory consolidation in mild cognitive impairment subtypes

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Thesis Overview

Sleep has shown to be beneficial to the consolidation of newly learnt information in young adults, however the sleep-memory relationship in older adults is less understood. Age-associated memory decline as well as sleep disturbances are a concern for up to 60% of older people. Greater non-rapid eye movement (NREM) sleep neurophysiology such as slow waves and spindles have been postulated to be important for overnight memory consolidation (OMC), however, these associations are unclear in those at greater risk of dementia, namely in Mild Cognitive Impairment (MCI). Furthermore, it is unclear whether structural brain integrity for regions important for sleep and memory in ageing, is associated with OMC in this 'at-risk' population.

The overall aims of this study were to determine if there are differences in OMC in older adults with and without MCI (and their subtypes), examine associations with NREM sleep slow waves and spindles, and investigate how OMC may relate to medial temporal lobe volumes and medial prefrontal cortex (mPFC) thickness. **Study one** showed that there is reduced visuospatial, but not verbal, episodic OMC in amnestic MCI compared to Controls. Greater relative slow wave activity was associated with better verbal episodic OMC in Controls, whereas in MCI, reduced fast spindle density was associated with improved OMC for both tasks in the MCI group, in particular the non-amnestic MCI subtype for visuospatial information. **Study two** included the development of a novel three-dimensional virtual task assessing spatial navigation (SN) memory (egocentric and allocentric SN respectively). The study found reduced SN OMC in MCI, notably reduced allocentric SN in aMCI. Worse SN OMC were associated with reduced spindles, right hippocampal CA1 and dentate gyrus volumes in MCI, whereas better SN OMC was associated with reduced mPFC thickness in Controls. Finally, **study three**, using high-density electroencephalogram, identified widespread SN OMC associations with fast spindles in multiple-domain MCI in lateral frontal, central, parietal and occipital brain regions. Overall, the findings of this thesis reveal that mPFC and SWA are involved in OMC in Controls, however spindles, notably fast spindles, and hippocampal subfields are relevant in MCI.

The results of this thesis make a **novel contribution to the literature** regarding the role of sleep for memory in MCI. Importantly, it incorporates various OMC tasks, and demonstrates the development and preliminary validation of a new SN task, thereby providing a foundation for future OMC studies in ageing and clinical samples. The **implications of the findings of this thesis** are relevant for the design of future studies as well as for the development of clinical trials targeting sleep neurophysiology and memory in cognitively intact and impaired older adults. Overall, the results of the thesis reveal the

complex relationship between memory, sleep neurophysiology and structural integrity in ageing. Future studies can now build upon this work to further delineate how structural, functional or molecular brain neurodegeneration may underpin changes in sleep neurophysiology, and in turn, memory, with an ultimate aim of developing targeted interventions for both sleep and memory.

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Thank you to the readers of this thesis for taking time out of your no-doubt busy schedules. This a body of work with so many contributors. I hope it is an enjoyable read.

Declaration of Originality

To the best of my knowledge, this thesis contains no copy or paraphrase of work published by another person, without acknowledgement and citation. This thesis contains no material that has been presented for a degree at The University of Sydney or any other University. All empirical studies were approved by Human Research Ethics at the University of Sydney with all studied conducted at the Brain and Mind Centre and Woolcock Institute of Medical Research.

I declare that I was the main contributor to this thesis, under the supervision of Professor Sharon Naismith (primary supervisor), Dr Angela D'Rozario (Auxilliary supervisor) and Associate Professor Ian Johnston (Auxiliary supervisor).

Carla Haroutonian

Date: 30/09/2022

Co-Author Declaration

We acknowledge the following statement:

This thesis principally represents the work of Miss Carla Haroutonian. Prof Sharon Naismith, Dr Angela D'Rozario and A/Prof Ian Johnston provided significant support in the preparation of this thesis. Prof Sharon Naismith provided support in study design, clinical management, data analyses, interpretation and editing written work. Dr Angela D'Rozario provided support for study design, notably for chapters 4 and 5, data analysis, notably for EEG data, data interpretation and editing written work. A/Prof Ian Johnston provided supported in the design of the virtual spatial navigation task outlined in chapters 4 and 5, interpretation of data and editing written work. Dr Andrew McKinnon provided support in the processing and interpretation of neuroimaging data. Dr Chein-Hui (Tancy) Kao provided support in the processing and interpretation of high-density EEG data. Aaron Lam, Andrea Ricciardiello, Dr Zoe Terpening and Prof Simon Lewis contributed to recruitment, data collection, and participant assessments.

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Sleep spindles and SWA differentially correlate with overnight episodic and visuospatial memory consolidation in older adults with and without mild cognitive impairment (2021). Haroutonian, C., D'Rozario, A., Terpening, Z., Lewis, S., & Naismith, S. doi: 10.1093/sleepadvances/zpab014.098

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Overnight consolidation of spatial navigation memories is impaired in Mild Cognitive Impairment and is associated with loss of sleep spindles and hippocampal subfield volumes (2022). Haroutonian, C., Johnston, I., Kao, T., A, McKinnon, A., Lam, A., Ricciardiello, A., D'Rozario, A., & Naismith, S.

List of Abbreviations

AD	Alzheimer's disease
Aβ	Amyloid-beta
AHI	Apnoea hypopnea index
aMCI	Amnestic Mild Cognitive Impairment
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
APOE-4	Apolipoprotein E epsilon 4 allele
BMI	Body mass index
CASNAT	Clinical allocentric spatial navigation task
CA	Cornu ammonis
CFC	Cross frequency coupling
CSF	Cerebrospinal fluid
DLB	Dementia with Lewy Bodies
DG	Dentate gyrus
DTI	Diffusion Tensor Imaging
ECG	Electrocardiogram
EEG	Electroencephalogram
ESS	Epworth Sleepiness Scale
ERC	Entorhinal cortex
GDS-15	Geriatric Depression Scale-15
GDS-30	Geriatric Depression Scale-30
GLM	General linear model
hdEEG	High-density electroencephalogram
ISI	Insomnia Severity Index
KSS	Karolinska Sleepiness Scale
LTP	Long-term potentiation
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
mMCI	Multiple-domain Mild Cognitive Impairment
mPFC	Medial prefrontal cortex
MTL	Medial temporal lobe

MWMT	Morris Water Maze Task
naMCI	Non-amnestic Mild Cognitive Impairment
OMC	Overnight memory consolidation
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
NREM	Non-rapid eye movement
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
qEEG	Quantitative electroencephalogram
RAVLT	Rey Auditory Verbal Learning Test
REM	Rapid eye movement
ROCFT	Rey-Osterrieth Complex Figure Test
rsfMRI	Resting-state functional magnetic resonance imaging
SCD	Subjective cognitive decline
SDMC	Sleep dependent memory consolidation
SDB	Sleep disordered breathing
SN	Spatial navigation
SO	Slow oscillations
SWA	Slow wave activity
SPSS	Statistical Package for Social Sciences
SWS	Slow wave sleep
SOL	Sleep onset latency
sMCI	Single-domain Mild Cognitive Impairment
TST	Total sleep time
WASO	Wake after sleep onset
WPT	Word-pair Associates Task
WTAR	Wechsler Test of Adult Reading

Chapter 1 – Introduction

1.1. Trajectory of Cognitive Decline Leading to Dementia

1.1.1. Dementia

Dementia is an umbrella term that encompasses several neurodegenerative disorders with independent neuropathological processes, characterised by significant cognitive and functional decline. Predominant forms of dementia include Alzheimer's disease (AD), vascular dementia, dementia with Lewy Bodies (DLB) and Frontotemporal dementia (FTD) (Prince et al., 2013). Around 50 million people worldwide live with dementia, and by 2050 this figure is expected to 152 million (Patterson, 2018). In Australia, AD is the second leading cause of death (Dementia Australia, 2018), and accounts for approximately 60-70% of all dementia cases (Word Health Organisation, 2019), of which up to half share mixed pathology (Schneider et al., 2007; Schneider et al., 2009). A predominant clinical feature of AD is deficits in declarative memory (Cuijpers & van Lente, 2015). Other features include language and visual decrements such as wayfinding and word-finding difficulties. The pathophysiology that causes degeneration of brain cells and consequently cognitive decline, is the build-up of toxic proteins called amyloid-beta (Aβ) and tau. These in turn lead to the hallmark plaques and tau neurofibrillary tangles characteristic of AD (Ballard et al., 2011). It is suggested that Aβ may even trigger the development of these tangles (Bloom, 2014). The accumulation of Aβ pathology has shown to be present up to one to two decades prior to any clinical symptom presentations (Sperling et al., 2011).

Currently no effective treatments have been identified for AD. Pharmacological trials have yielded small effect sizes improvements with respect to cognitive decline and clinical trajectory of the disease (Berk et al., 2014; Blanco-Silvente et al., 2019; Liu et al., 2021). Therefore, emphasis is now placed on early detection markers and identification of modifiable risk factors. A greater scientific understanding of modifiable risk factors will allow for the development of suitable early intervention trials, which has the ability reduce or slow onset of cognitive decline, reduce symptom severity, and increase quality of life. This is of significance given interventions are greatest in the prodromal phase, prior to disease onset (Petersen & Morris, 2005).

1.1.2. Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is considered a transitional period between healthy ageing and AD (Petersen, 2005; Petersen et al., 1999; Winblad et al., 2004) (Figure 1.1). The cognitive impairment is substantive enough to be noticed by the individual (or significant other) but not significant enough to cause major functional impairment in daily life. Clinical classification of MCI is determined via

various criteria which typically consider clinical profile, neuroimaging or other biomarkers and neuropsychological test scores. The decision to determine whether the person is normal or impaired includes careful history taking of functional abilities. Neuropsychological tests often consist of a battery of standardised tests ranging from tests of processing speed, attention, learning and memory, language, visuospatial and executive function skills, but can also address domains such as fine motor control and social cognition. This information is used to determine if a person is performing below a certain threshold (typically 1-1.5*sd)* relative to age and education matched individuals (Winblad et al., 2004). For persons at greater risk of developing AD, the decline in cognitive function can be quite subtle early on (Petersen, 2004). Those who meet formal criteria for MCI have a progression rate of 15% per year (Gao et al., 2018), with 45% converting to dementia over a within five years (Gauthier et al., 2006). The construct of MCI, whilst heterogeneous, helps both researchers and clinicians better predict the risk of development to dementia, early identification, and better disease management (Albert et al., 2011; Gauthier et al., 2006). Individuals with **subjective cognitive decline (SCD)** have concerns about their cognition yet still perform within limits on objective neuropsychological tests. Over time, however, they do exhibit greater rates of transition to dementia compared to healthy individuals (Mitchell et al., 2014).

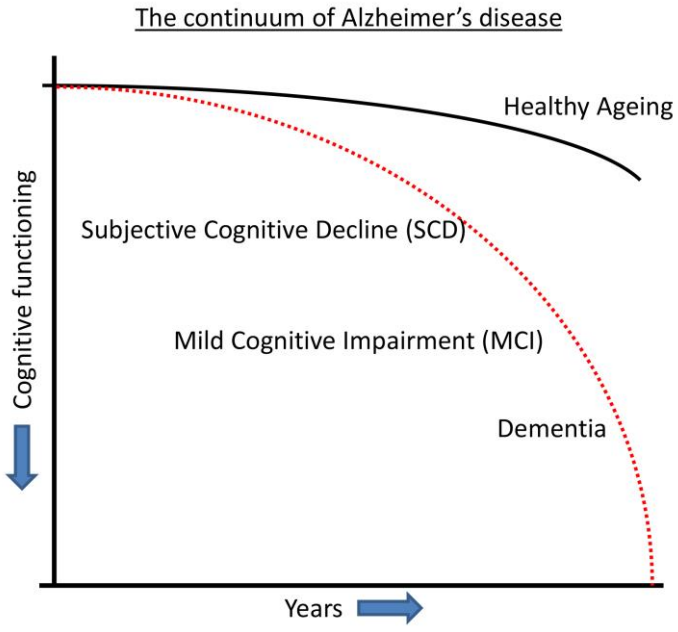


Figure 1.1. Trajectory of cognitive decline from healthy ageing, subjective cognitive decline, MCI to dementia (Figure adapted from R. A. Sperling et al. 2011).

Four subtypes have been established for the classification of MCI, based upon clinical and neuropsychological examination (Petersen, 2004; Petersen & Morris, 2005; Winblad et al., 2004)

(Figure 1.2). These are stratified into whether participants indicate impairment on at least one memory task, termed **amnestic MCI (aMCI)**, and those who show impairment on at least one non-memory task, termed **non-amnestic MCI (naMCI)**. If participants exhibit impairment on only one *vs.* multiple tasks, they are classified as **single-domain MCI (sMCI)**, or **multiple-domain MCI (mMCI)** respectively. Those with aMCI have a greater likelihood of developing AD over time (Levey et al., 2006), with multiple-domain aMCI patients more likely to progress to dementia than single domain aMCI (Michaud et al., 2017). Further to this, those with multiple-domain naMCI after a one year follow-up have shown to be less likely to convert to dementia compared to multiple-domain aMCI, but were also less likely to revert back to normal (Koepsell & Monsell, 2012). Individuals classified as naMCI present with a more diverse trajectories, possibly reflecting the various pathophysiology's underpinning the cognitive decline. As such, longitudinal trajectories may include depression (Gauthier et al., 2006), FTD (Petersen, 2016), and DLB (Petersen, 2016).

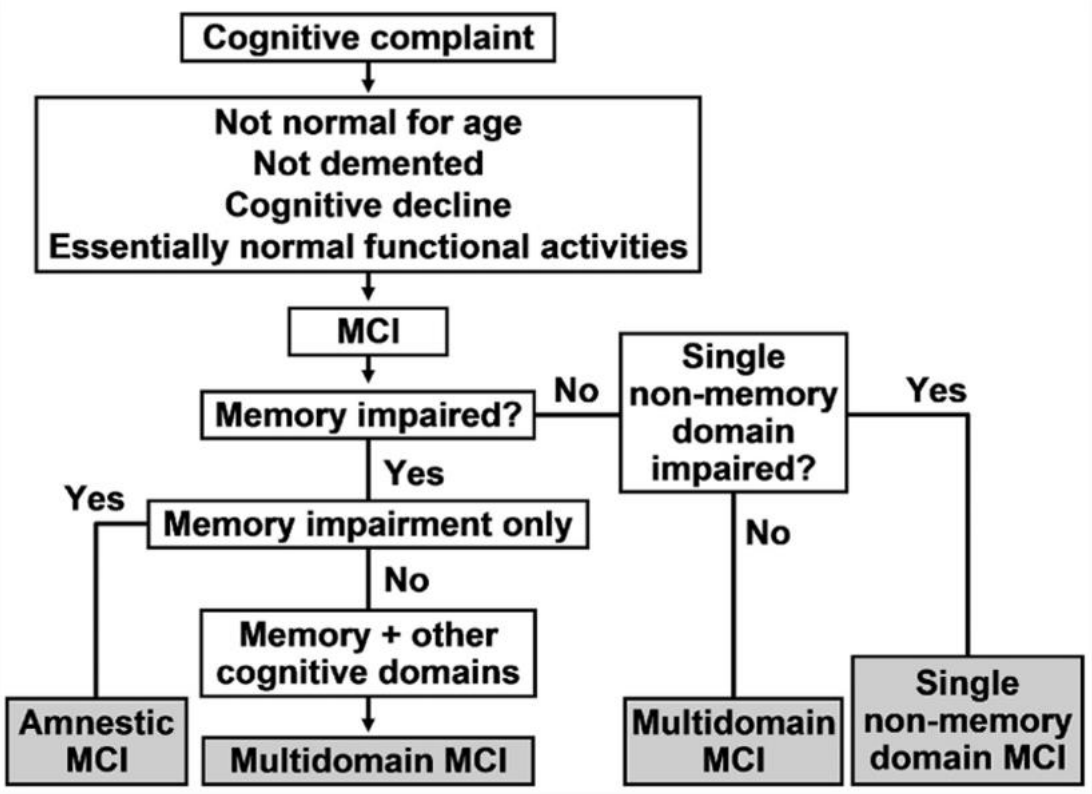


Figure 1.2. Subtypes of mild cognitive impairment. Image retrieved from Petersen (2004).

Several risk factors have been identified for dementia, notably AD, with the most well established of these being advanced age. In a longitudinal study (median follow up 5.1 years), factors that increased the risk of progression from MCI to dementia was found to be increased age, females compared to

males, mMCI compared to sMCI, apolipoprotein E epsilon 4 allele (APOE-4) carriers and those with worse functional status (Roberts et al., 2014). Other identified risk factors include stroke, depression, hypertension, diabetes, smoking, poor diet and a sedentary lifestyle (Livingston et al., 2020), with up to 40% of risk factors for AD being identified as modifiable. Therefore, as no cure is currently available for dementia, greater research is being drawn to preventative factors. One promising modifiable risk factor that has received significant attention over the last two decades is sleep (Bubu et al., 2017; Burke et al., 2016; Minakawa et al., 2019).

1.1.3. Structural and functional brain changes in MCI

One of the earliest structural brain changes occurring with age has been identified as total brain volume reduction (Fjell & Walhovd, 2010). In general, typical cases of AD neurodegeneration may begin in the hippocampus and medial temporal lobe regions (Mak et al., 2016) and then follow a network connectivity-based spreading (Filippi et al., 2020). Both whole brain and hippocampal brain atrophy rate have shown to predict progression to AD (Henneman et al., 2009). With **magnetic resonance imaging (MRI)** advancements, greater examination of hippocampal subfields has been possible, which consist of the anterior region including the subiculum and cornu ammonis (CA) 1 – 3 regions, and the posterior region which includes the CA4 and dentate gyrus (DG). Thickness of the entorhinal cortex, fusiform gyrus, isthmus of the cingulate gyrus, and the precuneus, and the volume of the amygdala and hippocampus have been reported to be reduced in aMCI compared to healthy controls (Csukly et al., 2016). The volumes of the hippocampus and entorhinal cortex, and entorhinal cortex thickness, are especially reduced in aMCI compared to naMCI (Csukly et al., 2016). Hippocampal subfields have been shown to differentiate amnestic and non-amnestic MCI subtypes (Broadhouse et al., 2019; Csukly et al., 2016). Specifically, hippocampal subfields CA1, CA4, subiculum and dentate gyrus were significantly reduced in aMCI compared to those with SCD. All regions except the CA1 differed between aMCI and naMCI, and only the right entorhinal cortex differed between aMCI and SCD. Furthermore, in those with aMCI, reduced CA1, CA4 and dentate gyrus volumes was associated with worse delayed memory recall performance (Broadhouse et al., 2019).

Impairments in cortical regions have also been identified in those ‘at-risk’ of dementia. In MCI, significantly reduced cortical thinning has been found over the right temporal, left anterior cingulate and left lateral occipital regions compared to healthy individuals (Cheng et al., 2018). Thinning within the temporal region has been associated with global cognition change, and therefore suggested as a useful tool in the prediction of progression from MCI to AD (Cheng et al., 2018). In aMCI participants, greater thinning is indicated the entorhinal, parahippocampal, frontal and parietal regions (Machulda

et al., 2020). Conversely, participants with naMCI indicate greater frontal lobe thinning compared to those without MCI (Whitwell et al., 2007; Zhang et al., 2012).

Whilst both cortical and subcortical structural volume loss and thinning are shown to distinguish impaired and unimpaired older individuals, evidence now suggests a wider network impairment is implicated in MCI. This suggests that networks rather than focal regions may have greater utility to distinguishing older adults cognitive impaired to those who are not. Using **resting-state functional MRI (rsfMRI)**, reduced connectivity within both the default mode network and frontal parietal network was reduced in AD and MCI. Furthermore, reduced connectivity in MCI has shown to precede impairment before structural atrophy (cortical thickness and hippocampal volume loss) (Broadhouse et al., 2021). However, a recent meta-analysis and systematic review has identified significant heterogeneity in the default mode network in those with MCI compared to healthy controls (Eyler et al., 2019). The results of this study were not better explained by methodological differences, highlighting the need to potentially examine rsMRI differences in MCI subtypes. Whilst structural differences have been outlined between aMCI and naMCI individuals, no studies have examined rsfMRI differences, namely in the default mode network, between aMCI and naMCI individuals. Overall, the thinning and/or volume loss of several brain regions have been identified in those with MCI. Most strikingly is the medial temporal region, namely the hippocampus and the entorhinal cortex. The goal of future studies should now be to identify to what extent the hippocampus, its subfields, and the entorhinal cortex are implicated in cognitive and behavioural outcomes. Such work would also help to inform the design of studies examining brain connectivity with measures of behaviour and functioning.

1.1.4. Spatial navigation memory in MCI

One of the earliest cognitive impairments observed in AD is seen in the domain of **spatial navigation (SN)**. This cognitive process is pivotal to many areas of independent living and daily functioning, such as driving, grocery shopping, and the ability to return home from a routine or new location. Two key frames of references utilised in SN are **egocentric** and **allocentric** SN (Figure 1.3). Egocentric processing is the encoding of landmarks/objects in the environment in relation to oneself ("object-to-self") (Li & King, 2019). Allocentric processing is by contrast, based on such that the ***relationship between*** objects in the environment are learnt ("object-to-object"), allowing for more flexible navigation. In practice though, individuals can at any given time switch between using egocentric or allocentric SN processes where required. The allocentric SN frame of reference is considered to utilise

more complex SN strategies, in the form of a "cognitive map" (Tolman, 1948), whereas the egocentric frame of reference utilises more simple strategies such as associating a goal with a single proximal landmark (beaconing strategy) (Figure 1.4). With advanced ageing, the use of allocentric SN frames of reference becomes more impaired (Laczo et al., 2021), and a greater of use of egocentric strategies is utilised. One explanation posited for the greater reliance on egocentric strategies with age is that the reduction in encoding objects and their spatial relationships between objects (Segen et al., 2021). This may be reflective of decrements in object-location binding (Muffato et al., 2019). Object-location binding refers to the knowledge about the locations of objects in the environment, a skill required to help determine whether a location is the same or different than a place encountered previously (Muffato et al., 2019).

The **Morris Water Maze Task (MWMT)** was one of the first measures of allocentric SN to be developed and examined (Morris et al., 1982). Whilst the original task has been developed in various formats (i.e. two dimensional computerised task, virtual reality etc.), the fundamental components of the MWMT are still considered the gold standard measurement of allocentric SN. Other tasks that have been used to measure SN include the radial arm maze task measuring spatial memory and working memory (Olton & Samuelson, 1976) and the T-maze (or Y-maze) task measuring spatial learning and memory via simple route learning (Olton, 1979). Whilst these maze tests tap into overlapping features of SN, it cannot be assumed that findings on one test will generalise to another (Hodges, 1996) as the cognitive and spatial demands differ between tasks. For example, the MWMT requires free search compared to constrained search in the Radial or T-maze test, and requires greater allocentric learning and less working memory demands compared to the latter two tasks. Of significance, the MWMT shows high reliably using various configurations and testing procedures (Kallai et al., 2005). The development of virtual reality tasks has increased with technological advancements, and whilst these may be more ecologically valid, they can pose limitations in older adults; such as vertigo, vestibular disturbances and increased stress.

Key allocentric SN tasks used in MCI and neurodegenerative disorders are the Hidden Goal Task, a human analogue of the virtual MWMT (Laczo et al., 2010; Laczo et al., 2009); the Four Mountains Task (4MT) (Chan et al., 2016; Moodley et al., 2015a), a virtual reality park and maze task (Weniger et al., 2011; Weniger et al., 2009); and the Supermarket Task (Tu et al., 2015; Tu et al., 2017) (Table 1.1). Route learning tasks have also been utilised in MCI samples (Delpoly et al., 2007; Peter et al., 2018), with route retracing being an important component of allocentric processing in ageing (Wiener et al., 2012). As summarised in Table 1.1, several of these tasks that measure egocentric and allocentric

SN are able to identify specific impairments in distinct components of MCI subtypes, as well as distinguishing between neurodegenerative disorders, notably AD and FTD. Individuals diagnosed with FTD present with changes in language, behaviour, and motor abilities, with varied clinical profiles such as the behavioural variant FTD (bvFTD) and language dominant impairment seen in the primary progressive aphasia subtype (Scarioni et al., 2020).

Allocentric SN has been shown to be significantly impaired in aMCI compared to naMCI (Rusconi et al., 2015), and in multiple-domain aMCI compared to single-domain aMCI (Hort et al., 2007), and in MCI participants who are **cerebrospinal fluid (CSF)** biomarker positive *vs*. negative (Laczo et al., 2022; Moodley et al., 2015a) for AD. Furthermore, the ability to recall the location of a landmark on a map may discriminate between aMCI and AD groups (Wang et al., 2013). Whilst landmark recognition remains intact in aMCI participants, they are significantly impaired in remembering a route compared to healthy controls (Peter et al., 2018). Other components of SN impairment in both aMCI and AD include path integration (Mokrisova et al., 2016), which utilises both egocentric and allocentric SN (Figure 1.4).

Whilst there are limitations in the use of virtual reality or "real world" environment SN testing due to feasibility (Puthusseryppady et al., 2020), computerised tasks of allocentric SN have shown to be predictive of conversion from mMCI to AD within 24 months (Wood et al., 2016) and four to five years (Levine et al. 2020). Despite this, SN remains an overlooked cognitive domain in neuropsychological tests (Coughlan et al. 2018). Several contributors to changes in SN may be brain degeneration, visual encoding strategies (Segen et al., 2021), or neuropsychiatric status (Balash et al., 2013; Sheardova et al., 2015). Whilst there is evidence for the role of sleep in SN memory consolidation for younger adults (Ferrara et al., 2008), and its change in healthy ageing (Varga et al., 2016), it is unclear what role sleep may play in allocentric SN, notably those with MCI. Given the suggested role of sleep in memory consolidation, as will be considered in this thesis, examining sleep as another possible contributing factor to SN in 'at-risk' samples is of importance.

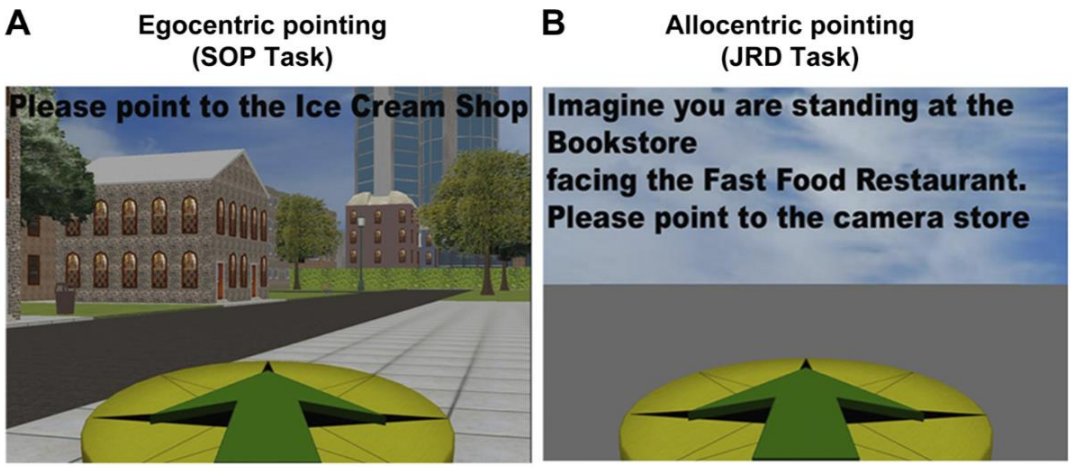


Figure 1.3. Canonical tasks used to assay egocentric and allocentric representations. Image A (left): The scene and orientation-dependent pointing (SOP) task. Image B (right): The judgements of relative direction (JRD) task. The tasks are used as examples of capturing egocentric and allocentric spatial navigation. The SOP task can be most easily solved based on knowledge of one's egocentric position relative to the target. It can also be solved with knowledge of the current location relative to a second store and its relationship to the probe (Ice Cream Shop). In this way, allocentric knowledge can be used to solve the SOP task, in some situations. The JRD task which includes three components (Bookstore, Fast Food store, and Camera store) is most easily solved based on knowledge about the relative positions of the three stores (allocentric knowledge), it can also be solved using one's memory for a visual snapshot that includes the two imaged target stores (Bookstore, Fast Food store) and probe (Camera store); see Wolbers and Wiener (2014) for more details. In this way, egocentric knowledge can also contribute to solving the JRD task. Image retrieved from Ekstrom et al., (2017).

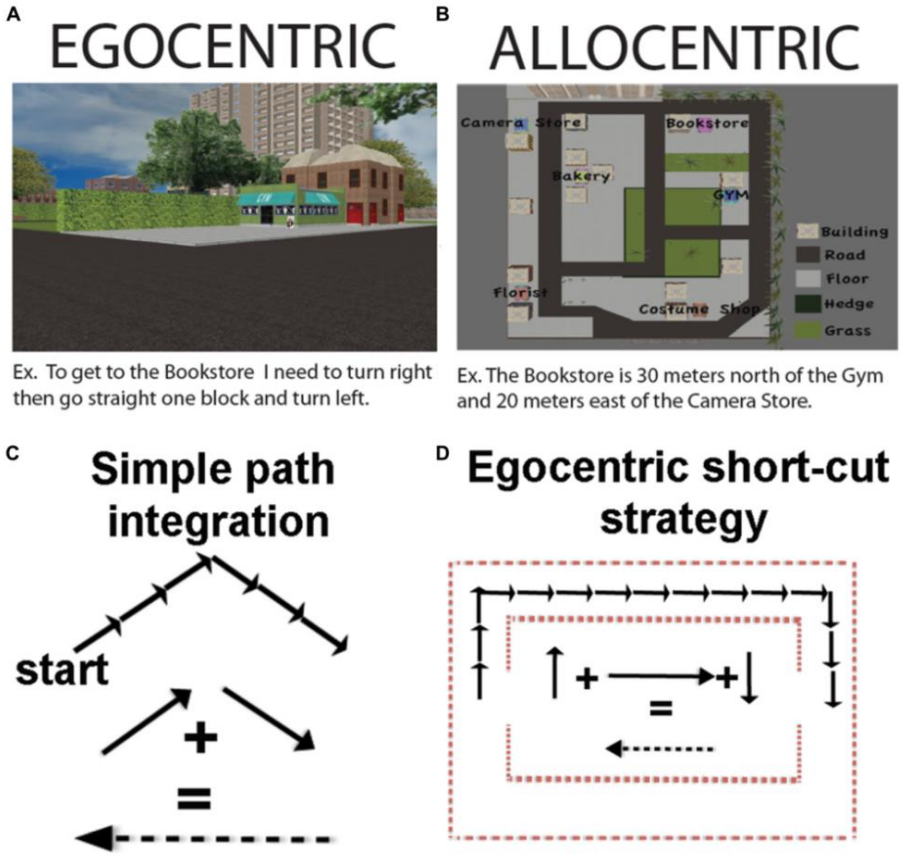


Figure 1.4. (A) An example of an egocentric coding strategy. (B) An example of an allocentric coding strategy. (C) How path integration can occur using a predominantly egocentric coding scheme. Path integration is a situation in which a participant produces a novel path on having completed two (or more) other components of the journey. (D) How navigation short-cuts can occur using a predominantly egocentric (path integration) strategy. This illustrates an example of how short-cuts could potentially be solved using a primarily egocentric form of representation. The importance of landmarks to path integration, however, suggests it is not purely an egocentric strategy either. Image retrieved from Ekstrom, (2014).

Converging structural and functional neuroimaging data has linked key brain regions to egocentric and allocentric SN (Ekstrom et al., 2017; Lithfous et al., 2013). As shown in Figure 1.5, regions identified include:

- Parietal regions for egocentric SN;
- The frontal lobe for spatial working memory (Lithfous et al., 2013); and,
- The medial temporal lobe, specifically the hippocampus and entorhinal cortex for spatial memory and allocentric SN.

The hippocampus has shown to be significantly associated with allocentric SN (Moodley et al., 2015a; Weniger et al., 2011), specifically the right hippocampus (Laczo et al., 2017; Laczo et al., 2015; Laczo et al., 2014; Nedelska et al., 2012). Using a route learning task, the right hippocampal tail is evidenced to be important for SN in aMCI individuals whereas CA2 and CA3 have been shown to be important for healthy controls (Peter et al., 2018). Whilst the hippocampus is also utilised for egocentric SN, greater involvement of parietal regions is used for this component of SN (Maguire et al., 1998; Wolbers & Wiener, 2014). In individuals with unilateral parietal cortex lesions, egocentric memory is impaired however allocentric memory remains intact (Weniger et al., 2009). Components of SN, specifically path integration, have shown to be related to hippocampal, entorhinal and parietal atrophy in aMCI and AD patients (Mokrisova et al., 2016). In healthy controls, aMCI and AD individuals who got lost on a route learning task, had lower right posterior hippocampal and parietal volumes compared to those who did not get lost (Delpoly et al., 2007). The hippocampus is strongly involved in object-location binding (Zimmermann & Eschen, 2017), a spatial feature important for allocentric SN. The contributing factors to changes to allocentric SN still require more research, including in MCI populations. Furthermore, whilst hippocampal subfields have been consistently noted in their involvement in SN processing such as the CA1, CA3, dentate gyrus and subiculum, the associations with of these subfields in MCI is unclear.

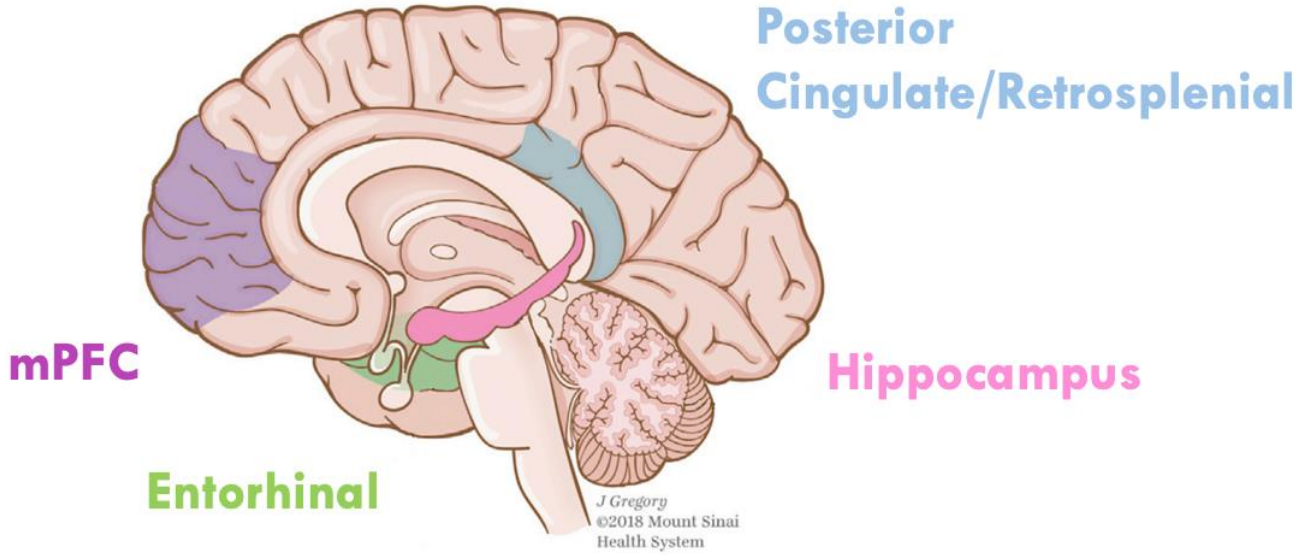


Figure 1.5. Visual summary of the key regions relevant in spatial navigation. Colours represent approximate functional distinctions. mPFC = medial prefrontal cortex. Image retrieved from Schiller, (2018).

Task	Author, Year, Sample	Summary of key findings
Human analogue of the virtual Morris Water maze task: Hidden Goal Task (real-space and/or virtual environment)	SDC, naMCI, single-domain aMCI, multiple-domain aMCI, probable AD (Hort et al., 2007)	↓ egocentric & allocentric SN in multiple-domain aMCI & AD, performed similarly. naMCI & Controls performed similarly on allocentric SN tests. ↓ SN performance in multiple-domain aMCI cf single-domain aMCI.
	Controls, naMCI, HaMCI[1], NHaMCI[2], AD (Laczo et al., 2009)	↓ Egocentric & allocentric SN in HaMCI cf NHaMCI. More pronounced in 2nd half of task suggesting ↓ learning. In 2nd half, HaMCI performed similarly to AD. NHaMCI indicated ↑ in performance & learning.
	naMCI, single-domain aMCI, multiple-domain aMCI, probable AD, aMCI (stratification into: APOE-4 [+ -] and HaMCI[1] & NHaMCI[2]) (Laczo et al., 2010)	↓ Egocentric & allocentric SN in multiple-domain aMCI & AD. ↓ Allocentric SN in single-domain aMCI. ↓ Egocentric & allocentric SN in HaMCI cf NHaMCI, HaMCI similar to AD. APOE-4+ aMCI similar to AD when cf APOE-4-.
	Controls, HaMCI[1], NHaMCI[2], AD (Laczo et al., 2012)	↓ Overall SN deficits in HaMCI cf NHaMCI except delayed recall. ↓ SN learning in HaMCI cf NHaMCI. HaMCI similar pattern of deficits cf mild AD. Strong correlation between virtual/computerised and real-space SN tests.
	Controls, aMCI, AD (Nedelska et al., 2012)	↓ right hippocampal volume associated with ↓ allocentric SN in both real-space and virtual, independent of total brain volume. Left hippocampus did not explain the association between right hippocampal volume & SN. Real-space and virtual SN task strongly correlated.

	aMCI (APOE-4 non-carriers, heterozygous carriers & homozygous carriers) (Laczo et al., 2014)	↓ Egocentric & allocentric SN in APOE-4 carriers. ↓ SN in APOE-4 homozygotes cf heterozygotes. Right hippocampal volume accounted for differences in allocentric but not egocentric SN.
	Controls, aMCI (Laczo et al., 2017)	Using exploratory factor analysis, allocentric & egocentric SN loaded on its own factor, separate from 6 established cognitive functions (verbal & non-verbal memory, executive function, visuospatial function, attention/working memory and language function). SN shares limited variance with other cognitive abilities. No associations between cognitive function on any tasks with SN in Controls. In aMCI, only executive function associated with allocentric SN, verbal memory associated with egocentric SN. Right or right hippocampal volume not associated with SN in Controls. Right & left hippocampal volume associated with allocentric SN in aMCI, explained 12% & 26%, respectively, of the variance in allocentric SN after age, gender & education adjustment.
Four Mountains Task (4MT)	Controls, MCI (subgroups Aβ + -), AD (Moodley et al., 2015) (UK & Italy population)	↓ allocentric SN in MCI & AD cf Controls. ↓ allocentric SN in Aβ + MCI cf Aβ -. ↓ allocentric SN associated with ↓ hippocampal volume & precuneus thickness in both groups. 100% sensitivity (both populations) & 90% & 50% sensitivity (UK & Italy population, respectively) for detection of MCI & AD.
	Controls, MCI (subgroups Aβ + -), mild AD (Chan et al., 2016)	↓ allocentric SN in MCI Aβ + cf Aβ –. No group differences on the Rey Auditory Verbal Learning Test (standardised neuropsychological test of episodic memory) between MCI Aβ + & Aβ –.

		↓ hippocampal volume, precuneus thickness & posterior cingulate gyrus associated with ↓ SN in MCI groups & AD.
	MCI (Wood et al.,2016)	At 24 months, 9/15 had converted to AD. Allocentric SN performance predicted conversion to AD with 93% accuracy compared to 64% using the Rey Auditory Verbal Learning Test & 79% on the Trail Making Test-B. Allocentric SN associated with ↓ CSF tau levels.
Virtual reality park and maze task	Controls, aMCI (Weniger et al., 2011)	aMCI unable to improve their performance across 5 trials, more frequently lost, reported more frequently being unable to find a navigation strategy cf Controls. ↓ Allocentric SN in aMCI cf Controls. ↑ Right precuneus associated with ↑ performance on egocentric SN. ↓ virtual maze & park performance did not predict conversion to dementia.
Supermarket task[4]	Controls, AD, FTD (bvFTD and semantic variant) (Tu et al., 2015)	↓ spatial orientation in AD cf FTD groups. Impaired spatial orientation in AD related to reduced grey matter volume in left lingual gyrus & retrosplenial region of posterior cingulate.
	bvFTD, AD (Tu et al., 2017)	↓ judging egocentric direction back to start location & estimating distances + locations on map cf bvFTD. Similar impairment on estimating distances and locations on a map (allocentric spatial representation).

Table 1.1. Key egocentric & allocentric spatial navigation tasks utilised in older adults with Mild Cognitive Impairment and neurodegenerative disorders**.**

SCD = subjective cognitive decline, MCI = mild cognitive impairment, aMCI = amnestic MCI, naMCI = non-amnestic MCI, HaMCI = hippocampal amnestic mild cognitive impairment, NHaMCI = non-hippocampal amnestic mild cognitive impairment, mMCI = multiple-domain MCI, AD = Alzheimer's Disease, FTD = Frontotemporal dementia, bvFTD = behavioural variant frontotemporal dementia, APOE-4 = Apolipoprotein E epsilon 4 allele. [1]Based upon Dubois criteria (Dubois & Albert, 2004), HaMCI group is classified as having very poor free recall despite adequate (and controlled) encoding and decreased total recall because of insufficient effect of cueing (less than 10 of 16 words, or 10-14 of 16 words with more than 30% recalled spontaneously) on the Grober and Bushke Test (Grober & Bushke, 1987). [2]Dubois criteria (Dubois & Albert, 2004), NHaMCI group is classified as having impaired free recall in the Auditory Verbal Learning Test and the Grober and Bushke Test with great improvement (10-14 of 16

words with 30% or less recalled spontaneously) or normalisation (15-16 words) with cueing on the Grober and Bushke Test. [3]$A\beta_{42}$ levels below 500 pg/ml. [4]Task engages largely egocentric memory with a low allocentric spatial map contribution of the environment.

1.2. Sleep Changes in Ageing and MCI

1.2.1. Sleep polysomnography measurement

Sleep-wake cycles comprise the two interconnected components of circadian rhythms and sleep. The integrity of circadian rhythms and circadian alignment can be measured in laboratory settings using the gold-standard measurement of melatonin (e.g. via urine, blood, or dim light melatonin onset). The rhythmicity of circadian rhythms can be ascertained by more broadly examining sleep-wake cycles using actigraphy (typically for 7-14 days), ideally combined with self-report diaries. Circadian rhythms and sleep-wake cycles will not be examined in this thesis.

Sleep can be measured in a multitude of ways (see Table 1.2), such as via self-report to determine sleep quality or duration or to ascertain symptoms of insomnia. It can also referred from actigraphy measures of the 'rest interval', which is an objective and ecological way to measure sleep efficiency, total sleep time and nocturnal awakenings (i.e. wake after sleep onset). While such methods are widely accessible and cost-effective, the gold standard for measuring sleep remains as an overnight in-lab polysomnography (PSG) study. During this assessment, sensors are placed on the scalp to measure electroencephalography (EEG) (Figure 1.6), as well as electrocardiogram (ECG) and respiratory measurements. In healthy individuals, delta waves/**slow wave activity (SWA)** (1 – 4.5 Hz) tend to occur in the earlier stages of the night, a marker for **slow wave sleep (SWS)**, whereas rapid eye movement sleep tends to be more pronounced in later half of the evening. Spindles and k-complexes are hallmark features of stage 2/N2 sleep whereas alpha brain waves are a feature of wake states. Each of these stages will cyclically alternate throughout the night, with each cycle lasting approximately 90 – 110 minutes.

Table 1.2. Ways in which to measure key measures of sleep.

Measurements	**Key variables derived**
Self-report	Pittsburgh Sleep Quality index (PSQI) (Buysse et al., 1989) Insomnia Severity Scale (ISI) (Bastien et al., 2001) Epworth Sleepiness Scale (ESS) (Johns, 1991)
Actigraphy	Sleep-wake rhythms or regularity Total sleep time (TST) derived from the rest interval Sleep onset latency (SOL) Wake after sleep onset (WASO)

	Sleep efficiency (SE)
Oximetry	Oxygen saturation of blood
Polysomnography (PSG)	Macroarchitecture features: - Total sleep time (TST) - Sleep onset latency (SOL) - Rapid eye-movement (REM) sleep onset latency (ROL) - Wake after sleep onset (WASO) - Sleep efficiency (SE) - Time spent in slow wave sleep (SWS)/ stage 3 of non-rapid eye movement (NREM) sleep - Time spent in REM - Obstructive sleep apnoea (OSA) by apnoea hypopnea index (AHI) or oxygen desaturation index (ODI) Microarchitecture features (EEG): - Slow oscillations (< 1 Hz) (typically seen in NREM sleep) - Slow wave activity (SWA) (0.1 – 4.5 Hz) (hallmark feature of stage 3 NREM sleep) - Sigma power (12 – 15 Hz) (hallmark feature of stage 2 NREM sleep) - Spindles (11 – 16 Hz) (hallmark feature of stage 2 NREM sleep, bursts of coherent waxing and waning EEG) - Fast spindles (13 – 16 Hz) - Slow spindles (11 – 13 Hz) - K-complexes (similar to spindles, a hallmark of stage 2, identified as a sharp, high-voltage, biphasic wave that lasts for more than 0.5 seconds (Cash et al., 2009) Note: Sleep neurophysiology can be examined via single-sensors placed on the scalp (6 – 19 channels) or by using high-density EEG (hdEEG) (256 channels)

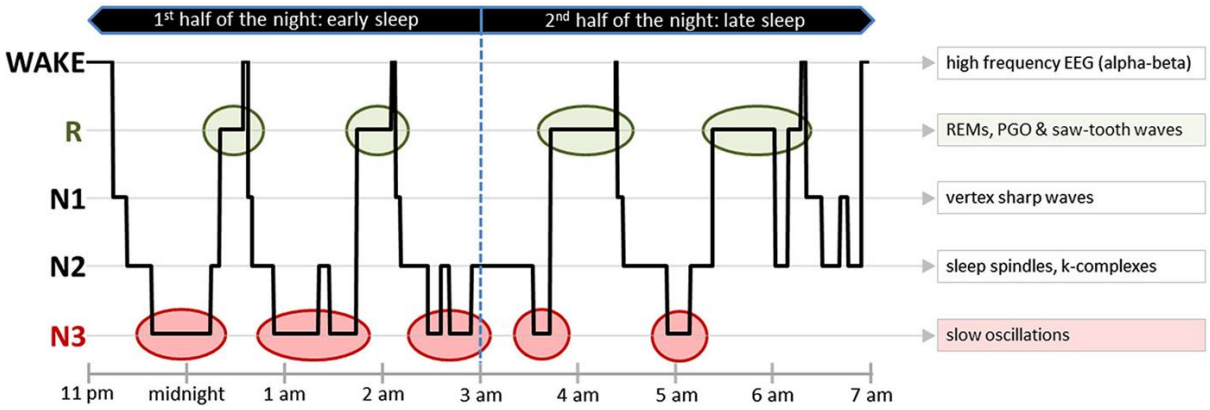


Figure 1.6. Sleep pattern from a healthy human. Hypnogram depicts sleep stages over an 8-hour sleep period. On the right side of the figure, typical EEG that occurs during each stage is listed. Image retrieved from Blume, del Giudice, Wislowska, Lechinger and Schabus (2015).

1.2.2. Key sleep microarchitecture changes

Common changes that are reported in healthy ageing include greater time in shallow sleep (stage 1/N2 and N2), reduced time in SWS, reduced REM sleep; particularly in the second half of the night, greater sleep fragmentation/number of awakenings and greater wake after sleep onset (WASO) (Figure 1.7) (Mander, Winer, et al., 2017b; Ohayon et al., 2004). However, sleep changes are even more pronounced in individuals with MCI. For example, they are three times more likely to exhibit poor sleep compared to healthy older adults (Palmer et al., 2018). In older adults with MCI, 63% report sleep disturbances, a figure significantly higher when compared to only 44% of controls (McKinnon et al., 2014). Objective measurements indicate increased napping (Foley et al., 2007; Milner & Cote, 2009), circadian misalignment (Naismith et al., 2014) and sleep-wake disruption (Yaffe et al., 2014) in those with MCI when compared to controls. A recent meta-analysis of 10 studies (n = 430 individuals) examining sleep abnormalities as assessed by overnight PSG identified sleep macroarchitecture disruptions to be significantly greater in MCI compared to healthy older individuals (D'Rozario et al., 2020). Specifically, reduced total sleep time, lower sleep efficiency, greater WASO, longer sleep onset latency, long REM onset latency, reduced REM sleep and greater N1 sleep were found in MCI participants compared to healthy older adults. Following this meta-analysis, a study by D'Atri and colleagues (2021) compared 50 healthy individuals, 50 MCI and 50 AD participants and found those with MCI and AD had reduced SWS and longer sleep latency compared to healthy individuals (D'Atri et al., 2021). Whilst slightly differing to the results of the meta-analysis by D'Rozario and colleagues, no group differences were identified in total sleep time, sleep efficiency, WASO, REM onset latency or time spent in REM. However, importantly, this study concluded that

beyond reduced time to fall asleep and reduced SWS, architecture remained preserved in clinical populations, compared to the significant EEG abnormalities observed in cognitively impaired older adults (D'Atri et al., 2021), warranting further examination of sleep microarchitecture and its cognitive and behavioural correlates. Finally, greater oxygen desaturation index (ODI) but not apnoea hypopnea index (AHI) scores have been found in MCI compared to cognitively unimpaired older adults, as well as greater severity of hypoxemia in MCI compared to controls (D'Rozario et al., 2020). Overall, prevalence of OSA in MCI is greater as measured by polysomnography (Kim et al., 2011; Wilson et al., 2014). While studies remain limited and varied with respect to diagnostic methods used to diagnose OSA (Mubashir et al., 2019), the OSA literature suggests that in both younger and older samples, the sleep fragmentation and hypoxemia that occur with OSA may be detrimental to brain health, as well as to memory (Cross et al., 2018; Lal et al., 2022). While there is a general dearth of literature examining the effects of OSA on overnight memory consolidation, some data in typical middle-aged OSA samples and MCI samples (Lam et al., 2021) suggest that OSA may well impede consolidation of the memory trace.

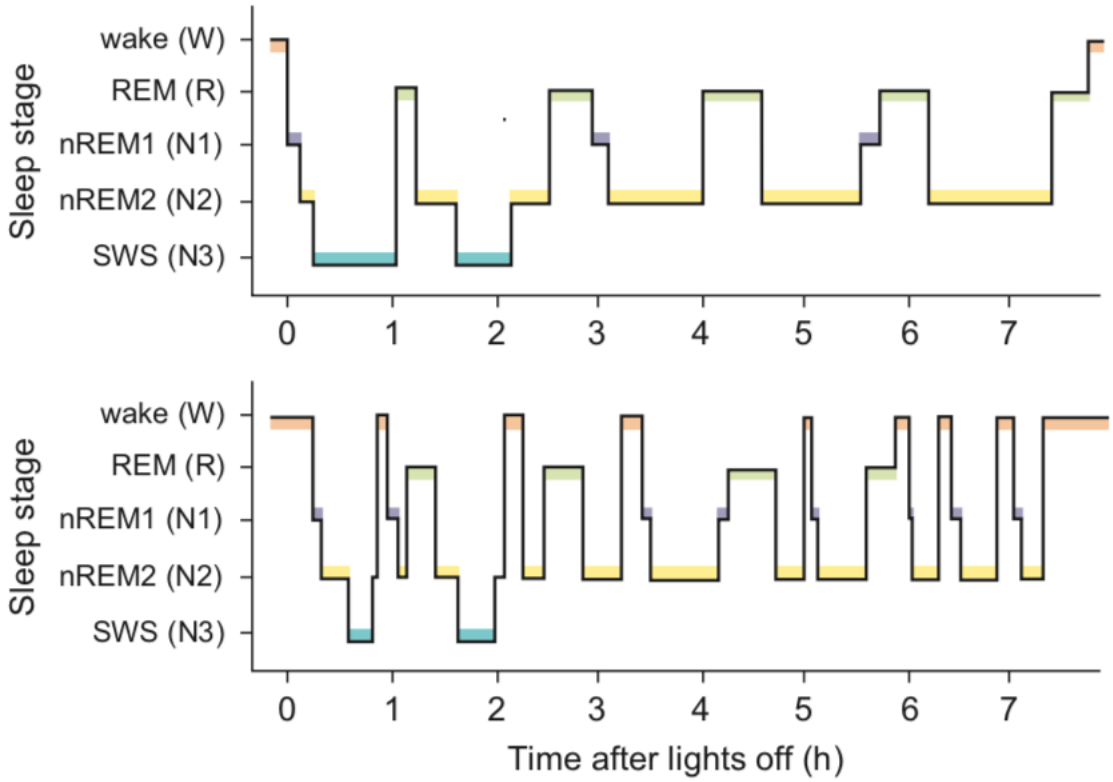


Figure 1.7. Hypnogram for younger adults (top panel) and older adults (bottom panel) illustrating the timing and transitions of slepe stages across an overnight sleep bout. REM = rapid eye movement, nREM = non-rapid eye movement, nREM2 = stage 2 NREM sleep, SWS = slow wave sleep. Image retrieved from Pace-Schott and Spencer (2011).

1.2.3. Microarchitecture changes in MCI

Less understood in the sleep and ageing research are the changes in sleep microarchitecture, in particular in MCI and its subtypes (Table 1.3). Converging studies have indicated that in healthy ageing, decreases are observed in SWA in frontal regions (Mander et al., 2013; Munch et al., 2004; Robillard et al., 2010; Varga et al., 2016), where they are maximal (Massimini et al., 2004); decrements that appear to begin from middle age (Carrier et al., 2011). Whilst most studies have utilised limited single sensor channels (6 – 19 channels), one study (Sprecher et al., 2016) utilised a 256-channel **high-density EEG (hdEEG)**, which offers superior temporal and spatial resolution. In this study of 92 participants aged 18-65 years, diminished global SWA was associated with greater age, similarly for reduced frontal sigma and theta, however these latter brain waves were not globally reduced as indicated for SWA. Reduced frontal fast but not slow spindles were also indicated with greater age, conversely, spindles in the 12-15 Hz range were shown to be preserved in the centro-parietal region (Sprecher et al., 2016). The use of hdEEG was able to highlight regional specificity of SWA and theta, and similarly for spindles during NREM that have previously shown to be topographically heterogenous (Zeitlhofer et al., 1997). Therefore, the use of hdEEG is particularly relevant in enriching the spatial and temporal resolution to better inform where EEG abnormalities occur.

Whilst changes in sleep neurophysiology are evident in healthy ageing, understanding how they change in MCI is vital in advancing our understanding of the neuroscience of sleep and its inter-relationship with alterations in relation to key cognitive and behavioural phenomena, structural and functional brain changes, and neurodegenerative disease more generally. Importantly, this information will inform whether sleep microarchitecture changes occur prior to cognitive changes, whether sleep disturbance is an early marker of neurodegeneration, and in turn inform potential targets for new interventions. In addition, the examination of such changes in the various MCI subtypes will reveal whether some clinical subgroups are more prone to sleep abnormalities, which could help clinical screening initiatives.

From the limited studies examining sleep microarchitecture in MCI (Table 1.3), reduced frontal SWA and theta during NREM appear to be reduced in amnestic MCI (D'Atri et al., 2021; Westerberg et al., 2012) (Table 1.3). However, there are some inconsistencies regarding spindles with one study showing reduced frontal (but not parietal) fast spindles in aMCI compared to controls (n = 24) (Westerberg et al., 2012), and another study with a larger sample (n = 45) showing the opposite findings (Gorgoni et al., 2016). Both studies however indicated no group differences in slow spindles. When comparing spindles between aMCI and AD individuals, a similar reduction is observed in fast spindles when compared to healthy controls (Gorgoni et al., 2016). These findings are in line with a recent study

indicating sigma EEG power was reduced in the posterior but not in the frontal regions in those with MCI and AD compared to controls (D'Atri et al., 2021). Whilst not a primary outcome of the study, Lam and colleagues identified no group differences in central NREM SO, SWA or spindles (slow or fast) (Lam et al., 2021). These converging studies highlight the role of NREM EEG such as SWA, theta and spindles, with strong evidence pointing to the relevance of fast spindles in distinguishing impaired and unimpaired older adults, however their topographical distribution remains unclear. Evidence also points to reduced K-complexes, being a stronger discriminant of AD and controls in comparison to SWA (0.6 – 1 Hz) (De Gennaro et al., 2017). Participants with AD indicate more than a 40% reduction in K-complex density in frontal regions, whereas in the same region, no significant group differences were identified in NREM SWA. Finally, in addition to neurophysiology changes in NREM in MCI, early studies have identified increased slowing (delta+theta/alpha+beta) during REM in early to moderate stages of AD (Petit et al., 1993). In more recent studies comparing aMCI, naMCI and controls, greater slowing was found in aMCI compared to naMCI and controls (Brayet et al., 2016), and as well as in AD compared to MCI and controls (D'Atri et al., 2021).

In summary, the literature above suggests that slow waves and spindles during NREM are reduced in both healthy ageing and MCI, and slowing in REM is greater in MCI. A gap in the literature remains regarding the topographical distribution and the regional specificity of these changes in MCI and their subtypes. Further work examining MCI using consistent metrics, and the utilisation of hdEEG to identify local abnormalities, are still required to understand sleep microarchitecture differences in older clinical samples. In addition to characterising how sleep neurophysiology changes, it is important to consider the impact of such changes on key functional outcomes such as daily functioning and cognition, and in particular how such changes might be linked to the key overnight neurophysiological processes that are pivotal to the consolidation of memory. Poor memory is a key feature of MCI, and a major cause of concern for older adults, having a pivotal impact on psychological wellbeing, workforce participation and in disability and societal engagement (Krueger et al., 2009; Silvaggi et al., 2020).

Table 1.3. Group differences in sleep microarchitecture in mild cognitive impairment.

Author, Year	Sample	Key findings of group differences in EEG
Westerberg et al., 2012	16 Controls 8 aMCI	↓ NREM frontal SWA & theta (N2 & N3 respectively) in aMCI cf Controls ↓ N2 frontal fast spindles but not slow spindles in frontal but not parietal regions in aMCI cf Controls ↓ REM frontal theta but not SWA in aMCI cf. Controls No group differences in alpha or sigma power
Gorgoni et al., 2016	15 Controls 15 aMCI 15 AD	↓ NREM parietal whole range and fast spindle density, but not slow spindles, in aMCI & AD cf. Controls. No differences in aMCI cf AD No group differences in frontal spindles.
Brayet et al., 2016	32 Controls 10 naMCI 22 aMCI	↑ REM frontal slowing (delta+theta/alpha+sigma+beta) in aMCI cf. naMCI & Controls. No group differences identified between aMCI and naMCI ↑ Wakefulness frontal slowing in aMCI, however greater in REM
D'Atri et al., 2021	50 Controls 50 MCI 50 AD	↓ NREM alpha in posterior temporo-parieto-occipital sites in AD cf MCI & Controls ↓ NREM occipital sigma in AD cf MCI & Controls ↓ NREM temporo-occipital sigma in MCI cf Controls ↑ REM fronto-temporal SWA in AD & MCI cf Controls, but differences between AD & MCI ↓ REM occipital-temporal beta in AD cf MCI & Controls
Lam et al., 2021	20 Controls 43 MCI	No group differences in absolute NREM SO and SWA, and NREM total spindle density, slow and fast spindle density, and spindle duration.

Note. aMCI = amnestic mild cognitive impairment, naMCI = non-amnestic mild cognitive impairment, AD = Alzheimer's disease, NREM = non-rapid eye movement, SO = slow oscillations, SWA = slow wave activity.

1.3. Overnight Memory Consolidation

The ability to stabilise and consolidate newly acquired information during the day has been partially attributed to the quality of sleep. Memory consolidation of newly learnt information has been described and analysed on a cellular/synaptic level called '*synaptic consolidation'* or on a brain systems level called '*systems consolidation'* (Dudai et al., 2015; Dudai & Morris, 2000). Both describe the post-encoding reorganisation and transformation of information into long-term storage. The process termed '***sleep dependent memory consolidation'*** **(SDMC)** refers to the notion by which information is transferred from short-term to long-term storage, dependent upon several key macro- and microarchitecture features during distinct sleep stages. Whilst this memory consolidation process is hypothesised to be automatic and outside of conscious awareness, several contributing factors are involved in influencing the strength of the memory trace. One of these contributing factors include the memory domain that it tested, broadly categorised into declarative *vs.* non-declarative memory.

One of the earliest studies supporting the notion that sleep is required for optimal memory consolidation, was conducted by Jenkins and Dallenbach (Jenkins & Dallenbach, 1924). That study indicated that sleep was able to protect memories from the natural memory decay that occurs during wakefulness (Jenkins & Dallenbach, 1924). One method that has provided evidence for the benefit of sleep for memory consolidation are sleep restriction paradigms that compare participants who are asked to stay awake/sleep deprived, compared to participants who are given a sleep opportunity (Drummond et al., 2001; Ferrara et al., 2006; Mander et al., 2011). Sleep deprivation studies have provided insights into the neurobiological underpinnings of the link between sleep and memory. Event related function MRI (fMRI) has identified deficits in the bilateral posterior hippocampal regions in those who are sleep deprived compared to those who have slept (Yoo et al., 2007). Sleep dependent memory consolidation has commonly be measured by asking participants to learn new information prior to their evening sleep time, and then re-testing participant's recall of that same material in the morning (i.e. after wake). Daytime nap studies utilising the same methodology of pre-sleep encoding and post-sleep memory recall have provided significant scientific advancement of the sleep, learning and memory consolidation relationship. However, given the pronounced alterations that occur in both sleep and circadian rhythms with age, in particular those at greater risk of or in the early stages of dementia, napping paradigms may not be as robust in uncoupling this relationship.

Research in younger adults has suggested that SDMC favours weaker memories (Bauml et al., 2014; Roediger & Butler, 2011). When using a Word-Pair Associates Task (WPT), a common test used in SDMC studies, greater sleep-related consolidation has been shown for words with low compared to high semantic relatedness (Lo et al., 2014; Payne et al., 2012). In a meta-analysis of younger adults (n = 640) and older adults (n = 529) comparing sleep-based memory consolidation, results indicated a benefit of sleep for memory in younger, but not older adults (Gui et al., 2017). Impairment was specifically indicated for declarative memory consolidation in older adults, whereas procedural memory remained relatively intact. Further to this, when retrieval demands are increased in order to mitigate ceilings effects, SDMC also appears to benefit strong memories (Petzka et al., 2021). However, the same results have not extended to cognitively or MCI participants (Lam et al., 2021). These converging studies suggest that not all memories are consolidated in the same manner or that findings may differ in healthy compared to clinical groups. This may be in part due to the strength of the memories as suggested, the memory domain, or the integrity of sleep neurophysiology and/or brain structure.

As highlighted by several reviews on cognition-sleep in ageing, the literature in declarative memory SDMC in older adults has been inconsistent (Scullin, 2013; Scullin & Bliwise, 2015; Stickgold & Walker, 2007). It is therefore unclear as to the exact role of sleep in memory consolidation with advancement of age and in particular, in MCI and its subtypes. Several challenges have been raised in the complex interpretation of studies seeking to understand the relationship between sleep, memory and ageing. One of these challenges include whether EEG and memory correlations are sleep specific, or rather reflective of trait-based EEG correlations that could also be observed during wake-states (Scullin & Bliwise, 2015; Vlahou et al., 2014). An overall caution is required when interpreting sleep EEG associations with memory consolidation, in particularly in MCI where both sleep and cognitive function is significantly impaired. Therefore, this thesis will utilise the term ***'overnight memory consolidation'*** **(OMC).** As studies are significantly limited in MCI, it remains unclear as to whether sleep is able to confer benefits to memory in the same manner that has been evidenced in younger adults.

1.3.1. Function of non-rapid eye movement sleep for declarative memory

Neural signatures postulated to be crucial for declarative memory consolidation are slow oscillations (SO), SWA, and spindles during NREM (Clemens et al., 2005, 2006; Schabus et al., 2004; Tamminen et al., 2013). The hippocampal to neocortex transfer model, or active systems consolidation model, has been used to explain how declarative memory is consolidated overnight (Molle & Born, 2011;

Steriade, 2006). This model suggests that events experienced during wake are encoded in parallel in neocortical networks and the hippocampus. Slow oscillations generated in the neocortex, not only synchronise neuronal activity in the neocortex, but also drive and synchronise hippocampal fast wave ripples and thalamocortical spindles (Molle & Born, 2011) (Figure 1.8). During the synchronisation of sharp wave ripples with spindles, events are created between these two oscillations such that reactivation memory information becomes nested into the spindle troughs (Molle & Born, 2011). The reactivation of hippocampal-dependent memories during SWS are transferred to the neocortex for long-term storage (Rasch & Born, 2013).

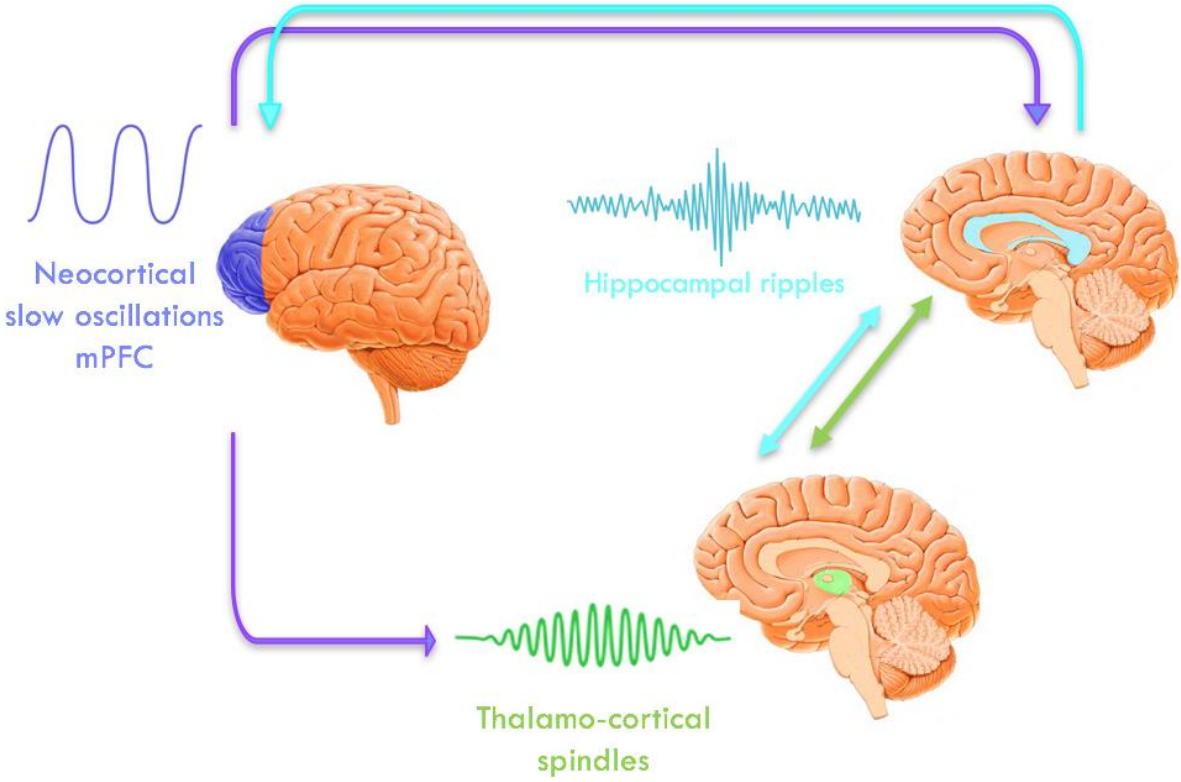


Figure 1.8. Hippocampus to neocortex model that describes the transfer of declarative information from short-term to long-term storage. During NREM sleep, slow oscillations (< 1 Hz) in the medial prefrontal cortex drive and synchronise spindles within the thalamus and with hippocampal ripples. A reactivation of information learnt during the day occur within the hippocampus that are nested within these ripples. Slow oscillations work to bind together the content of ripples and spindles, supporting an effective transfer of information from the hippocampus to the neocortex (Molle & Born, 2011).

1.3.2. Overnight declarative memory consolidation in healthy ageing and MCI

A significant body of research has examined OMC in healthy older compared to younger adults (Aly & Moscovitch, 2010; Cherdieu et al., 2014; Mander et al., 2014; Mander et al., 2013; Muehlroth,

Sander, et al., 2020) indicating decrements in OMC with advance age (Aly & Moscovitch, 2010; Leong et al., 2021; Mander et al., 2013; Scullin et al., 2019; Varga et al., 2016). Studies suggest that a decline in declarative memory consolidation begins from midlife, and that changes in SWS may underpin such changes (Backhaus et al., 2007). A WPT has been commonly used to assess for declarative memory consolidation, particularly in the non-verbal domain. Mixed findings in OMC and its sleep correlates may partially reflect variations in the methodological design and the nature of the task administered (Muehlroth, Rasch, et al., 2020).

Features of NREM sleep such as SO, SWA and spindles have shown to be relevant for OMC in healthy younger and older adults, however, experimental manipulation of SWA for memory consolidation has yielded inconsistent findings in older adults (Muehlroth, Rasch, et al., 2020). As younger adults show a similar benefit of sleep irrespective of sleep time (e.g. nap *vs.* full night's sleep) (Hokett et al., 2021), the optimal length of sleep required for memory performance in older adults is not clear. More recent yet preliminary evidence has highlighted that the coupling between SO and spindles may be relevant, indicating greater SO-spindle coupling with better OMC in both younger and older adults (Helfrich et al., 2018; Muehlroth et al., 2019).

The preservation of SN memory with advanced age is paramount given its relevance for functional capacity, quality of life independent living in older adults. Overnight consolidation of SN information has been examined in younger adults (Ferrara et al., 2006; Ferrara et al., 2008; Peigneux et al., 2004; Varga et al., 2014) and recently in a napping paradigm (Bastian et al., 2022; Samanta et al., 2021). Only one study has compared SN OMC in younger compared to older adults (Varga et al., 2016), and older adults with and without OSA (Mullins et al., 2021), both using a virtual maze task measuring reaction time of maze completion. Allocentric SN has been examined in a nap paradigm comparing younger adults to rodents (Bastian et al., 2022), indicating preliminary evidence for the role of sleep in hippocampal-dependent SN OMC. However, allocentric SN OMC has not yet been examined in clinical MCI samples.

To date, two studies in MCI (Lam et al., 2021; Westerberg et al., 2012) and two studies in AD (Hot et al., 2011; Rauchs et al., 2008) have examined declarative OMC (Table 1.4). Individuals with MCI show reduced OMC on a WPT (Lam et al., 2021; Westerberg et al., 2012), and show negative associations with spindles (Lam 2021; Westerberg 2021). Similarly, individuals with AD show reduced OMC compared to healthy older adults on a 15-word list task, and negative associations with NREM spindles (Rauchs et al., 2008) and theta in AD participants (Hot et al., 2011). Several questions

remain unclear as to the relationship between sleep EEG and OMC in ageing. Of significance are the potential differences in associations between sleep EEG and OMC in MCI subtypes. Given the differences in brain structure between amnestic and non-amnestic MCI subtypes, it can be hypothesised that potentially; 1) aMCI subtype may have greater decrements in spindles given its link to hippocampus via fast-wave ripples, and 2) naMCI subtype may have greater SWA impairment due to frontal lobe atrophy. Other key questions include the regional specificity of spindles for declarative memory in ageing, and whether these findings extend to other declarative memory tasks, specifically those in the non-verbal domain.

Table 1.4. Overnight declarative memory consolidation in mild cognitive impairment and neurodegenerative disorders

Author, Yr	Sample	OMC Task	OMC group differences Associations with sleep and MRI
Rauchs et al., 2008	14 YA 14 HOA 14 AD	15 words (YA- 3 trials; HOA & AD- 5 trials) 12-item story recall	Ceiling effects in YA and HOA ↓ rate of forgetting (%) in AD on both tasks ↑ NREM fast spindle intensity = ↑ immediate story recall in AD
Hot et al. 2011	14 HOA 14 mild-moderate AD	15 words	↓ rate of forgetting (%) in AD ↑ SWS fast theta = ↑ recall in AD* *associations with HOA not examined
Westerberg et al., 2012	16 HOA 8 aMCI (5 for EEG correlations)	44 word-pair associates task Face-fact recognition task Object priming task	↑ NREM SWA + theta = ↑ OMC in Controls ↑ NREM & REM WWA + theta = ↑ OMC combined groups
Lam et al., 2021	20 HOA 43 MCI	32 word-pair associates task	↓ NREM spindle duration = ↓ OMC in MCI ↓ CA1 and CA3 volume = ↓ OMC in MCI ↑ AHI = ↓ OMC in Controls ↓ daytime episodic memory = ↓ OMC in MCI

Note. Association with sleep neurophysiology and structural brain integrity. YA = younger adults, HOA = healthy older adults, MCI = mild cognitive impairment, aMCI = amnestic mild cognitive impairment, AD = Alzheimer's disease. NREM = non-rapid eye movement, AHI = apnoea hypopnea index, SWS = slow wave sleep, REM = rapid eye movement.

1.3.3. Potential mediating role of brain structures between sleep and OMC

One possibility for the mixed findings in OMC in ageing and its associations with sleep is that there is a potential functional disconnection between sleep and memory consolidation systems in ageing (Scullin, 2013). The weakening of this relationship may be due to the emergence of brain atrophy, diminishing the function of sleep in the memory consolidation process in older adults. Few studies have used various MRI modalities to understand the bidirectional nature of sleep and brain integrity and its impact on memory.

Available evidence points to a direct relationship between reduced mPFC thickness with SWA (Dube et al., 2015), SO-spindle coupling (Helfrich et al., 2018) and OMC (Mander et al., 2013) in healthy older adults. One possible pathway as highlighted in the study by Mander and colleagues (2013) is that increased age is associated with greater mPFC atrophy, which in turn causes SWA reduction and consequently, impaired OMC (Mander et al., 2013) (Figure 1.9). In partially similar findings, mPFC was found to be associated with SWA in healthy younger and older adults, but not with SN OMC (Varga et al., 2016). Greater Aβ pathology in the mPFC has also shown associations with reduced frontal SWA in healthy older adults (Mander et al., 2015). The disruption in SWA suggests that Aβ may interfere with OMC via disruption of frontal NREM SWA. In healthy older adults, using hdEEG, tau pathology and fast spindles were associated in the fronto-central derivations, and this cluster of electrodes were significantly associated with OMC using a WPT (Mander et al., 2022). Only one study has examined OMC and structural brain integrity in MCI which found that reduced volumes in hippocampal subfields CA1 and CA3 were associated with reduced OMC in MCI participants (Lam et al., 2021). However, no associations have been found between OMC and mPFC thickness in either the MCI or control group (Lam et al., 2021), a finding which is aligned with previous studies in healthy older adults (Varga et al., 2016).

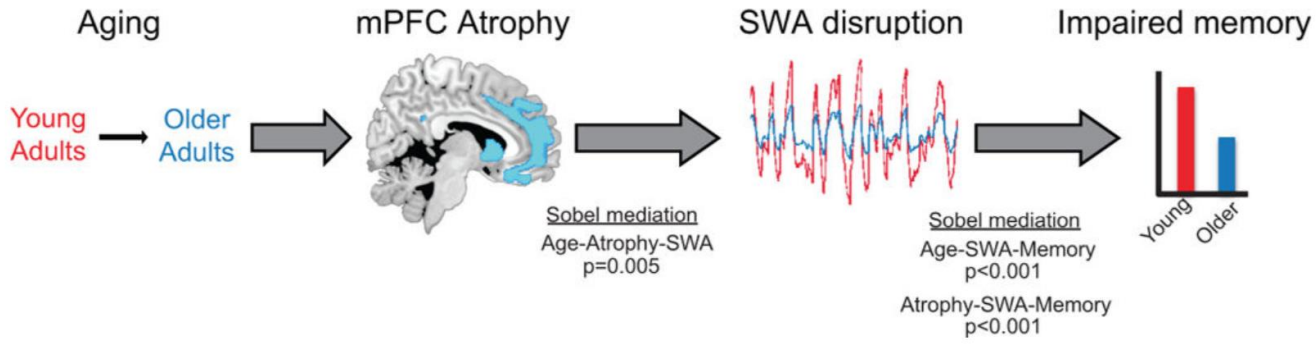


Figure 1.9. Link between ageing, brain atrophy, slow wave activity and overnight memory consolidation. Image retrieved from Mander at al., (2013).

1.4. Limitations in Overnight Memory Consolidation Research to Date

Whilst there has been significant advancement in the understanding of OMC changes with ageing, significant limitations still remain:

- First, despite the heterogeneity in cognitive function in ageing, studies are notably limited in MCI and those 'at-risk' of dementia, and as described, OMC studies in ageing have largely compared older with younger samples. Even amongst these studies, cognitive phenotyping using neuropsychological testing remains a significant limitation. As memory consolidation is dependent upon an overall cognitive functioning ability, thorough cognitive phenotyping is paramount.
- Second, given the long-delay in memory recall, established tasks sensitive to capture subtle differences across differing at-risk profiles within the ageing and MCI population are limited. This is of significance given the time-sensitivity of the OMC paradigm as tasks are administered in the evening before sleep. Furthermore, sufficient encoding time is required for this population in particular when testing after a long-delay (~12 hours).
- Third, memory domains examined in ageing and notably in those with MCI, have been limited to verbal episodic memory. Limited studies have examined visuospatial OMC in ageing, no studies have examined allocentric SN OMC in ageing, and neither memory domain has been examined in MCI.
- Fourth, whilst few studies have included multi-modal techniques to understand the neurobiological underpinnings associated with OMC, such as sleep neurophysiology and structural and functional neuroimaging, these again, remain limited in older and MCI samples. The use of multi-modal techniques comparing cognitively intact *vs.* impaired older adults will allow a better understanding of key brain regions and functions involved in the sleep-memory relationship.
- Fifth, as most studies have used single-sensor channels to examine associations between sleep neurophysiology with OMC, the regional specificity of sleep-OMC associations remains unclear. Therefore, the use of hdEEG, which allows for optimal spatial and temporal resolution, is required in order to understand the topographic distribution of this relationship.
- Finally, sleep neurophysiology studies have overall been limited in MCI samples, notwithstanding the few emerging studies that have examined sleep microarchitecture. However, gaps still remain as to which cognitive profiles of MCI participants show the greatest decrements, and how these in turn relate to overnight consolidation outcomes.

1.5. Rationale for Thesis and Aims

In order to understand whether sleep is indeed beneficial for memory consolidation in older adults with and without cognitive impairment, robust methodological designs must be utilised that include testing times close to sleep-wake times. Furthermore, there is a need to design tasks that can be utilised for an MCI population. Tasks measuring OMC need to be designed and assessed across varied memory domains in order to understand whether they are consolidated differently and if they differ across MCI subtypes. This may in turn help inform clinical practice in identifying sleep as a protective factor for memory in certain ageing profiles. Identifying sleep microarchitecture features associated with OMC will in turn hopefully inform the development of targeted treatments for sleep and memory and ascertain whether these need to be tailored for cognitively healthy *vs.* MCI populations. Examining OMC associations with both neurophysiology and structural integrity of key brain regions for sleep and memory will help advance the scientific understanding of the pathways and processes involved in OMC. Measuring both sleep neurophysiology and structural brain integrity will help to better understand whether OMC is impacted by sleep neurophysiology, or largely by underlying brain degeneration. It has been suggested that the changes in memory consolidation in ageing may in fact be a combination of changes in the neuroanatomy of cognitive systems, alterations in sleep spindle and slow wave neurophysiology, changes in encoding abilities, or a combination of these sleep microarchitecture, behavioural and neurological mechanisms (Muehlroth, Rasch, et al., 2020). Therefore, as a first step, studies employed capturing overall cognitive status, sleep neurophysiology, and structural brain integrity are necessary in untangling the various components involved in OMC in ageing.

As studies have been limited in examining OMC associations with sleep neurophysiology in MCI, the rationale for the examination of specific NREM EEG features in this thesis is based on prior literature with younger adults that have found a positive benefit of NREM slow waves and spindles for declarative memory consolidation, as well as the theoretical model 'hippocampus to neocortex transfer model' used to describe the consolidation of declarative information (figure 1.8). The objective of this thesis is to build on two key studies in MCI examining OMC and NREM slow waves and spindles (Lam et al., 2021; Westerberg et al., 2012). The empirical chapters aim to replicate these key neurophysiology features examined, as well as the structural regions examined (hippocampal subfields and mPFC) in association with OMC. In addition, this empirical chapters of this thesis also extend upon these studies by examining MCI subtypes and assessing spatial memory. As described earlier,

given the structural differences between aMCI and naMCI, there is a need to identify whether these differences differentially impact OMC and these key NREM neurophysiology features.

In order to understand sleep neurophysiology and the associated brain regions relevant for OMC in cognitively intact and MCI samples, it is important to first clarify to what extent sleep benefits memory in ageing, and how this differs in an 'at-risk' population and their cognitive subtypes. While sleep neurophysiology and structural integrity changes have been observed in MCI, how they impact the overnight consolidation of newly learnt information is unclear, in particular for visuospatial and allocentric SN memory domains. Of significance, the regional specificity of sleep neurophysiology and OMC decrements has not yet been examined in MCI and its subtypes.

The overall aims of this thesis are to:

1. Identify if there are differences in verbal episodic, visuospatial and spatial navigation OMC between cognitively intact Controls and older people with clinical MCI (and its subtypes; aMCI, naMCI) (**Chapter 3 and 4**);
2. Characterise the associations between OMC and NREM slow waves (slow oscillations and slow wave activity) and spindles (slow and fast) (**Chapter 3, 4 and 5**); and,
3. Investigate the associations between OMC and medial prefrontal cortex thickness and medial temporal lobe volumes (hippocampal CA1 and dentate gyrus, and entorhinal cortex) (**Chapter 4**).

Note: some information in the introduction and discussion within each of the chapters may be repetitive as **Chapters 3, 4 and 5** have been prepared for publication and are thus presented to represent as close as possible, the submitted manuscript.

Chapter 2 – Overall Methodology

The section below describes the general methodology used in this thesis including the medical and neuropsychological assessment, polysomnography, and neuroimaging. In addition, each empirical study details study-specific detailed methodology.

2.1. Healthy Brain Ageing Clinic

Participants

All participants described in this thesis attended the Healthy Brain Ageing Clinic at the Brain and Mind Centre, University of Sydney. The clinic specialises in the early assessment and intervention of those 'at-risk' of dementia. Participants were health seeking with concerns about their mood and cognitive function and required a general practitioner or specialist referral.

After referral, participants underwent telephone screening and if eligible, they were sent a participant information sheet, self-report forms and booked in for a three-hour visit. On the day of the clinic visit, all participants completed a medical, mood and neuropsychological assessment, and were then offered a cerebral magnetic resonance imaging (MRI) and sleep polysomnography (PSG) study. Participants had their MRI and PSG assessment within four weeks of their neuropsychological assessment.

Eligibility criteria for referral to the HBA clinic:

Inclusion criteria:

- Aged 50-90 years;
- Fluent in English; and,
- Referral from medical practitioner (general practitioner, neurologist, psychiatrist).

Exclusion criteria:

- History or current neurological condition (e.g. Parkinson's disease, epilepsy);
- History of stroke or transient ischemic attack;
- History or current severe psychiatric disorder (e.g. bipolar, psychosis, schizophrenia, ADHD);
- History of head injury with loss of consciousness $\geq$ 30 minutes;
- History of or current substance abuse or dependence;
- Mini-Mental State Examination (MMSE) $\leq$ 24; and/or
- Intellectual disability.

2.1.1 Medical assessment

A neurologist or geriatrician conducted a semi-structured interview. A comprehensive medical history was gathered, which probed for diagnosed conditions (e.g. vascular, respiratory, gastrointestinal tract, liver, renal, neurological, metabolic, cancer and thyroid disorders), risk factors for cognitive decline (e.g. hypertension, stroke/transient ischaemic attacks, alcohol consumption, smoking history, sleep disorders), current medications, and familial history of neurodegenerative disorders, psychiatric disorders and other serious medical illness. Medical burden was recorded using the Cumulative Illness Rating Scale – Geriatric Version (Miller et al., 1992) and daily functioning was assessed using the Activities of Daily Living Index (Hindmarch et al., 1998).

2.1.2 Mood assessment

A research psychologist conducted a semi-structured interview to record participant's current and previous psychological status, as well as sleep status. Lifetime and current Major Depression was assessed using the Structured Clinical Interview for Psychiatric Disorders (DSM-IV) (First, 1997). The 17-item Hamilton Depression Rating Scale (Hamilton, 1960) was also used to rate depression severity. Also, as noted below, participants self-rated their mood using the Geriatric Depression Scale 15-item version (Yesavage & Sheikh, 1986b).

2.1.3 Neuropsychological assessment

A comprehensive battery of standardised neuropsychological tests was administered by a clinical neuropsychologist. This included a test of global cognition using the MMSE, pre-morbid intelligence quotient (IQ) using the Wechsler Test of Adult Reading (Wechsler, 2001), executive function, processing speed, attention, language, visuospatial learning and memory, and verbal learning and memory. Scores on tests were age and education adjusted using appropriate normative data where relevant. This is summarised in Table 2.1 below.

Table 2.2. Summary of neuropsychological tests used at the Healthy Brain Ageing Clinic.

Cognitive domain	Neuropsychological test	Normative data
Verbal learning and memory	Rey Auditory Verbal Learning Test (Lezak et al., 2012)	(Senior, 1999)
	Wechsler Memory Scale III – Logical Memory subscale (Wechsler, 1997)	(Wechsler, 1997)

Visuospatial learning and memory	Rey-Osterrieth Complex Figure Test (Rey, 1941)	(Meyers & Meyers, 1995)
Executive function	Trail Making Test – Part B (Reitan & Wolfson, 1985)	(Tombaugh, 2004)
	Delis Kaplan Executive Functioning System Colour-Word Interference Test: Inhibition, Inhibition/Switching (Delis et al., 2001)	(Delis et al., 2001)
Processing speed	Trial Making Test – Part A (Reitan & Wolfson, 1985)	(Tombaugh, 2004)
	Delis Kaplan Executive Functioning System Colour-Word Interference Test: Word reading (Delis et al., 2001)	(Delis et al., 2001)
Language	Boston Naming Test (Kaplan et al., 2001)	(Lansing et al., 1999)
	Controlled Oral Word Association Test: Phonemic (letters F, A and S) and semantic (animal) fluency (Benton et al., 1994)	(Tombaugh et al., 1999)
Attention	Wechsler Memory Scale II – Digit Span subtest (Wechsler, 1997)	(Wechsler, 1997)

2.1.4 MCI classification

Classification of MCI was determined by a consensus meeting by a geriatrician or neurologist and two clinical neuropsychologists using Winblad's Criteria (Winblad et al., 2004). Criteria used in order to determine clinical classification include the following:

1) Participant does not meet criteria for dementia,

2) Cognitive decline evidenced by objective neuropsychological assessment,

3) Subjective cognitive decline evidenced by participant or informant report,

4) Activities of daily living and functioning are preserved or minimally impaired.

Mild Cognitive Impairment is determined by a score on any neuropsychological test that is 1.5 standard deviations below the participant's estimated pre-morbid functioning but is always considered in the context of the clinical history and imaging results when available. The classification of MCI is further categorised as amnestic (aMCI) or non-amnestic (naMC); the former indicates an impairment in memory, and the latter an impairment to a non-memory domain (see Figure 1.2, page 16). Impairment on only one task was classified as single-domain (sMCI), and impairment on two or more was classified as multiple-domain (mMCI).

2.2. Self-report questionnaires

Within the empirical studies within this thesis, sleep quality, insomnia severity and depressive symptoms were measured using self-reported questionnaires, including:

- *Geriatric Depression Scale (GDS-15)*: The 15-item GDS-15 (Yesavage & Sheikh, 1986b) is a measure of current depressive symptoms specifically for older adults. Scores range from 0 to 15, with higher scores indicating greater depression symptoms. Scores > 5 are suggestive of depression. The test-retest reliability for GDS-15 is high (0.85 measured by Cronbach's alpha coefficient) based on a review of 338 studies (Kieffer & Reese, 2002).
- *Geriatric Depression Scale (GDS-30*): The 30-item GDS-30 (Yesavage & Sheikh, 1986b) is a measure of current depressive symptoms specifically for older adults. Scores range from 0 to 15, with higher scores indicating greater depression symptoms. Scores between 10-19 suggest mild depressiveness and between 20-30 suggest severe depressiveness.
- *Pittsburgh Sleep Quality Index (PSQI)*: The PSQI (Buysse et al., 1989) is a measure of sleep quality ranging from 0 to 21. Higher scores on the PSQI indicate poor subjective sleep quality. A cut off score ≥ 5 is used to distinguish good sleepers from poor sleepers. The test-retest reliability of for the PSQI is high (0.87 measured by Cronbach's alpha coefficient) (Backhaus et al., 2002) and has been validated as a measure of insomnia for older adults (Spira et al., 2012)
- *Insomnia Severity Index (ISI)*: The ISI (Bastien et al., 2001) measures symptoms of insomnia. It uses seven questions which are summed to a total score ranging from zero to 28. Score categories include, 0-7 = no clinically significant insomnia, 8-14 = subthreshold insomnia, 15-21 = clinical insomnia (moderate severity), and 22-28 = clinical insomnia (severe). The ISI has shown a strong test-retest reliability (0.91 measured by Cronbach's alpha coefficient) (Morin et al., 2011).

- *Epworth Sleepiness Scale (ESS)*: The ESS (Johns, 1991) is intended to measure daytime sleepiness. Scores ranges from 0 to 24. Numbers within the range of 0-6 = enough sleep, 7-8 = tend to sleepy during the day, 9-15 = very sleepy, and > 16 = dangerously sleepy. The ESS has shown high internal consistency of responses (0.90 as measured by Cronbach's alpha coefficient) and high test-retest reliability (Pearson correlation *r* from 0.78 to 0.93) (Cho et al., 2011). Furthermore, it has also been validated in older adults (Spira et al., 2012)
- *Karolinska Sleepiness Scale (KSS)*: The KSS (Akerstedt & Gillberg, 1990) is a measure of subjective sleepiness at a particular time during the day. A 9-point scale is used (1 = extremely alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy – but no difficulty remaining awake, 9 = extremely sleepy – fighting sleep). The KSS has shown strong validity and reliability as a measure of sleepiness when measured against EEG and behavioural variables (Kaida et al., 2006a).

2.3. Overnight memory testing, polysomnography, quantitative electroencephalogram and neuroimaging

2.3.1. Overnight memory testing in the sleep laboratory

Memory tests for verbal episodic, visuospatial, and spatial navigation memory consolidation were administered pre- and post-sleep on the night of participant's scheduled sleep PSG at the Brain and Mind Centre (Chapter 3) and Woolcock Institute of Medical Research (Chapters 4 and 5). Two standardised neuropsychological tests were administered in Chapter 3. These included the Rey Auditory Verbal Learning Test (Lezak et al., 2012) which measures verbal episodic memory, and the Rey-Osterrieth Complex Figure Task (Meyers & Meyers, 1995) which measures visuospatial memory. The spatial navigation task, used in Chapter 4 and 5, was developed by the candidate as a human analogue version based on the MWMT (Morris et al., 1982), adapted from studies using the task with rodents. The task was designed to measure primarily allocentric spatial navigation using Unity software. Participants were administered the task 2-3 hours before their scheduled sleep time (pre-sleep), and memory recalled was tested again one-hour after wake (post-sleep). Scores of overnight memory consolidation (OMC) for all tasks was calculated as:

([Post-sleep recall score/pre-sleep recall score]*100)

Upon initial development, the spatial navigation task was administered to ten participants. Based upon the quantitative and qualitative results, several amendments were made. These included:

- An additional familiarisation phase of locating the treasure chest (target item) to help participants familiarisation with the task instructions and keyboard.
- Mountains added in the background behind landmarks in the arena to give more of the perception of moving closer and further away from landmarks in the arena.
- Catchment of the target item which participants need to find is bigger, as initially too small causing floor effects.
- Participant viewpoint when navigating the arena is placed at the same height as the objects in the target items in the arena.

2.3.2. Polysomnography

On the night of their polysomnography participants were asked to abstain from alcohol, abstain from caffeine at least three hours prior to their sleep study, and maintain their usual sleep and wake. All participants were given an eight-hour sleep opportunity. For descriptive purposes, empirical studies report the following measures:

- *Total sleep time (TST):* Calculated as the time spent between sleep onset (first epoch of any sleep stage) and offset (last epoch of any sleep stage), while deducting wake after sleep onset during these two periods (measured in minutes).
- *Sleep onset latency (SOL):* Time difference between lights off and sleep onset (measured in minutes).
- *Rapid-eye movement sleep latency (ROL):* Time difference between lights off and rapid-eye movement sleep onset (measured in minutes).
- *Wake after sleep onset (WASO):* Total number of minutes awake after initial onset of sleep.
- *Sleep efficiency:* The percentage of time asleep in relation to the amount of time in minutes in bed. Calculated by total sleep time/total time in bed. Poor sleep efficiency is considered to be < 85%.
- *Non-rapid eye movement sleep minutes (NREM mins):* Total time spent in non-rapid eye movement sleep calculated by the sum of N1, N2, and N3 stages of sleep (measured in minutes).
- *Slow wave sleep (SWS) %:* Number of minutes spent in slow wave sleep (stage 3 sleep) divided by total sleep time.
- *Rapid-eye movement sleep minutes (REM mins):* Total time spent in rapid-eye movement sleep (measured in minutes).

- *Oxygen desaturation index (ODI):* Number of SpO2 desaturation events per hour.
- *Apnoea hypopnea index (AHI):*Number of apnoeas and hypopneas per hour of sleep. Commonly used to indicate severity of obstructive sleep apnoea (mild = AHI of 5 – 14, moderate = AHI of 15 – 29, severe = AHI of $\geq$ 30).

2.3.3. Power spectral analysis

Chapters 3 and 4 in thesis used Profusion 4 (Compumedics, Melbourne, VIC, Australia). Artefact-free epochs were analysed using a standard fast Fourier transform (FFT) for the following derivations: F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1, and midline regions Fz-M1+M2/2, Cz-M1+M2/2 and Pz-M1+M2/2 derivations. The primary derivations used in this thesis were Fz-M1+M2/2 and Pz-M1+M2/2. Absolute spectral power (μV^2) in delta, theta, alpha, sigma and beta bands was calculated. An automated spindle identification algorithm was used to detect sleep spindle events. The primary spindle metric used in this thesis were slow spindle density (spindle events 11 – 13 Hz per minute of N2 sleep); and, fast spindle density (spindle events 13 – 16 Hz per minute of N2 sleep).

2.3.4. High-density EEG

High-density EEG was used on a subset of participants (Chapter 5). Electrophysiology data were collected with a 256-channel geodesic EEG system with HydroCell Sensor Nets (Electrical Geodesics, Eugene, OR). Artefacts and arousals in the EEG signals were identified by semi-automatic algorithms and then visualised by sleep experts. The frequency resolution of EEG was 0.25 Hz. In order to increase signal-to-noise ratio, analyses were restricted to 164 electrodes and EEG spectral power density (uV^2/Hz) was quantified between 0.5 Hz and 45 Hz and frequency ranges of interest were computed during NREM (N2 + N3). A threshold-free cluster enhancement (TFCE) technique with permutation-based statistics was used to measure all NREM EEG variables of interest. This takes the data for the selected frequency range of each channel during the specific timepoint while controlling for multiple comparisons. The permutation approach determines the p-value by comparing the original statistic to a data-driven distribution (Smith & Nichols, 2009).

2.3.5. Neuroimaging

All MRI scans were performed at the Brain and Mind Centre using a T-Tesla General Electric (GE) Discovery MR750 scanner (GE Medical Systems, Milwuakee, WI) with an 8-channel or 32-channel phased array head coil. The following scans were obtained:

- Sagittal 3D T1-weighted BRAVO Spoiled Gradient-Recalled (SPGR)

- T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR)
- T2-weighted high-resolution hippocampus (subset of participants)
- Diffusion weighted image (DWI)
- Resting-state functional MRI (rsfMRI)

For the purposes of this thesis we used T1-weighted MPRAGE to measure the medial prefrontal cortex thickness, and T2-weighted high-resolution hippocampal images to measure hippocampal subfields CA1 and dentate gyrus, and the entorhinal cortex. Diffusion weighted image and resting-state functional MRI were not used in this thesis.

Chapter	Memory, Sleep and MRI methods used
1	▪ Overnight memory consolidation task verbal episodic (RAVLT) and visuospatial (ROCFT) ▪ Routine polysomnography ▪ Power spectral analysis and spindle algorithm at Fz and Pz channels
2	▪ Overnight memory consolidation task: Clinical allocentric spatial navigation task (CASNAT) ▪ Routine polysomnography ▪ Power spectral analysis and spindle algorithm at Fz and Pz channels ▪ T1 structural neuroimaging of medial prefrontal cortex using Freesurfer v6 ▪ T2 high resolution structural neuroimaging of entorhinal cortex and hippocampal subfields using ASHS
3	▪ Overnight memory consolidation task: CASNAT ▪ High-density EEG (hdEEG) ▪ T1 structural neuroimaging of medial prefrontal cortex using Freesurfer v6 ▪ T2 high resolution structural neuroimaging of entorhinal cortex and hippocampal subfields using ASHS

Table 2.2. Summary of methodology used in **Chapter 3**, **4** and **5**. Details of each methodology is further outlined within referenced chapters.

Chapter 3

Sleep spindles and slow wave activity differentially correlate with overnight verbal episodic and visuospatial memory consolidation in older adults with and without mild cognitive impairment

3.1. ABSTRACT

Objective: This study aimed to examine overnight memory consolidation (OMC) in older adults with and without mild cognitive impairment (MCI) and across the MCI subtypes to determine how OMC relates to slow wave activity (SWA) and spindles.

Method: Cognitively intact older adults (Controls, n= 25) and those with MCI (n= 32) underwent medical, neuropsychological and overnight polysomnography assessment. Conventional neuropsychological tests of verbal episodic and visuospatial memory were administered pre- and post-sleep, and OMC was calculated ([post-sleep/pre-sleep score]*100). Power spectral analysis was used to determine relative non-REM SWA (0.5-4.5 Hz), and N2 slow (11-13 Hz) and fast (13-16 Hz) spindles.

Results: Those with MCI had poorer verbal episodic memory in the evening and morning compared to Controls, however OMC did not differ between groups. The amnestic-MCI subtype had reduced visuospatial OMC compared to Controls ($omega^2$= .06, p= .031), but no other group differences were found. Poorer verbal episodic OMC was associated with reduced SWA in Controls (r= .515, p= .006), but in MCI, poorer verbal episodic (r= -.352, p= .044) and visuospatial (r= -.409, p= .013) OMC was linked to having greater fast spindle density, notably in the non-amnestic MCI subtype (r= -.543, p= .005).

Conclusion: For cognitively intact older adults, our data supports the notion that SWA is important for overnight consolidation. In contrast, in patients with MCI, fast spindle density appears more relevant, possibly suggesting the recruitment of different, compensatory neural networks. For visuospatial material, there is suggestion of preferential OMC impairment in the non-amnestic MCI subtype, but further studies are now needed to examine visuospatial OMC more comprehensively. To better understand OMC in MCI, future studies should carefully phenotype cognitive profile and neurodegenerative disease status using dementia biomarkers.

Keywords: Memory, Mild Cognitive Impairment, Neurodegeneration, Sleep Spindles, Slow Wave Activity

3.2. INTRODUCTION

With ageing, there are a number of changes to sleep macroarchitecture, including a decrease in total sleep time (Bliwise et al., 2005; Landolt & Borbely, 2001), poorer sleep efficiency (Landolt & Borbely, 2001), increased fragmentation (Lim et al., 2013), obstructive respiratory events (Ancoli-Israel et al., 1991; Hoch et al., 1990), reduced time in slow wave sleep (SWS) (Dijk et al., 2010) and rapid eye movement (REM) sleep (Ohayon et al., 2004). Changes in sleep microarchitecture in healthy older adults compared to younger adults include decreased slow wave activity (SWA) (0.5-4.5 Hz) and spindles (11-16 Hz) during non-rapid eye movement (NREM) sleep (Crowley et al., 2002; Fillmore et al., 2021; Mander et al., 2013; Martin et al., 2013; Nicolas et al., 2001; Sprecher et al., 2016). Slow wave activity are large amplitude brain waves characteristic of SWS (stage 3/N3) that appear to be generated in the frontal lobe and travel posteriorly (Massimini et al., 2004). In contrast, spindles are waxing and waning sharp EEG brain waves that are characteristic of stage 2 (N2) sleep (Astori et al., 2013) generated in the thalamus (Contreras et al., 1997; Ueda et al., 2000). These key neurophysiology markers captured by overnight polysomnography (PSG) are also integral to optimal learning and memory.

In healthy older and younger adults both SWS (Backhaus et al., 2007) and spindles (Mednick et al., 2013; Tamminen et al., 2013) during NREM sleep are likely to be critical for memory, but the benefits of sleep for memory are substantially attenuated with ageing (Scullin, 2013; Scullin & Bliwise, 2015). The process of offline consolidation of declarative memories is hypothesised to occur via sharp wave ripples in the hippocampus, as measured by in-vivo EEG, that promote the reactivation of newly learnt information (Molle & Born, 2011). These ripples are then coupled with frontal slow waves and thalamocortical spindles (Sirota et al., 2003; Staresina et al., 2015), with findings indicating reduced slow waves (Mander et al., 2013) are related to decreased consolidation of verbal material. Although evidence points to the functional role of fast spindles in learning and memory consolidation (Mander et al., 2014; Molle et al., 2011), associations between spindles and memory in ageing are inconsistent. Previous studies have indicated a positive association between memory and spindles (Lafortune et al., 2014; Mander et al., 2014), whereas others have indicated negative association (Fillmore et al., 2021).

While there has been some progress in understanding how OMC changes with normal ageing, there has been relatively little attention devoted to those with dementia and cognitive impairment. In particular, there is a paucity of knowledge regarding OMC changes in those with Mild Cognitive Impairment (MCI), an ‘at risk’ group, whereby around 45% convert to dementia within five years

(Gauthier et al., 2006). Given memory deficits are pronounced in MCI, particularly those with the amnestic (i.e. predominant memory impairments) subtype (aMCI) compared to non-amnestic (naMCI) subtype (i.e. predominant impairment in non-memory domain such as processing speed) (Winblad et al., 2004), further understanding of OMC in this group could yield new scientific insights into OMC, and potentially lead to new treatments that target sleep to alleviate memory deficits. Current evidence indicates that those with MCI do exhibit sleep macroarchitecture changes compared to cognitively intact healthy older people (D'Rozario et al., 2020; Hu et al., 2017), but it is not yet clear if alterations in sleep microarchitecture also occur in MCI due to limited studies (D'Atri et al., 2021; Gorgoni et al., 2016; Westerberg et al., 2012), and the field examining sleep microarchitecture in relation to OMC is nascent.

A small study comparing eight participants with aMCI and 16 controls showed that those with aMCI had reduced frontal but not parietal N2 fast spindles (Westerberg et al., 2012). The same study showed that in the aMCI participants, OMC was reduced on a 44-item Word-Pair Associates Task (WPT) and a fact recognition task, but not on an object priming recognition task. Furthermore, no associations were found between WPT retention with N2 spindles, although poorer WPT retention was associated with reduced SWA and theta in both NREM and REM in the Control group only, which failed to reach significance in the aMCI likely due to small sample size (Westerberg et al., 2012). In a sample of 45 older adults (AD, aMCI, healthy Controls), reduced NREM parietal fast spindle density was reported in people with aMCI and AD relative to Controls (Gorgoni et al., 2016), with no group differences observed for frontal slow or fast spindles, or parietal slow spindles. Whilst greater parietal fast spindles were associated with improved performance on a gross cognitive measure, associations with OMC were not examined. More recently, in a larger sample of 43 MCI and 20 Controls using a 32-item WPT, those with multiple-domain MCI had poorer OMC compared to Controls, and this was associated with shorter duration of central spindle events in the MCI group (Lam et al., 2021).

Whilst no study to date has examined overnight visuospatial memory consolidation in MCI, evidence suggests that sleep efficiency (as measured by actigraphy) may be related to consolidation of visuospatial information. Specifically, in a sample of 59 ‘at-risk’ older adults, reduced sleep efficiency over a twenty-four hour and two-week period was related to poorer visuospatial memory at two-week recall. By contrast, reduced verbal memory recall after two weeks was associated with left hippocampal atrophy but not sleep efficiency (Lee et al., 2021). This provides preliminary evidence that long term consolidation of visuospatial and verbal information in older adults at-risk of dementia may have differential clinical predictors.

In summary, the above research highlights the importance of NREM neurophysiology for OMC in MCI, but the specific components of sleep microarchitecture that are pertinent to OMC in MCI remain unclear. In addition, some work suggests that non-verbal OMC should also be examined, as it may be underpinned by distinct neural networks or unique components of sleep (Lee et al., 2021). Whilst some preliminary evidence from two studies points to the relevance of slow waves and spindles during NREM as beneficial for verbal OMC, further studies are required in well phenotyped samples to better understand this relationship. A more precise understanding of NREM features important for memory in ageing will aid in the development of sleep interventions. In turn, improved memory and cognitive function may positively impact functional capacity such as workforce participation and societal engagement.

For neuropsychologists working in clinical practice, it would be helpful to understand how memory traces on commonly used neuropsychological tests are susceptible to sleep disturbance especially in clinical populations where time-consuming experimental tasks cannot be administered. Therefore, this study aimed to investigate OMC in a well phenotyped sample of people with clinical MCI. The primary aim was to determine differences in overnight verbal episodic and visuospatial memory consolidation between healthy older cognitively intact individuals and those with MCI, as well as exploring any differential patterns across the MCI subtypes (aMCI and non-amnestic MCI [naMCI]). It was hypothesised that there would be reduced OMC in MCI compared to Controls, with the greatest decline predicted for verbal episodic memory within the aMCI group. The secondary aim was to determine whether frontal NREM SWA and N2 spindles (slow and fast density) are associations with OMC. On the basis of the limited studies mentioned, it was hypothesised that reduced NREM SWA and N2 spindles would be associated with poorer OMC in both Controls and MCI.

3.3. METHOD

Participants

Seventy-eight older adults aged 44-85 years were recruited from the community attended the Healthy Brain Ageing Program at the Brain and Mind Centre, Sydney, Australia. This clinic specialises in early assessment and intervention for individuals experiencing cognitive and/or mood concerns. Exclusion criteria were: history of stroke; neurological disorder; dementia; Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score < 24; head injury with loss of consciousness > 30minutes; medical conditions known to affect cognition (e.g. cancer); intellectual disability; consumption of >

14 standard alcoholic drinks per week; shift-workers; transmeridian travel within the prior 60 days; sleep-affecting medications including beta-blockers and lithium. Patients taking sedative hypnotics were requested to have a two-week washout period monitored by their treating physician. The University of Sydney Ethics Committee approved this study and all participants gave written and verbal consent.

Clinical and Neuropsychological Assessment

All participants received a medical assessment by an Old Age Psychiatrist using a semi-structured interview including medical and sleep history, medication use, measurement of body mass index. They also recorded depression history, as per the affective component of the Structured Clinical Interview for DSM-IV-R (Kübler, 2013).

A comprehensive standardised neuropsychological assessment was conducted by a clinical neuropsychologist as detailed previously (Duffy et al., 2014) and assessed the domains of processing speed, memory, language, visuospatial and executive function and. Premorbid intellectual ability was estimated using the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) and for descriptive purposes, global cognition was measured using the MMSE (Folstein et al., 1975).

A clinical classification of MCI was obtained via consensus of two neuropsychologists and the medical specialist using Winblad's criteria (Winblad et al., 2004). This requires cognitive decline of at least 1.5 standard deviations on at least one neuropsychological test, relative to age and education adjusted normative data. As previously described (Broadhouse et al., 2019), participants were classified as the aMCI subtype, determined by 1.5*sd* score below normative expectation on a delayed recall component of a memory task, as well as qualitative clinical information where relevant, or naMCI, defined by 1.5*sd* score below expected limits on non-memory tasks. Participants were also classified as single-domain MCI if decrements were present on one cognitive domain or multiple-domain if decrements were present on two or more domains.

Subjective sleep quality was measured the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and morningness-eveningness circadian rhythm preference was captured with the Horne & Österberg questionnaire (Horne & Ostberg, 1976). Depression severity was also self-reported recorded using the Geriatric Depression Scale (GDS-30) (Yesavage & Sheikh, 1986a).

Polysomnography Assessment

Following clinical assessment, participants were scheduled for two consecutive nights of polysomnography (PSG) in the Chronobiology and Sleep Laboratory at the Brain and Mind Centre, Sydney, Australia and asked to complete two weeks of actigraphy and sleep diary monitoring which was used to determine habitual bedtime. For in-laboratory PSG, participants were asked to maintain their usual bedtime and wake-up schedule times and were all given a 7 to 8 hour sleep opportunity, aligned with their habitual bedtime. While in the laboratory, participants were monitored physiologically and behaviourally at all times under controlled conditions, with fixed light levels (< 50 lux during waking; < 1 lux during scheduled sleep periods) and ambient temperature (24 ± 1 °C). Night 1 was considered an adaption night and included pulse oximetry recordings. Respiratory events were recorded using the oxygen desaturation index (number of SpO2 desaturation events/hr) as well as EEG arousal index (events/hour). On the second night, memory tasks were administered in the evening 2 hours prior to habitual sleep time and one hour after wake. Participants were asked to abstain from alcohol on the day of evening memory testing and prior to morning testing, and caffeinated beverages at least three hours before evening testing and to consume no caffeinated beverages prior to morning testing.

Overnight PSG recordings (Compumedics Siesta, Melbourne, Vic, Australia) were collected using four-channel electroencephalographic (EEG) montage (Fz-M1+M2/2, C3-M2, Pz-M1+M2/2 and O2-M1); two electrooculographic (EOG) channels (left and right outer canthi) and electromyogram (EMG) (submentalis, left and right leg). EEG data were sampled at 250 Hz and a notch filter of 50 Hz was used. Sleep stages were scored manually in 30-second epochs by a sleep technician using Rechtschaffen and Kales standardised scoring criteria (Rechtschaffen & Kales, 1968), with modifications for older participants (Webb & Dreblow, 1982).

EEG artefact processing

All night PSG recordings were subjected to automated EEG artefact processing. An algorithm identified artefactual EEG data at a resolution of five seconds epochs based on previously validated artefact detection threshold parameters (D'Rozario et al., 2015). Contaminated five second epochs were subsequently excluded from EEG analysis. Quantitative EEG (qEEG) measures were derived from all artefact-free sleep EEG recordings during overnight PSG.

Power spectral analysis

Artefact-free epochs were analysed using a standard fast Fourier transform (FFT) with a rectangular weighted window for each non-overlapping five second epoch of EEG for the frontal (Fz-M1+M2/2) channel. We calculated absolute spectral power (μV^2) in delta, theta, alpha, sigma and beta bands

defined as EEG activity in each of the respective frequency ranges 0.25-1, 0.5–4.5, 4.5–8, 8–12, 12-15 and 15 – 32 Hz and relative spectral power for NREM SWA ([delta/delta+theta+alpha+sigma+beta] * 100), in order to account for the potential effects of psychotropic (anti-depressant and antipsychotic) medication use on SWA (Wichniak et al., 2017) in the subset of MCI participants. The EEG power for each sleep-staged 30 seconds epoch of the PSG recording was calculated by averaging data from up to six artefact-free five second epochs of EEG that comprised that 30 seconds recording segment. The weighted-average spectral power within the defined frequency bands was then computed for NREM and REM sleep stages.

Sleep spindle event detection algorithm

A spindle identification algorithm developed and written in Java (Version 1.6, Oracle, Santa Clara, CA, USA) and validated in an older sample of MCI participants (Lam et al., 2021) automatically detected sleep spindle events. The algorithm computationally performed the following steps: a band-passing finite-impulse-response filter (11 – 16 Hz) was applied to the raw EEG signal, yielding a time course of EEG activity in the sigma frequency range. A Hilbert transformation was applied to extract envelopes of the sigma EEG activity using a threshold calculated independently for Fz-M1+M2/2 and Pz-M1+M2/2 derivation. The threshold value for each channel was given by the formula: median amplitude (μV) + 1.0 x standard deviation amplitude of the signal. The duration threshold for spindle events was 0.5 – 3.0 seconds. An index of sleep spindle events per minute (primary spindle measures) of N2 was calculated for slow (11 – 13 Hz) and fast (13 – 16 Hz) spindle density, as well as mean spindle duration (11 – 16 Hz).

Sleep EEG variables of interest

The primary EEG measures of interest were: frontal relative SWA power (0.5 – 4.5 Hz) during NREM; slow spindle density (spindle events 11 – 13 Hz per minute of N2 sleep); and, fast spindle density (spindle events 13 – 16 Hz per minute of N2 sleep). Secondary EEG measures were: frontal absolute SWA power (reported for completeness), frontal spindle event duration (11 – 16 Hz, spindle duration per second in N2 sleep) and parietal slow and fast spindle density in N2 based on previous findings in MCI (Gorgoni et al., 2016; Lam et al., 2021).

Overnight Memory Consolidation (OMC) Tasks

Rey Auditory Verbal Learning Test (RAVLT): Verbal episodic memory

As per standardised instructions (Lezak et al., 2004), participants were read aloud 15 words across five consecutive trials. After each trial, participants were given an opportunity to recall the 15 words in any

order. Following the five trials, a second list of words was read (List B) and participants were then asked to recall as many of the words as they could from that list. Participants were then asked to recall the first again with no further presentation of the list. After a 20-minute delay, participants were asked to recall as many words as possible from the first list. For the purpose of this study, we further adapted the test to include a long delay recall following sleep. That is, participants were again asked to recall as many words as possible in the morning, one hour after wake. OMC was calculated ([RAVLT morning raw score/RAVLT evening 20-min delay raw score] * 100).

Rey-Osterrieth Complex Figure Test (ROCFT): Visuospatial memory

Participants were administered the test according to standardised instructions including copy, and three minute recall conditions. In addition, the test was adapted to include a long delay recall, following sleep. The traditional method for scoring the ROCFT (Meyers & Meyers, 1995) by points and percentiles was used. All 18 elements of the complex figure were scored individually with a maximum of two points if drawn and placed correctly, one point if drawn correctly but placed improperly or drawn incorrectly but recognisable and placed properly, 0.5 points if drawn incorrectly but recognisable and placed poorly, and zero points if absent or not recognisable. Single elements are summed to devise a total score out of 36 points. OMC was calculated ([ROCFT morning raw score/ROCFT evening three-minute delay raw score] * 100).

Statistical Analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS version 28, IBM Corp. Sydney, Australia) for Macintosh. An independent samples t-test and chi-square goodness of fit test was used for two groups (MCI, Controls) where applicable. One-way analysis of variance (ANOVA) was used for three groups (aMCI, naMCI, Controls) to examine group differences in clinical and sleep characteristics, and evening and morning raw scores on OMC tasks. A univariate general linear model (GLM) was used to assess group differences in sleep measures to adjust for psychotropic medication use in MCI.

A 2 x 2 repeated measures ANCOVA was used to assess overnight performance change from evening to morning between MCI and Control groups on tasks of OMC whilst controlling for age. Here, group (MCI, Controls) was the between-subjects variable and test time (evening, morning) was the within-subjects variable. Post-hoc analysis using Bonferroni assessed MCI subgroup differences. Overnight memory consolidation % was calculated by ([evening score/morning score]*100), which was used as our primary dependent variable and associations with sleep microarchitecture measures. A student t-

test and welch's t-test was used where applicable, and cohen's *d* for effect sizes was used for two groups to measure evening score, morning score and OMC, and a one-way ANOVA was used for three groups and omega^2 for effect sizes. Cohen's d effect size were calculated as; small = 0.2, medium = 0.5, large = 0.8, and omega^2 were calculated as; small = .01, medium = .06, large = .14 (Cohen, 1988; Lakens, 2013). A univariate GLM was used to confirm OMC results were not driven by age or depression. All frontal spindle variables were log transformed to normalise right tail skewness. Pearson partial correlations were used to assess associations between sleep microarchitecture and OMC on episodic and visuospatial tasks, controlling for age and psychotropic (antidepressant and antipsychotic) medication. All analyses were two-tailed with an alpha level of 0.05.

3.4. RESULTS

Clinical characteristics: demographics, sleep and mood questionnaires

The sample included 78 participants, which comprised 32 cognitively-intact Controls and 46 participants with MCI, of which 13 met Winblad's criteria for aMCI and 33 for naMCI. Upon further examination of cognitive profile, of the aMCI group 1 met criteria for single-domain MCI and 12 for multiple-domain MCI, and from the naMCI group 15 met criteria for single-domain MCI (45%) and 18 for multiple-domain MCI (55%).

The Controls and MCI groups did not differ on age, sex, or years of education (Table 3.1). In total, 25 participants from the MCI group (7 aMCI, 18 naMCI) reported current psychotropic medication use (tricyclic antidepressant, n = 5; selective serotonin reuptake inhibitors, n = 4, selective and norepinephrine reuptake inhibitors, n = 11; noradrenergic and specific serotonergic antidepressant, n = 4; Quetiapine, n =1 [low dose]). No Controls were taking psychotropic or sleep medications. As expected, participants with MCI performed worse than Controls on the MMSE (p = .020). They also had greater depression severity on the GDS-30 (p <.001) compared to Controls and a trend towards self-reported poorer sleep quality on the PSQI (p = .052). When examining MCI subtypes (aMCI, naMCI), the aMCI subgroup were older than the naMCI subgroup (p = .004) and trending towards significance with Controls (p = .052). The aMCI group had lower MMSE scores compared to naMCI (p <.001) and Controls (p <.001). The naMCI group had greater depression scores on the GDS-30 (p <.001) compared to Controls, and a trend towards greater PSQI scores compared to Controls (p = .053) (Table 3.1).

Table 3.1. Demographics, clinical & sleep microarchitecture.

	Controls *M, sd*	MCI *M, sd*	*t, F*	*p*	aMCI *M, sd*	naMCI *M, sd*	*F*	*p*
Demographic	*n*= 32	*n*= 46			*n*= 13	*n*= 33		
Age, *yrs*[a, d]	64.7, 8.2	64.9, 9.2	-.10	.923	71.5, 9.7	62.4, 7.9	5.47	**.006**[3,4]
Gender[a] % n female[b]	17, 53%	18, 39%	1.50	.222	5, 38%	13, 39%	1.50	.473
Education, *yrs*[a, d]	13.8, 3.0	13.3, 3.5	.68	.510	13.8, 3.7	13.1, 3.0	.37	.681
Body Mass Index[a, d]	29.6, 12.5	26.4, 5.4	1.57	.122	25.1, 5.4	26.9, 5.5	1.41	.252
MMSE[a, d]	29.1, 1.2	28.3, 1.5	2.37	**.020***	27, 1.8	28.8, 1.2	12.13	**<.001**[1,3]
WTAR (Predicted IQ)[a, d]	106.6, 8.0	105.8, 10.3	.34	.739	109.8, 9.4	104.3, 10.1	1.49	.234
Clinical								
PSQI Global Score[a, d]	5.6, 4.2	7.6, 3.7	-2.04	**.045***	6.2, 3.0	8.1, 3.9	3.08	.052
PSQI Sleep efficiency %[a, d]	81.7, 19.0	79.6, 14.9	.53	.600	80.7, 16.0	79.2, 14.8	.17	.846
Horne & Ostberg[a, d]	61.3, 9.4	57.5, 9.5	1.67	.099	59.9, 11.1	56.7, 9.0	1.85	.165
GDS-30[a, d]	4.9, 6.0	12.4, 8.5	-4.44	**<.001****	10.8, 8.4	13.0, 8.6	8.79	**<.001**[2]
Sleep macroarchitecture								
Total Sleep Time, *mins*[c]	386.1, 53.9	372.9, 77.9	.50	.483	353.9, 99.3	382.1, 66.5	.92	.402
Sleep onset latency, *mins*[c]	15.4, 13.8	21.4, 18.9	.07	.793	17.2, 15.3	22.7, 19.7	.40	.672
REM onset latency, *mins*[c]	89.0, 46.0	135.0, 89.9	.10	.749	114.7, 94.9	141.4, 88.5	.45	.638
WASO, *mins*[c]	86.2, 44.2	103.9, 65.4	2.83	.097	137.2, 78.0	91.2	4.10	**.021***[1,3]
Sleep efficiency %[c]	79.4, 9.7	75.2, 12.8	2.27	.137	69.7, 16.9	77.3 10.5	2.91	.062
NREM (min)[c]	284.0, 44.8	271.1, 62.3	.85	.360	264.2, 75.7	273.7, 57.8	.53	.592
Slow wave sleep %[c]	15.3, 8.9	13.6, 10.9	.03	.866	11.5, 14.1	14.4, 9.5	.41	.667
REM (min)[c]	83.8, 25.4	80.1, 34.2	<.00	.967	65.6, 32.2	85.5, 33.8	1.86	.173
Arousal Index (TST) p/ hr[c]	25.2, 9.7	34.8, 21.4	.73	.397	43.5, 33.0	31.2, 13.3	2.80	.067
ODI (SpO2 desat p/hr)[c]	15.2, 12.9	15.7, 14.3	<.00	.960	15.7, 17.9	15.7, 13.4	<.00	.999

Note. ***p<.05. ****p<.01.** n=8 participants with no polysomnography data. [a]Independent samples t-test for two groups. [b]Chi-square goodness of fit test. [c]Univariate GLM controlling for psychotropic medication. [d]One-way ANOVA for three groups. MMSE = Mini Mental State Examination. WTAR = Wechsler Test of Adult Reading. PSQI =

Pittsburgh Sleep Quality Index. GDS-30= Geriatric Depression Scale. NREM = Non-Rapid Eye Movement. REM = Rapid Eye Movement. WASO = wake after sleep onset. ODI = Oxygen Desaturation Index. [1]Significant group differences between aMCI and Controls. [2]Significant group differences between naMCI and Controls. [3]Significant group differences between aMCI and naMCI. [4]Did not reach significance between aMCI and Controls (p = .052).

Overnight Memory Consolidation (OMC)

Verbal Episodic Memory

In comparison to Controls, the MCI group had poorer memory recall scores in the evening and morning (controlling for age) as indicated by a significant main effect of group ($F(1, 68) = 6.71$, $p = .012$). However, testing the within-group interaction revealed no significant time (evening, morning) by group (MCI, Controls) interaction ($F(1, 68) = .001$, $p = .977$). Accordingly, by examining OMC% ([morning score/evening score] * 100), both groups had similar rates of forgetting ($t = .52$, $p = .604$) (Table 3.2.a). No group differences were found for OMC% when controlling for age ($F(1, 69) = .26$, $p = .610$). Scores greater than 100% on OMC% indicate participants recalled a greater number of words in the morning compared to what they recalled in the evening.

When examining MCI subtypes (aMCI, naMCI) and Controls (controlling for age), there was a main effect of group ($F(2, 67) = 5.88$, $p = .004$). Post-hoc analysis revealed significant group differences between aMCI and Controls ($p = .003$), with aMCI remembering a reduced number of words in the evening and morning compared to Controls. Similarly, aMCI remembered less than naMCI in the evening but not in the morning, and Controls and naMCIs performed similarly in the evening and morning. The time by group interaction was not significant ($F (2, 67) = 1.02$, $p = .367$), and no group differences on OMC % were observed ($F(2, 69) = .41$, $p = .677$) (Figure 3.1 and Table 3.2.b). No group differences were found for OMC% when controlling for age ($F(2, 68) = .69$, $p = .503$) or depression severity on the GDS-30 ($F(2, 65) = .016$, $p = .984$).

No group differences were found when comparing MCI subtypes (single and multiple-domain MCI) OMC% ($F(2, 69) = .23$, $p = .795$), nor when controlling for age ($F(2, 68) = .17$, $p = .846$) or depression severity ($F(2, 65) = .42$, $p = .657$) (see Appendix Table 1A).

Visuospatial Memory

No significant main effect of group was indicated ($F(1, 75) = 1.88$, $p = .174$) nor was there a significant time (evening, morning) by group (MCI, Controls) interaction ($F(1, 75) = .64$, $p = .425$). Scores on OMC % did not significantly differ between MCI and Controls ($t = 1.76$, $p = .082$) (table 2.a) nor when controlling for age ($F(1, 75) = 3.11$, $p = .082$). Scores greater than 100% on OMC% indicate participants recalled a greater number of items from the image in the morning compared to what they recalled in the evening.

When examining MCI subtypes (aMCI, naMCI) and Controls (controlling for age), there was a non-significant trend for the main effect of group ($F(2, 74) = 2.96$, $p = .058$). Specifically, there was a trend towards group differences between aMCI and Controls ($p = .055$) on memory scores in the evening and morning. On observation, Controls and naMCI performed very similar in the evening and morning, however aMCI remembered less than both groups at both time points. A significant group difference with a medium effect size (omega^2 = .06) was indicated on OMC% ($F(2, 75) = 3.63$, $p = .031$), and post-hoc analysis revealed aMCI had significantly reduced OMC% scores compared to Controls ($p = .026$) (Figure 3.1 and Table 3.2.b). The aMCI group retained 17% ($\pm$ 6.2) less material overnight compared to Controls. However, when controlling for age ($F(2, 74) = 2.71$, $p = .073$), only a trend group difference between aMCI and Controls remained ($p = .071$), as Controls were younger than aMCI (Table 3.2.b). Group differences remained after controlling for depression severity on the GDS-30 ($F(2, 70) = 4.97$, $p = .010$), and post-hoc analysis between Controls and aMCI ($p = .007$).

No group differences were found when comparing MCI subtypes (single and multiple-domain MCI) visuospatial OMC% ($F(2, 75) = 1.81$, $p = .171$), nor when controlling for age ($F(2, 74) = 1.6$, $p = .214$), however when controlling for depression severity ($F(2, 70) = 5.30$, $p = .007$), significant group differences were found between multiple-domain MCI and Controls ($p = .012$) (see Appendix, Table 1A).

Table 3.2.a. Performance on the verbal episodic (RAVLT) and visuospatial (ROCFT) including pre-sleep (PM), post-sleep (AM) and overnight memory consolidation (OMC).

	Controls	MCI			
	M, sd	*M, sd*	*t*	*p*	*Cohen's d*
RAVLT PM (/15)[a]	9.7 (3.1)	7.6 (3.3)	2.9	**.005***	.67
RAVLT AM (/15)[a]	7.8 (3.0)	6.0 (3.1)	2.4	**.018***	.58
RAVLT OMC %[b]	81% (16.1)	79% (25.4)	.5	.604	.12
ROCFT PM (/36)[a]	17.7 (6.1)	16.0 (6.2)	1.2	.235	.28
ROCFT AM (/36)[a]	16.8 (5.8)	14.7 (6.7)	1.5	.151	.33
ROCFT OMC %[a]	97% (15.3)	89% (21.7)	1.8	.082	.41

Note. ***p<.05.** [a]Student t-test. [b]Welch's t-test. Correct responses in evening and morning. Overnight memory consolidation calculated by ([pre-sleep score/post-sleep score]*100). PM = pre-sleep, AM = post-sleep. RAVLT OMC: Controls = 30 MCI = 42. ROCFT OMC: Controls = 32, MCI = 46.

Table 3.2.b. Verbal episodic and visuospatial pre- and post-sleep memory and overnight memory consolidation (OMC).

	aMCI	naMCI			
	M, sd	*M, sd*	*F*	*p*	*omega*^{2}
RAVLT PM (/15)	5.3 (2.4)	8.5 (3.1)	9.9	**<.001*[1,3]**	.19
RAVLT AM (/15)	4.5 (1.8)	6.6 (3.3)	5.2	**.008*[1]**	.11
RAVLT OMC %	83% (25.0)	77% (25.8)	.4	.667	-.02
ROCFT PM (/36)	12.3 (5.2)	17.5 (6.0)	4.3	**.017*[1,3]**	.08
ROCFT AM (/36)	10.7 (6.1)	16.3 (6.3)	5.2	**.008*[1,3]**	.10
ROCFT OMC %	80% (22.8)	93% (20.5)	3.6	**.031*[1]**	.06

Note. ***p<.05.** One-way ANOVA. Correct responses in evening and morning. Overnight memory consolidation was calculated by ([pre-sleep score/post-sleep score]*100). PM = pre-sleep, AM = post-sleep. RAVLT OMC: aMCI = 12, naMCI = 30, Controls = 29. ROCFT OMC: aMCI = 13, naMCI = 33, Controls = 32. [1]Significant group differences between aMCI and Controls. [2]Significant group differences between naMCI and Controls. [3]Significant group differences between aMCI and naMCI.

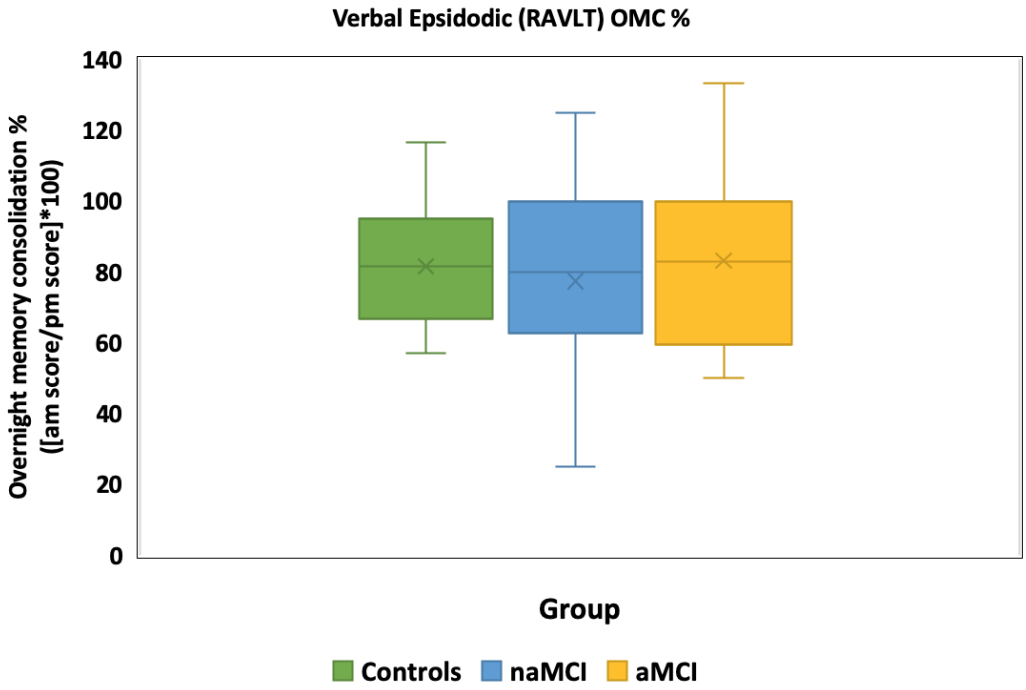


Figure 3.1. Verbal episodic overnight memory consolidation (OMC) %. OMC calculated by: ([pre-sleep score/post-sleep score]*100). PM = pre-sleep, AM = post-sleep. No group differences indicated in verbal episodic OMC % between Controls and MCI subtypes (aMCI, naMCI).

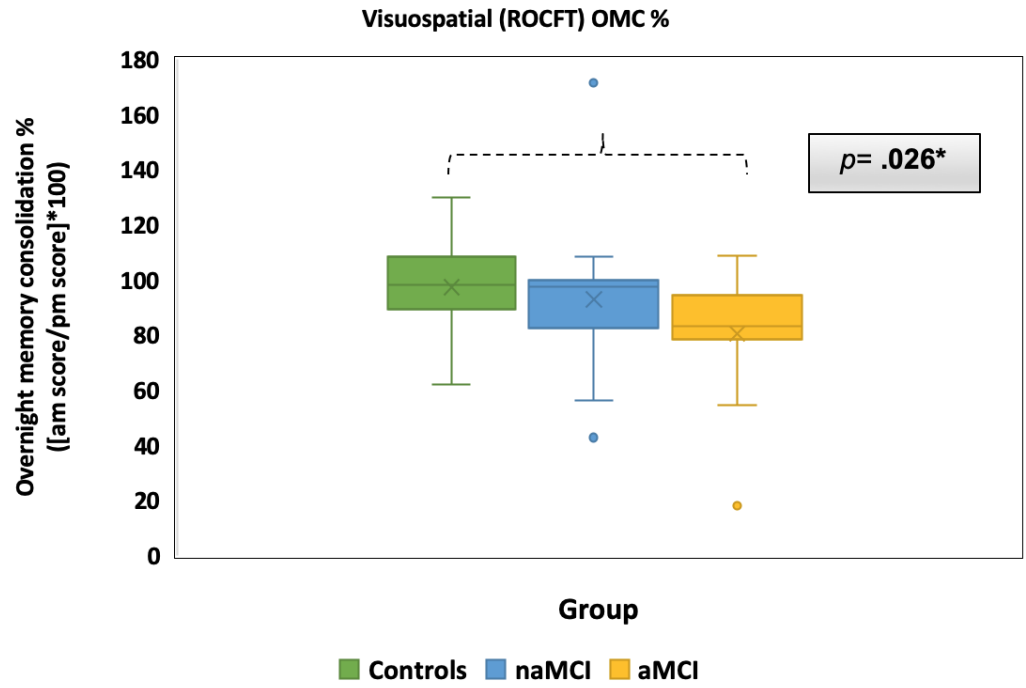


Figure 3.2. Visuospatial overnight memory consolidation (OMC) %. OMC calculated by: ([pre-sleep score/post-sleep score]*100). PM = pre-sleep, AM = post-sleep. Significant group differences on visuospatial OMC % indicated between aMCI and Controls (p = .026), with aMCI group showing reduced OMC %. However, results did not not remain significant after controlling for age (p = .07).

Polysomnography group differences: Macroarchitecture and Microarchitecture

For descriptive purposes, a univariate GLM was used to assess group differences between Controls and MCI, and its subtypes, on sleep PSG measures, whilst controlling for psychotropic medication use. No group differences were found for any macroarchitecture or frontal microarchitecture variables between MCI and Controls. However, post-hoc analysis revealed aMCI had greater WASO compared to Controls (p = .026) and naMCI (p = .040). There was a non-significant trend for reduced frontal N2 fast spindles in aMCI compared to both Controls (p = .053) and the naMCI subgroup (p = 0.59) (Table 3.1 and 3.3).

Table 3.3. Sleep microarchitecture (μV) group differences.

	Controls	MCI			aMCI	naMCI		
	M, sd	*M, sd*	*F*	*p*	*M, sd*	*M, sd*	*F*	*p*
Frontal SWA relative power (0.5-4.5 Hz)	83.1 (5.8)	84.8 (4.0)	1.4	.240	83.9 (4.2)	85.2 (4.0)	1.0	.388
Frontal fast spindle density (13-16 Hz)	.8 (.5)	.8 (.8)	1.2	.279	.4 (.3)	.9 (.8)	3.5	**.036*[1]**
Frontal slow spindle density (11-13 Hz)	1.2 (.6)	1.1 (.5)	.2	.625	.917 (.6)	1.1 (.5)	1.4	.270

Note. ***p<.05.** Univariate GLM controlling for psychotropic medication that was used. Participants with poor quality EEG signals removed. All spindles log transformed due to right curtail skewness. Spindle density = events p/min. SWA/delta calculated for total NREM and spindles for N2. [1]Did not reach significance in post-hoc analysis between aMCI and Controls (p = .053), and aMCI and naMCI (p = .059).

Sleep microarchitecture associations with OMC

Controls: Greater NREM relative SWA was significantly associated with greater verbal episodic OMC% (Figure 3.3) but not with visuospatial OMC%. No significant associations were found between absolute SWA or any frontal or parietal spindle measures with OMC % (Table 3.4.a and 3.4.b).

MCI: Greater frontal N2 fast spindle density was significantly associated with reduced verbal episodic and visuospatial OMC%. Similarly, greater parietal N2 fast spindle density was significantly associated with poorer visuospatial but not verbal episodic OMC%. Greater frontal N2 spindle duration was also significantly associated with reduced visuospatial OMC %. Since there was one outlier in the dataset for visuospatial OMC% that was skewing results with spindles, analyses were repeated with the removal of that case, and significance remained unchanged for associations with frontal and parietal N2 fast spindle density but not frontal N2 spindle duration. No significant associations were

observed between relative or absolute SWA, nor frontal or parietal slow spindle density with OMC% (Table 3.4.a and 3.4.b).

MCI subtypes

naMCI: Greater frontal N2 fast spindle density was significantly associated with reduced visuospatial OMC% but not verbal episodic OMC% (Table 3.4.b and Figure 3.4.b). Similar findings were observed for parietal N2 fast spindle density. After removing the outlier for visuospatial OMC%, results remained unchanged. No significant associations were found between relative or absolute SWA, nor frontal or parietal slow spindle density or frontal spindle duration with OMC%.

aMCI: No significant associations were found between relative or absolute SWA or any spindle measures with OMC% (Table 3.4.a and 3.4.b).

Table 3.4.a. Correlations between verbal episodic (RAVLT) OMC and sleep microarchitecture.

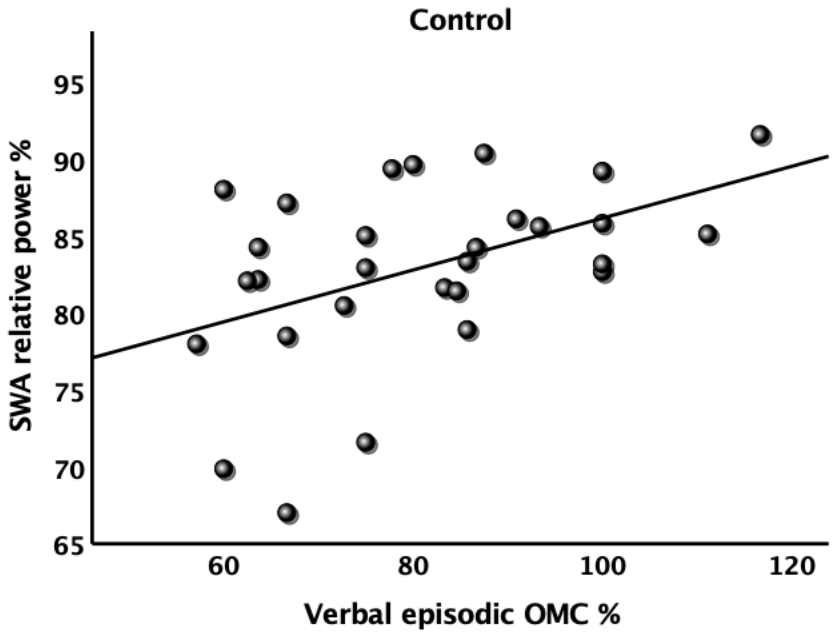
	Controls		MCI		aMCI		naMCI	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
	n=27		n=33		n=10		n=24	
SWA relative power (0.5-4.5 Hz)(*f*)	.515	**.006***	-.034	.853	-.410	.314	.173	.441
SWA absolute power (0.5-4.5 Hz)(*f*)[a]	.091	.647	.153	.402	.224	.316	-.386	.345
Fast spindle density (13-16 Hz)(*f*)	.031	.879	-.352	**.044***	.057	.894	-.412	.051
Slow spindle density (11-13 Hz)(*f*)	-.339	.084	-.193	.281	.276	.509	-.348	.103
Spindle duration (11-16 Hz)(*f*)[a]	-.083	.676	-.139	.427	.305	.463	-.220	.291
Fast spindle density (13-16 Hz)(*p*)[a]	-.170	.407	.134	.488	.551	.200	.225	.339
Slow spindle density (11-13 Hz)(*p*)[a]	-.204	.318	.059	.760	.576	.176	-.114	.633

Note ***p<.05.** Univariate person's partial correlations analysis controlling for age and psychotropic medication that was used. Participants with poor quality EEG signals removed. Relative delta/SWA power was calculated by (absolute delta power/[absolute delta+theta+alpha+sigma+beta]*100) and expressed as %. All spindles log transformed due to right curtail skewness. Spindle density = events p/min. SWA/delta were calculated for total NREM and spindles were calculated during N2. *f*= frontal, *p*= parietal. [a]Secondary variables of interest.

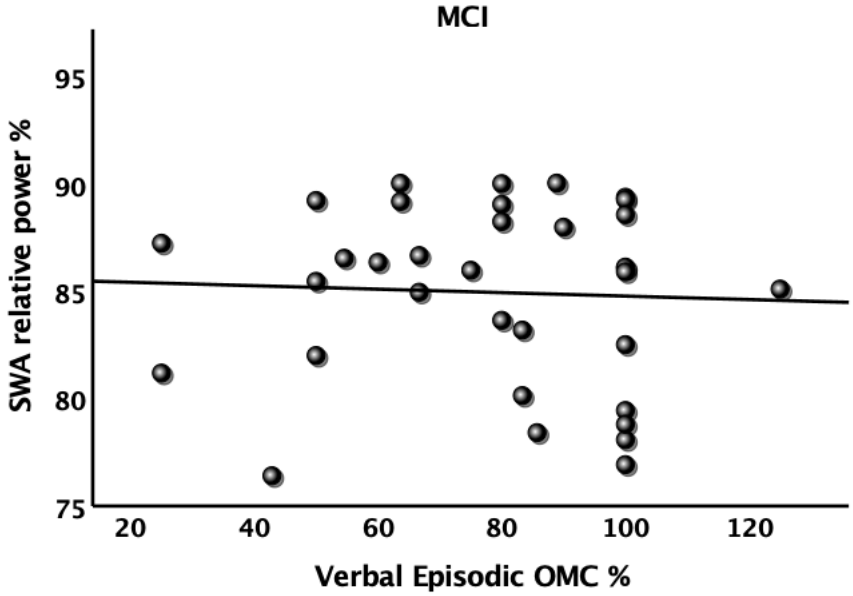
Table 3.4.b. Correlations between visuospatial (ROCFT) OMC and sleep microarchitecture.

	Controls		MCI		aMCI		naMCI	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
	n=28		n=35		n=11		n=29	
SWA relative power (0.5-4.5 Hz)(*f*)	-.073	.712	.135	.432	-.063	.872	.145	.490
SWA absolute power (0.5-4.5 Hz)(*f*)[a]	-.219	.253	-.144	.403	-.152	.695	-.103	.625
Fast spindle density (13-16 Hz)(*f*)	.149	.448	-.409	**.013***	-.538	.135	-.543	**.005***
Slow spindle density (11-13 Hz)(*f*)	-.198	.314	-.153	.373	-.158	.684	-.157	.454
Spindle duration (11-16 Hz)(*f*)[a]	.012	.951	-.186	.263	-.592	.093	-.278	.153
Fast spindle density (13-16 Hz)(*p*)[a]	.163	.426	-.362	**.039***	-.456	.256	-.442	**.035***
Slow spindle density (11-13 Hz)(*p*)[a]	-.099	.630	.060	.741	-.218	.604	.184	.400

Note ***p<.05.** Univariate pearson's partial correlations analysis controlling for age and psychotropic medication that was used. Participants with poor quality EEG signals were removed. Relative delta/SWA power was calculated by (absolute delta power/[absolute delta+theta+alpha+sigma+beta)]*100) and expressed as %. All spindles log transformed due to right curtail skewness. Spindle density = events p/min. SWA/delta were calculated for total NREM and spindles were calculated during N2. One outlier was removed from the MCI group (naMCI subtype) for frontal spindle analysis as it was having an undue influence on the correlation. SWA/delta were calculated for total NREM and spindles were calculated during N2. *f*= frontal, *p*= parietal. [a]Secondary variables of interest.

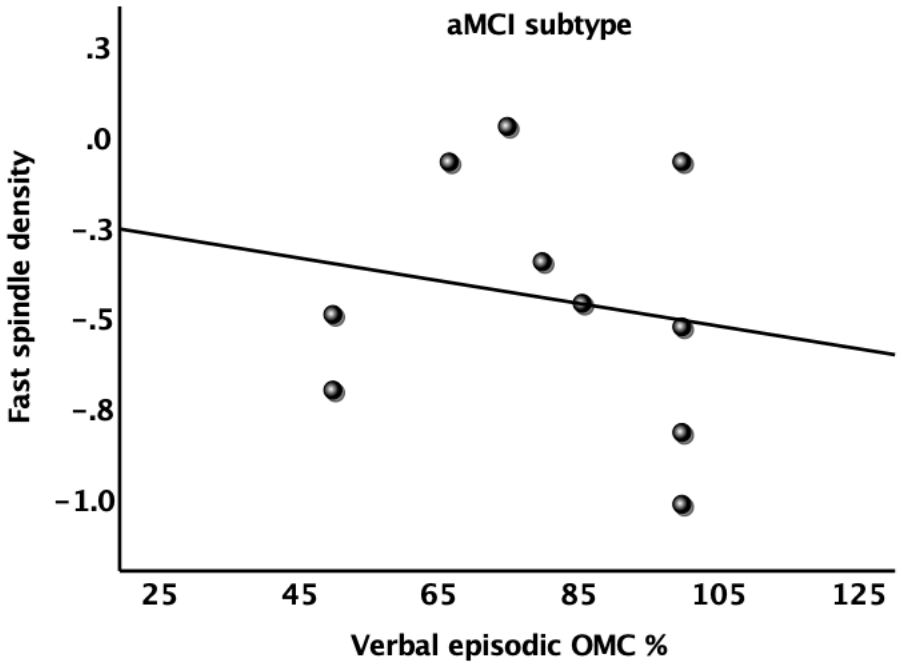


a.

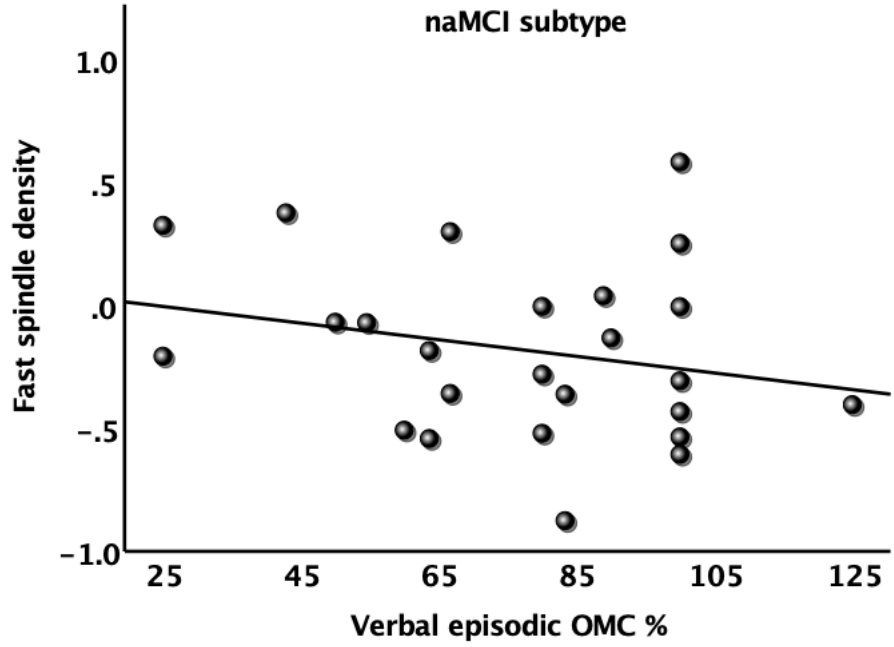


b.

Figure 3.3. Scatterplots showing a) significant associations between relative frontal SWA durign NREM and verbal episodic OMC % in Controls (r = .515, *p* = .005), and b) no significant associations between relative frontal SWA in NREM and verbal episodic OMC % in MCI paritcipants (r = -.034, *p* = .853). Pearson's correlation were used to examine associations between frontal relative SWA during NREM with verbal epsiodic OMC %. Figure 3.3.a demonstrates a medium magnitude between relative SWA and verbal episodic OMC % in Controls. It illustrates that increases in relative SWA power is associated with better verbal episodic OMC on the RAVLT. Figure 3.3.b indicates no associations between relative SWA power and verbal episodic OMC in MCI group.

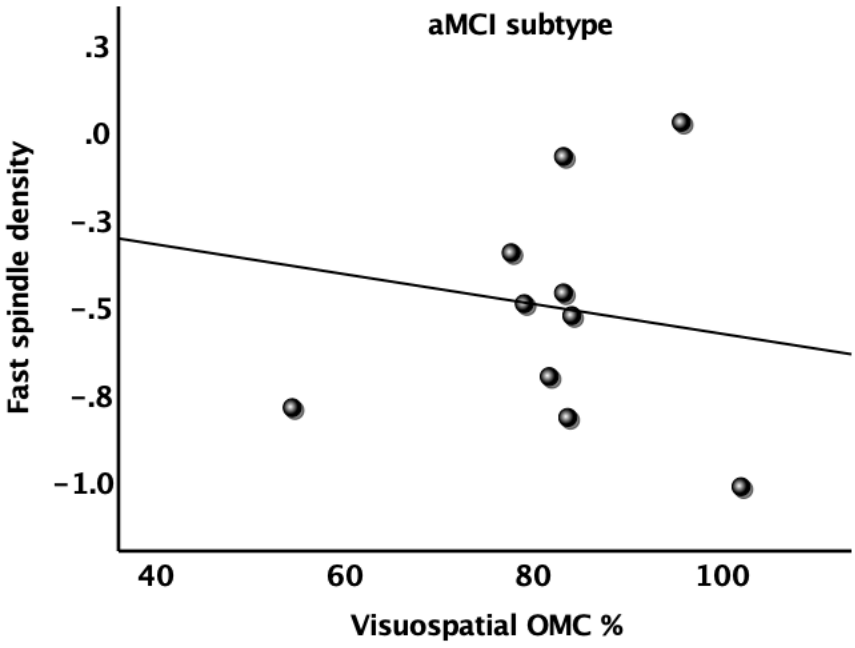


a.

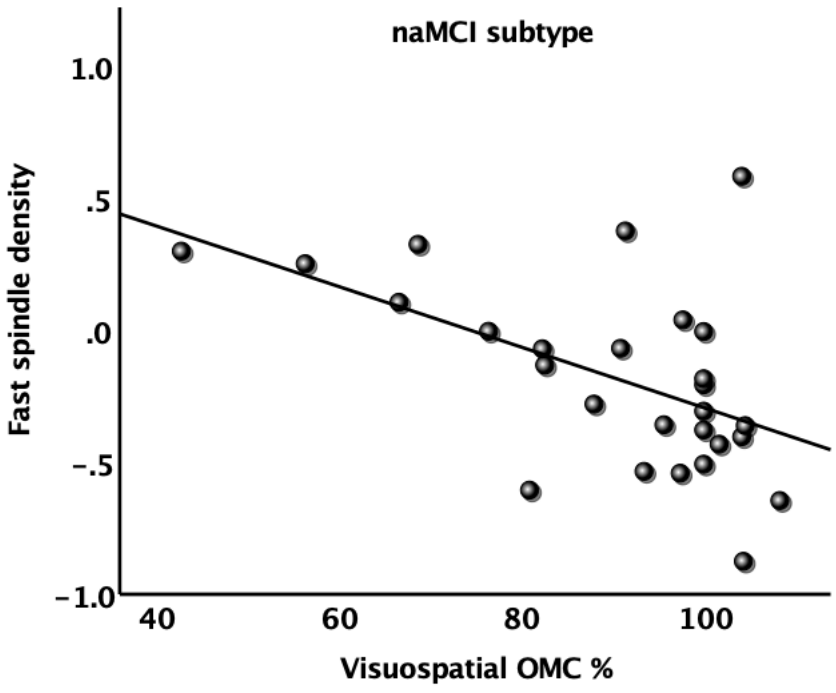


b.

Figure 3.4. Scatterplot in Figure 3.4.a showing no significant associations between frontal fast spindle density in N2 with verbal episodic OMC % in aMCI participants (r = .057, *p* = .894), and Figure 3.4.b showing a trend towards significant between frontal fast spindle density in N2 with verbal episodic OMC % in naMCI group (r = -.412, *p* = .051). Pearson's correlation were used to examine associations between frontal N2 fast spindle density with verbal episodic OMC % in MCI subtypes. Figure 3.4.a shows no significant associations in aMCI, however a medium effect size trending towards significance is indicated in naMCI subtype in Figure 3.4.b. Such that, greater frontal N2 fast spindle density is associated with worse verbal episodic OMC %.



a.



b.

Figure 3.5. Scatterplot in Figure 3.5.a showing no significant associations between frontal fast spindle density in N2 with viuospatial OMC % in aMCI group (r = -.538, *p* = .135), and in Figure 3.5.b showing significant associations between frontal fast spindle density in N2 with visuospatial OMC % in naMCI group (r = -.543, *p* = .005). Pearson's correlation were used to examine associations between frontal N2 fast spindle density with visuospatial episodic OMC % in MCI subtypes. No significance associations indicated in aMCI as shown in Figure 3.5.a. A medium magnitude effect size indicates a greater fast spindle density significantly associated with worse OMC in naMCI subtype in Figure 3.5.a.

3.5. DISCUSSION

This study is the first to examine how OMC using standardised neuropsychological tests differs in clinical MCI subgroups, and how OMC differentially relates to sleep neurophysiology. The results show that using a traditional neuropsychological task of unstructured list learning, those with MCI performed more poorly than Controls, but OMC was not disproportionately compromised. There was, however, poorer visuospatial OMC in those with aMCI, relative to Controls, although this effect appeared to be mediated by age. Interestingly, our findings show that there are differential relationships between sleep microarchitecture and OMC for the MCI group compared to Controls. For Controls, greater verbal episodic (but not visuospatial) OMC was associated with having more SWA. By contrast, for MCI, poorer verbal episodic and visuospatial OMC was associated with having *greater* frontal and parietal fast (but not slow) spindle density. These negative associations were largely driven by the naMCI subtype, particularly for the visuospatial domain. Despite these findings, no group differences were indicated in EEG measures between groups; although reduced fast spindles in aMCI in comparison to Controls and naMCI was observed, this failed to reach significance. This is in line with previous findings that have also found no group differences in frontal slow and fast spindles between Controls and aMCI (Gorgoni et al., 2016), with average slow and fast spindle means being similar to that presented in this study.

A limited body of prior work has examined verbal OMC in MCI, albeit using vastly different experimental tasks, designed for in-lab experimental studies. Our results differ to previous findings that found aMCI (Westerberg et al., 2012) and multiple-domain MCI (Lam et al., 2021) perform significantly worse than Controls on verbal episodic OMC using a word paired-associate task. However, our results are aligned with those of Lam and colleagues (2021) who did not find verbal episodic OMC differences between MCI (or aMCI and naMCI subtypes) and Controls. It is possible that the inconsistencies with respect to verbal episodic OMC between MCI (and its subtypes) and Controls across these three studies, may be attributed to differences in task design. Since the task used here would appear conceptually simpler, with reduced verbal information to learn (15 words *vs.* 32 or 44 word-pairs), it is therefore possible that our study may have lacked sensitivity to detect OMC decrements. Notably, this study incorporated a broad array of MCI participants including a proportion of those with single-domain MCI within the naMCI subtype, which may have resulted in a more heterogeneous MCI sample. These discrepancies suggest the need to consider both task design and clinical MCI subtype when interpreting results.

Whilst age-related changes have been identified in OMC for visuospatial memory (Cherdieu et al., 2014), no known study has examined visuospatial OMC in a MCI sample. For this study, we used a standardised paper and pen visuospatial task measuring free recall, however various other methods have been developed, in particular the use of computerised visuospatial tasks (Ladenbauer et al., 2017; Ladenbauer et al., 2016; Sonni & Spencer, 2015). In a sample of 16 MCI participants, Ladenbauer and colleagues (2017) assessed whether object and location memory using a computerised task could be improved by utilising slow oscillatory transcranial direct current stimulation *vs.* sham condition during a daytime nap, whilst controlling for sleepiness (Ladenbauer et al., 2017). Visual memory, assessed by picture recognition accuracy, but not location retrieval nor verbal memory, improved in the slow oscillatory transcranial direct current stimulation condition. Significant associations were found between an increase in slow oscillations and fast spindles with visuospatial recognition; indicating a potential suitable task that could be implemented in future OMC studies in this clinical sample. Comparing younger and healthy older adults, Sonni and Spencer (2015) used a visuospatial object recognition and recall task, with an interference component, indicating that only older adults who performed greater on the task had a benefit of sleep (Sonni & Spencer, 2015). Overall, relative to the studies examining verbal episodic OMC in healthy ageing (Aly & Moscovitch, 2010; Baran et al., 2016; Mander et al., 2014; Wilson et al., 2012) and MCI (Lam et al., 2021; Westerberg et al., 2012), there is an evident gap in purpose designed experimental sleep tasks suited to MCI samples (Lam et al., 2021), as well as the assessment of other memory domains such as visuospatial memory, procedural memory (Terpening et al., 2013), declarative memory such as lexical integration (Dumay & Gaskell, 2007; Tamminen et al., 2017) and spatial navigation (Varga et al., 2016).

In this study, we a-priori selected relative EEG power to quantify NREM SWA in order to account for medication use in MCI and the intra-individual variability described in EEG (Sprecher et al., 2016). Previous studies have reported absolute SWA to be directly linked to verbal episodic OMC in healthy older adults (Westerberg et al., 2012), and indirectly via medial prefrontal cortex atrophy (Mander et al., 2013). Similar findings have been observed in participants with subjective cognitive decline (Manousakis et al., 2019), and trending towards significance in participants with aMCI (Westerberg et al., 2012). Our findings are not concordant with this literature, as this study found no such associations with absolute SWA in our Control sample, and the aMCI sample showed a negative trend with both absolute and relative SWA with verbal episodic OMC. However, both our study and prior studies (Westerberg et al., 2012) are limited by small aMCI sample sizes. With regard to visuospatial OMC, our study is partially concordant with previous studies that have found significant associations with relative SWA power and OMC of spatial navigation information in a sample of both younger and

healthy older adults combined (Varga et al., 2016). Whilst there are significant differences in task design, there have been no known studies examining sleep microarchitecture associations with visuospatial OMC in MCI. From the limited studies that have examined NREM EEG and OMC in MCI, it appears that SWA does not confer the same benefit for this clinical group (Lam et al., 2021; Westerberg et al., 2012) and indeed, the sleep-memory pattern may be the opposite to that observed in healthy Controls.

In relation to sleep spindles, our non-significant findings between OMC and spindles in Controls are aligned with previous findings (Lam et al., 2021; Westerberg et al., 2012). However, they differ to studies in healthy older adults that have found that greater frontal fast spindle density (13 – 15 Hz) to be related to superior verbal episodic OMC (Mander et al., 2014) and greater central spindle density (12 – 16 Hz) to be associated with improved OMC on the Rey-Osterrieth complex figure task (Seeck-Hirschner et al., 2012). In addition, they also differ to recent findings indicating greater frontal spindle density (10 – 16 Hz) is related to worse episodic OMC (Fillmore et al., 2021). Our negative associations between spindles and OMC observed in MCI differ to findings showing that NREM central spindle duration may be pivotal to verbal episodic OMC in MCI (Lam et al. 2021) and those that found no associations with N2 frontal spindles (both slow and fast density) in aMCI (Westerberg et al., 2012). Comparability of these studies examining spindles in cognitively intact and MCI older samples are difficult given the differences in selected electrode placement, staging, frequency ranges and spindle metrics, which may be one explanation for the mixed findings observed to date (Muehlroth & Werkle-Bergner, 2020). It is plausible that structural and functional changes that occur in those with early forms of brain degeneration, disrupt the neural networks required for OMC that are utilised in cognitively healthy older adults. Consequently, those with MCI may rely on alternate sleep neurophysiology to consolidate information, or perhaps rely on known key sleep features for learning and memory consolidation, such as spindles, as a compensatory mechanism. Alternatively, given the MCI sample in this study had greater scores of depression, notably in the naMCI subtype, and were using psychotropic medication, this may partially explain negative associations with OMC, as previous findings indicate associations with spindle dysregulation and memory consolidation (Nishida et al., 2016). In addition to greater depression scores, brain pathology differences between aMCI and naMCI may be one possible explanation for the differences in strength of OMC and sleep associations. With aMCI indicating increased amyloid burden (Yeung et al., 2022) and being at greater risk of development of AD (Levey et al., 2006), individuals with naMCI appear to be at greater risk of fronto-temporal and dementia with Lewy Bodies (Petersen, 2016).

An alternative explanation for the inconsistencies in findings between OMC and spindles in MCI could be that slow wave and spindle cross-frequency coupling are more pertinent for OMC compared to these frequencies examined on their own (Hoedlmoser et al., 2022). Preliminary evidence points to a delay in the phase lag between spindles and slow waves in older adults compared to younger adults (Helfrich et al., 2018), and preliminary evidence indicates this temporal coupling may facilitate OMC (Helfrich et al., 2018; Latchoumane et al., 2017; Molle et al., 2011). Structural integrity deficits in brain regions where key oscillations occur for memory consolidation such as the medial pre-frontal cortex, hippocampus, thalamus and entorhinal cortex have also been associated with disrupted coupling in ageing (Muehlroth et al., 2019). Additionally, slow oscillation and spindle cross-frequency coupling disruption has been shown to be further predictive of greater tau accumulation in the medial temporal lobe (Winer et al. 2019). This suggests that cross-frequency coupling between slow waves and spindles may potentially be a stronger indicator of cognitive decline compared to the examination of these brain waves in isolation.

Therefore, moving beyond examining slow waves and spindles in isolation, there is also a need to confirm whether there is a misalignment in the phase lag between these two brain waves in MCI samples. Our results in those with MCI reveal the importance of examining both slow and fast spindles in relation to OMC. Evidence from studies using slow oscillatory transcranial direct current stimulation during a nap paradigm in healthy older adults, provide further insights into the function of slow and fast spindles, with results indicating an increase in frontal slow oscillations (0.5-1 Hz) paralleled by a gain in fast spindle activity (power and density) at frontal and parietal derivations results in improvements in visuospatial but not verbal memory (Ladenbauer et al., 2016). Promising clinical interventions for sleep EEG and memory include transcranial direct current stimulation (Ladenbauer et al., 2016; Marshall et al., 2006; Marshall et al., 2011) and acoustic stimulation (Harrington & Cairney, 2021), which have been shown to have positive benefits in younger and older adults (Salfi et al., 2020). Clinical trials now need to be conducted with MCI to determine if directly targeting sleep neurophysiology can improve OMC, despite underlying brain degeneration, and how such interventions may need to be modified for those with MCI, and the MCI subtypes.

Limitations

While this study represents an important advance in understanding OMC in MCI, some limitations warrant mentioning. It is important to note that the MCI sample were characterised according to clinical criteria (Winblad et al., 2004) and the pathology underpinning their cognitive decline could not be confirmed with Alzheimer's Disease biomarkers (Albert et al., 2011). Further work examining

OMC in biomarker confirmed MCI is still required. In addition, the memory tasks utilised in this study were standardised neuropsychological tasks. Whilst this offers some benefit in interpretation, feasibility, scientific understanding within the literature and potential translation to the clinical environment, tasks comprising more items learned to criterion in the evening might be necessary to adequately probe the full range of memory decay, circumvent potential ceiling effects with simpler, shorter tasks or even determine factors which capture an optimal memory trace over a long sleep interval. However, it is worth noting that this sample did not appear to exhibit ceiling effects on next day memory recall, somewhat negating this possibility. Furthermore, whilst all participants received comprehensive neuropsychological testing, many of the cognitively intact control participants had subjective cognitive complaints which may have limited our ability to detect between group differences. This is of significance, as such subjects may still have preclinical AD or other early neurodegenerative brain changes.

Future directions

Based on the current findings and mixed results of previous literature, there is a need for future studies to report both absolute and relative SWA in order to account for intra-individual variability in EEG. In addition to this, studies in MCI should consider using consistent sleep parameters and methodology designs when examining OMC (Mantua, 2018). With recent evidence pointing to NREM characteristics as predictive of cognitive decline (Lucey et al., 2021; Taillard et al., 2019), there is a greater need to employ Alzheimer's disease biomarkers (Lucey et al., 2019) and structural neuroimaging (Lam et al., 2021; Mander, Zhu, et al., 2017) to better elucidate how the sleep-memory relationship changes with ageing as well as with the onset of cognitive decline. Examining underlying structural brain integrity would be beneficial in order to observe whether OMC is largely mediated by sleep changes alone, or at least partially attributed to underlying brain degeneration (Lam et al., 2021; Mander et al., 2015; Mander et al., 2014; Mander et al., 2013; Varga et al., 2016). In addition, utilising functional MRI-EEG during sleep may provide insights as to whether those with MCI are recruiting differing brain networks for memory consolidation, that may also provide more regional specificity for electrode placement choice when examining OMC and designing clinical trials. Given the clinically meaningful cognitive impairment in MCI, studies examining OMC in this group should consider tasks that are feasible to implement in a clinical setting and do not suffer from floor effects. Finally, given our secondary findings indicating that visuospatial OMC was significantly impaired in multiple-domain MCI compared to Controls only after controlling for depression, and previous studies showing the deleterious effects of sleep disturbance on memory in older adults with depression (Naismith et al., 2009; Naismith et al., 2011), future studies should also consider examining OMC in older adults with

depression. This information would provide critical information in the development of clinical trials for sleep and memory in older adults with and without MCI, such as cognitive behavioural therapy for insomnia (Cassidy-Eagle et al., 2018) and providing sleep strategies (Naismith et al., 2019).

Conclusion

This study overall revealed that using standardised neuropsychological tasks, visuospatial OMC is impaired in those with aMCI compared to Controls, though this may be partly mediated by age. Whilst verbal episodic memory is impaired more generally in MCI compared to Controls, no differences are observed in OMC. Of significance, there appears to be differential relationships between sleep neurophysiology and memory consolidation in Controls *vs.* those with MCI, with SWA being important for the former whilst greater fast spindles may well be detrimental to OMC in those with MCI, or alternatively could suggest the existence of compensatory mechanisms or the use of different neural networks for OMC due to underlying neurodegeneration. Further studies in biomarker confirmed MCI samples are now required to identify which clinical subtypes are most sensitive to sleep neurophysiology abnormalities and OMC impairment, as well as clinical trials to examine whether targeting spindles impacts memory consolidation in MCI samples.

Chapter 4

Overnight consolidation of spatial navigation memories is impaired in mild cognitive impairment and is uniquely related to loss of sleep spindles, hippocampal CA1 and dentate subfields.

4.1. ABSTRACT

Objective: Spatial navigation (SN) memory impairment is a hallmark feature of Alzheimer's disease (AD). However, its associations with sleep in older adults with mild cognitive impairment (MCI) are unknown. This study aimed to examine overnight memory consolidation (OMC) of an allocentric SN task and its associations with sleep microarchitecture, medial temporal lobe (MTL) volume and medial prefrontal cortex (mPFC) thickness.

Methods: Participants included cognitively intact Controls (n= 25, M_{age}= 66), persons with non-amnestic MCI (n= 22, naMCI) (M_{age}= 69) and amnestic MCI (n= 10, aMCI) (M_{age}= 67). All were phenotyped medically and neuropsychologically, received neuroimaging, and underwent overnight polysomnography (PSG). Participants were trained on a novel clinical allocentric SN task (CASNAT) pre-sleep. SN memory was assessed pre- and post-sleep and OMC was calculated by the % change in error scores when tested from familiar or novel start locations ([morning score/evening score]*100) to assess egocentric or allocentric memory respectively. From PSG, slow oscillation EEG power (SO; 0.25–1 Hz), slow wave activity (SWA; 0.5–4.5 Hz), and slow and fast sleep spindle density were derived. Right CA1, dentate gyrus (DG) and entorhinal cortex (ERC) volumes were computed using ASHS software, and thickness of the mPFC was measured using Freesurfer. Spearman's and pearson's correlations were used to examine associations between OMC % with EEG and neuroimaging.

Results: In the familiar location, Controls retained what they had learnt overnight, and improved slightly in the novel location. Compared to controls, aMCIs performed significantly worse on overnight SN from the novel start location (*omega*^{2}= .09, *p*= .032). The pooled MCI sample performed significantly worse than Controls on OMC from a familiar location (*Cohens d*= -.67, *p*= .016), however no differences were found for the MCI subgroups. Worse OMC from a novel location was associated with reduced frontal slow spindles and there was a trend with parietal fast spindles in aMCI. Greater mPFC thickness was associated with worse OMC in Controls, and in MCI, right CA1 and DG volume was associated with worse OMC. Age partially influenced associations with mPFC and CA1, but not DG.

Conclusion: On a novel task of egocentric and allocentric SN, spatial OMC is impaired in MCI and this relates to both reduced slow sleep spindles as well as smaller volumes of key hippocampal subfields. Further research examining key mediators of impaired allocentric SN OMC is now warranted, particularly in the aMCI subtype.

Keywords: mild cognitive impairment, dementia, sleep, spindles, hippocampus, dentate, CA1.

4.2. INTRODUCTION

Non-rapid eye movement (NREM) sleep changes occur in ageing; a component of sleep postulated for long-term memory consolidation (Rasch & Born, 2013). Changes are evidenced using overnight polysomnography, indicating reduced time in slow wave sleep (SWS) (Carrier et al., 2011; Ohayon et al., 2004), reduced slow wave activity (Mander et al., 2013) and reduced fast spindle density (Sprecher et al., 2016). These features of sleep are further attenuated in mild cognitive impairment (MCI) (D'Atri et al., 2021; D'Rozario et al., 2020; Gorgoni et al., 2016; Westerberg et al., 2012); a prodromal phase of dementia (Gauthier et al., 2006). Two established MCI subtypes classified by neuropsychological assessment are amnestic (aMCI) and non-amnestic (naMCI) MCI, defined by predominant impairment in memory and non-memory (e.g. processing speed, executive function) domains respectively (Petersen et al., 1999). Subtypes of may MCI differ with respect to markers of structural brain integrity (Broadhouse et al., 2019; Csukly et al., 2016) and disease trajectory and prognosis (Alexopoulos et al., 2006; Rountree et al., 2007), with the aMCI subtype most likely to develop Alzheimer's disease (AD) (Jungwirth et al., 2012; Levey et al., 2006).

The relationship between cognitive impairment and changes in sleep neurophysiology have been under-explored in MCI and its subtypes. There is a dearth of research examining how overnight memory consolidation (OMC) might be impacted in MCI, and how this may relate to alterations in sleep macro and microarchitecture. Beyond advancing our scientific understanding of these inter-relationships, such work would facilitate development of targeted interventions to improve memory in MCI.

To date, there have been two studies that have examined associations between sleep microarchitecture and OMC in persons with MCI (Lam et al., 2021; Westerberg et al., 2012). Using a 44-item verbal Word-Pair Associates Task, Westerberg and colleagues found that relative to Controls, a small sample of persons with aMCI had reduced OMC but such decrements were not evident on an object priming task (Westerberg et al., 2012). Using a 32-pair verbal word pair task, a more recent study by Lam and colleagues found no overall group differences between MCI participants and Controls (Lam et al., 2021). However when analyses were restricted to only those with multiple-domain (impairment on two or more tests of memory and/or non-memory domain age and education matched), deficits in OMC were evident relative to Controls (Lam et al., 2021). For these two studies, no clear pattern regarding NREM sleep neurophysiology correlates of OMC has yet emerged. Specifically, Westerberg and colleagues (Westerberg et al., 2012) found that reduced frontal SWA and theta (but not spindles)

in NREM and REM were associated with impaired OMC performance in the Control group. By contrast, Lam and colleagues reported that reduced central spindle duration (but not SWA or slow oscillations) was associated with worse OMC in MCI (Lam et al., 2021). Both studies demonstrate the inconsistencies in sleep benefits on OMC in ageing (Baran et al., 2016; Cherdieu et al., 2014; Gui et al., 2017; Scullin, 2013; Sonni & Spencer, 2015) and highlight the need to assess OMC across the cognitive spectrum. Furthermore, the role of sleep for OMC in other memory domains has not been explored in MCI. Therefore, the specific sleep microarchitecture features most salient for successful OMC in MCI remain unclear.

Of relevance, spatial navigation (SN) changes in ageing and AD significantly impact functional capacity such as driving (Pavlou et al., 2017), navigating a familiar environment or learning new routes (Guariglia & Nitrini, 2009). Two key frames of reference for SN include *egocentric* SN - self to object relation encoding, and *allocentric* SN - reference between objects and relation between environmental characteristics from one another (Li & King, 2019). Allocentric self-reference requires higher-order processing, which can be referred to as a 'cognitive map' (Tolman, 1948). This type of self-reference allows for a more flexible navigation system. A typical test of SN is the Morris Water Maze task (MWMT) (Morris et al., 1982), which has been used in laboratory rodents and in humans. Participants in the MWMT are trained to find a hidden goal location in a pool or arena surrounded by distal landmarks and spatial cues. If the start location on each trial remains constant, they can learn to use egocentric strategies to find the goal location (e.g. by learning a simple path from the start to the goal location [route learning] or by associating the goal with a single proximal landmark [beaconing]) and/or the location of the goal in allocentric space (e.g. by learning the goal's location with reference to multiple distal landmarks). Evidence shows that both egocentric and allocentric SN is impaired in ageing (Tuena et al., 2021), in particular allocentric SN (Moffat & Resnick, 2002), and this decrement is especially pronounced in MCI and early AD (Colombo et al., 2017; Gazova et al., 2012; Laczo et al., 2012; Laczo et al., 2010; Laczo et al., 2009; Serino et al., 2015). Allocentric SN has been shown to predict conversion from participants with multiple-domain MCI to AD (Wood et al., 2016) using the Four Mountains Task; a well-established measure of allocentric SN (Hartley et al., 2007). Egocentric and allocentric SN have also be shown to be predictive of MCI subtypes (Laczo et al., 2009); and those with aMCI in particular, have been shown to have impairment in allocentric SN. Using a battery of SN tests, which included allocentric subtests (landmark replacement and map drawing), aMCI participants performed significantly worse compared to naMCI participants and Controls across all SN tests, whereas naMCI and Controls performed similarly (Rusconi et al., 2015). Given that research is showing that having a greater overall risk of dementia (Exalto et al., 2013) is

linked with compromised allocentric (but not egocentric) SN (Ritchie et al., 2018), there is a greater need to investigate factors affecting allocentric SN in older prodromal populations.

Converging studies have identified key brain regions that underpin effective egocentric and allocentric SN (Ekstrom et al., 2017). The significant role of the medial temporal lobe (MTL) for SN was identified with the early discovery of hippocampal 'place cells' (O'Keefe & Dostrovsky, 1971), in particular within the CA1 and CA3 (McNaughton et al., 1983), and later the discovery of 'grid cells' in the entorhinal cortex (Hafting et al., 2005). When recording cells within the MTL when person is placed in a virtual environment, cells within this region 'respond' (i.e. spike rate) when the participant is viewing landmarks (Ekstrom et al., 2003). Egocentric SN has shown to rely on the parietal and retrosplenial cortex (Burgess, 2006; Ekstrom et al., 2014; Maguire et al., 2000; Nemmi et al., 2017; Weniger et al., 2011; Wolbers & Wiener, 2014), whereas for allocentric SN the hippocampus, in particular right hemisphere and entorhinal cortex are significant (King et al., 2002; Laczo et al., 2017; Maguire et al., 1998; Mokrisova et al., 2016; Nedelska et al., 2012; Suthana et al., 2009; Tolman, 1948). In people with aMCI, smaller hippocampal size, notably the right hippocampus, has been linked to allocentric SN impairment (Laczo et al., 2017; Laczo et al., 2014; Lithfous et al., 2013; Weniger et al., 2011), and has been shown to account for the differences in allocentric (but not egocentric) SN memory (Laczo et al., 2014). Of interest, the hippocampal CA1 subfield undergoes significant loss of neuronal density in AD (Padurariu et al., 2012), and has been linked to reduced verbal OMC in MCI (Lam et al., 2021). Furthermore, both the CA1 and dentate gyrus subregions of the hippocampus have found to distinguish aMCI from naMCI and those with subjective memory complaints (Broadhouse et al., 2019). These studies highlight the overlap between MTL regions important for SN memory and those impaired in MCI. However, as yet, we do not know how the hippocampal subregions may be linked to overnight consolidation of SN memories in older healthy controls or those with MCI.

Indeed, relative to the wealth of studies examining the overnight consolidation of verbal material, there is currently a dearth of research examining how egocentric and allocentric SN are consolidated overnight during sleep, and whether consolidation is further compromised in MCI. Studies in younger adults have confirmed the benefit of sleep on topographical orientation, route learning in an unfamiliar environment and memory 'binding' (i.e. memory for object-location as whole) performance in a virtual environment (Abichou et al., 2019; Ferrara et al., 2006; Ferrara et al., 2008; Nguyen et al., 2013; Noack et al., 2021; Noack et al., 2017). Specifically, greater SWS (Peigneux et al., 2004) and NREM hippocampal slow waves (2.1 – 4 Hz, in-vivo) have been shown to be beneficial to SN recall in younger adults (Moroni et al., 2014), whereas obstructive sleep apnoea in REM has been shown to disrupt

spatial performance in middle aged (mean age 54 years) adults (Varga et al., 2014). Age has been identified as having a negative effect on SN OMC (Varga et al., 2016), with younger adults gaining benefit for sleep, but not older adults (Varga et al., 2016). Furthermore, greater relative SWA during NREM sleep in a pooled sample of healthy younger and older adults, was positively associated with SN OMC, but no associations were indicated with mPFC thickness (Varga et al., 2016). By contrast, previous findings identify the direct role of mPFC thinning negatively influencing verbal OMC (Mander et al., 2013), and indirectly via disruption to SWA (Mander et al., 2013). In older adults with and without obstructive sleep apnoea (mean age 67 years), the overnight change in completion time of a maze did not differ between groups, however in the morning, obstructive sleep apnoea participants performed significantly worse in completion time over three trials, compared to those without obstructive sleep apnoea. Greater SWA but not slow oscillations (<1 Hz), was positively associated with navigation completion time in the obstructive sleep apnoea group only. Spatial navigation tasks employed in these studies are a measure of orientation and spatial cognition (Mullins et al., 2021; Nguyen et al., 2013; Varga et al., 2016; Varga et al., 2014) that do not capture allocentric SN memory.

Recently, two studies have examined egocentric and allocentric memory consolidation in a napping paradigm in a younger sample. The first using young adult humans and rodents that contrasted egocentric and allocentric SN learning conditions. Both rodents and younger adults improved on SN memory performance after a nap compared to wake. The effect of sleep was numerically larger in the allocentric group, and marginally significant interactions were found between sleep and SN condition in rodents, but not in humans (Samanta et al., 2021). A follow-up study showed that the increase in performance in allocentric and egocentric learning after a nap was associated with an increase in slow oscillation and spindle cross-frequency coupling and a decrease in connectivity in the hippocampal network (Bastian et al., 2022).

There remain significant gaps in our understanding of how SN OMC is altered in MCI. Given the level of allocentric SN impairment in MCI, notably aMCI, and its function as a cognitive marker for AD progression (Allison et al., 2016; Lithfous et al., 2013; Wood et al., 2016), examining factors influencing SN is of clinical relevance. It is also of significance to distinguish whether allocentric SN OMC is preferentially impaired in aMCI compared to naMCI as indicated on daytime SN tests. Such findings will help inform the development of other SN OMC tasks such as those assessing egocentric SN, which may potentially be more important in naMCI given the differential brain regions involved.

Whilst the relationship between NREM neurophysiology and OMC is not a linear one, with level of encoding (Muehlroth, Sander, et al., 2020) and underlying brain pathology at play (Mander et al., 2015; Mander et al., 2016; Mander, Zhu, et al., 2017; Varga et al., 2016), OMC research in MCI is still within its infancy, hindering attempts to draw conclusions about the role of NREM neurophysiology in this prodromal population. However, if known, treatments targeting sleep neurophysiology may be developed and tested to determine if improving sleep can improve aspects of memory and in particular the consolidation of spatial material, highly relevant to optimal daily functioning.

The primary aim of the study was to determine whether older people with MCI differ from cognitively intact Controls in overnight consolidation of egocentric and allocentric SN memory. It was hypothesised that participants with MCI would have poorer pre-sleep learning and OMC scores compared to Controls, in particular those with aMCI would show preferential decrements in allocentric SN compared to naMCI and Controls, and that naMCI would show decrements compared to Controls. The second aim was to determine whether slow waves (SO, SWA) during SWS and spindle density (slow and fast) during stage 2 (N2) are associated with OMC. It was hypothesised that reduced frontal slow waves and frontal and parietal fast spindles would be associated with lower allocentric SN OMC. Finally, this study sought to determine whether mPFC thickness and key MTL volumes of the right hemisphere are associated with OMC. It was hypothesised that reduced mPFC thickness, and right CA1, dentate gyrus and entorhinal cortex volumes would be associated with worse OMC. As an exploratory aim, this study sought to investigate whether spatial strategies (allocentric, egocentric or random search) are related to OMC performance.

4.3. METHOD

Participants

Participants were recruited from the Healthy Brain Ageing Program at the Brain and Mind Centre, University of Sydney, a specialist assessment and intervention clinic for older people with cognitive and/or mood concerns. Clinical classification of MCI was conducted via consensus (two neuropsychologists, one geriatrician), whereby MCI criteria was met if performance was 1.5SD below age and education-matched norms on any neuropsychological test and in reference to pertinent clinical criteria (Winblad et al., 2004). Classification of aMCI was defined by impairment on at least one measure of delayed recall, and naMCI was defined by impairments in non-memory domains including attention, working memory, processing speed, visuospatial, language and executive functions. Where there was evidence of impairment in learning, but not delayed recall, and where this was supported by a lack of clinical evidence of memory impairment, individuals were classified as naMCI (Broadhouse et al., 2019).

Exclusion criteria were: a dementia diagnosis or Mini Mental State Examination (MMSE) (Folstein et al., 1975) <24; neurological disorders (e.g. Parkinson's disease, epilepsy); a history of (or current) psychosis; psychiatric disorder (e.g. bipolar, schizophrenia); intellectual disability; prior stroke or head injury (with loss of consciousness >30 minutes); alcohol or substance misuse; shiftwork; current sleep affecting medications (i.e. benzodiazepines, sedatives, hypnotics, lithium, tricyclics) and inadequate English to complete neuropsychological testing. Approval for this study was granted by the University of Sydney Human Research Ethics Committee and all participants gave written informed consent prior to study participation.

Clinical Assessment

Medical and mood assessment

Using a semi-structured interview, a geriatrician assessed medical history, medication use, alcohol use, sleep history, and obtained anthropometrics from which body mass index was derived. Depressive symptoms were self-reported using the 15-item Geriatric Depression Scale (GDS-15) (Yesavage & Sheikh, 1986a). Self-reported sleep quality measures were reported for descriptive purposes using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), Insomnia Severity Index Scale (ISI) (Bastien et al., 2001), Epworth Sleepiness Scale (ESS) (Johns, 1991). In addition, the Karolinska Sleepiness Scale (KSS) (Akerstedt & Gillberg, 1990; Kaida et al., 2006b) was administered pre- and post-sleep.

Neuropsychological assessment

As previously detailed (Duffy et al., 2014), a clinical neuropsychologist conducted a standardised neuropsychological assessment for each participant. Raw scores were converted to z-scores or scaled scores using age and (where relevant) education adjusted normative data. The neuropsychological battery included tests of:

- Episodic memory: Wechsler Memory Scale-3rd ed. (WMS-III) Logical Memory (LM) (Wechsler, 1997), Rey Auditory Learning Test (RAVLT) (Lezak et al., 2012);
- Visuospatial functions and memory: Rey Osterrieth Complex Figure Task (ROCFT) (Meyers & Meyers, 1995);
- Processing speed: Trail Making Test (TMT-A) (Tombaugh, 2004), Stroop: Color and Word Naming Test (Delis et al., 2001);
- Executive function: Trail Making Test (TMT-B) (Tombaugh, 2004), Controlled Oral Word Association Test (COWAT, letters F, A, S) (Lezak et al., 2004; Tombaugh et al., 1999); Stroop: Color-Word Interference test (Delis et al., 2001);
- Language: Boston Naming Test (BNT) (Roth, 2011);
- Global cognition was assessed using the MMSE (Folstein et al., 1975) and pre-morbid intellectual ability was estimated using the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001).

Overnight memory consolidation procedure

Participants completed an overnight in-laboratory polysomnography (PSG) at the Woolcock Institute of Medical Research. Participants were kept to their usual sleep and wake times and given a 7-8 hour sleep opportunity and were required to abstain from caffeinated beverages and alcohol at least three hours before evening testing and prior to morning testing. Memory tests were administered three hours prior to sleep, polysomnography set up one hour prior to sleep, and the Karolinska sleepiness scale was administered 10 minutes prior to sleep. In the morning the Karolinska sleepiness scale was again administered 10 minutes after wake and two spatial navigation recall tests (from familiar location and novel location) and a Spatial Navigation Questionnaire (SN-Q) (Appendix Table 1A) was administered one hour after wake (Figure 4.1).

Figure 4.1. Overnight process of Spatial Navigation (SN) testing on the CASNAT. Participants arrived at sleep laboratory where they were greeted by a researcher and had dinner prior to the commencement of memory testing. The CASNAT was administered three-hours prior to sleep, and a sleep technician set up the polysomnography (PSG) one-hour prior to sleep. After an eight-hour sleep opportunity, participants completed the morning recall one-hour after wake from a familiar and novel location, and the completed the Spatial Navigation Questionnaire.

Clinical allocentric spatial navigation task (CASNAT)

Evening

The CASNAT was developed using Unity software 2017 version 2. It consisted of three components administered in the evening; familiarisation phase I and II, learning phase, and recall phase. The overall evening task took 20-25 minutes to complete.

i) Familiarization phase I

Participants were given an opportunity to become familiar with using the four directional arrows on the keyboard. They were placed in the centre of an arena with no landmarks and were instructed to first look around and practice moving using the four arrows. Six white spheres surrounded the surface area participants could move on; participants were instructed to move towards them and try to hit each of them one by one. As they hit them, they would disappear (Figure 4.2.a).

ii) Familiarisation phase II

Once all six spheres disappeared, a new scene appeared of the same arena. Participants were instructed to explore as much of the small space as possible to find a treasure chest that is not visible. Once they made contact with the target item (treasure chest), it would appear. Once the chest was located, participants were directed to the learning phase. Participants had an unlimited amount of time to find the target item.

iii) Learning phase

The learning phase consisted of a circular open field arena with 20 landmarks surrounding it. The landmarks were arranged in three rings with the inner proximal ring consisting of four landmarks, and the middle and outer rings with eight landmarks each. The virtual environment was surrounded by a

mountain range and a sky box to increase the sense of parallax motion with the landmarks as participants moved in the central arena (Figure 4.2.b). Participants were asked to find a hidden treasure chest in the central arena across a series of five trials. Distance travelled in the arena was limited to 100m diameter from the center (XY: 0,0). The hidden target item was placed at XY: 50, 50 with the start location for each learning trial being from XY: -50, 50. The participants had four minutes to find the hidden chest, which would become visible when the participants collided with it. If participants did not find the target after two minutes they were provided a prompt with instructions again. If after four minutes they did not find it, they were teleported to the target item. They could not move to the next trial unless a 360 degree turn had been made so participants could get a sense of where the target item was in relation to the surrounding landmarks. Error scores in the learning phase were calculated as the distance between the participant's final position at the end of each trial and the goal location in virtual metres.

iv) Recall phase

After 30 minutes participants were given two test trials and they were instructed to move to where they thought the target item should be and press the letter 'x' on the keyboard to indicate where they think it might be. In the first test trial, participants started from the familiar start location (XY: -50, 50). Immediately after, participants began a second test trial beginning from a novel start location being from XY: 50, -50, opposite to where the familiar start location is but equidistant to the hidden goal location (Figure 4.2.c). Error scores were calculated as the distance between the participant's position at the end of each test and the goal location in virtual metres.

Morning

The morning component consisted of the two recall phases which took five minutes to complete and then participants undertook the SN-Q, one-hour post-sleep:

i) Recall phase

Recall from the familiar training starting location followed by the novel location was administered in the same format as the evening. Each participant had two tests – one starting from the familiar start location used in training and the second starting from the novel start location. As before, they were asked to move to the location where they thought the hidden chest would be and to press an 'x' key on the keyboard. Error scores were calculated as per the evening tests. Evening and morning error scores were converted to OMC% scores to indicate the change in error scores from evening to morning. OMC% was calculated as ([morning error scores] / [evening error scores] * 100). The OMC% scores

were then used as the dependent variables in subsequent correlation and regression analyses with the neurological and neuroimaging data.

ii) Spatial navigation questionnaire (SN-Q)

Immediately upon completing the spatial navigation task, participants were asked questions regarding their subjective experience of the task as well as cognitive strategies used during the learning and recall components of the task. The full questionnaire is provided in Appendix, Figure A1.

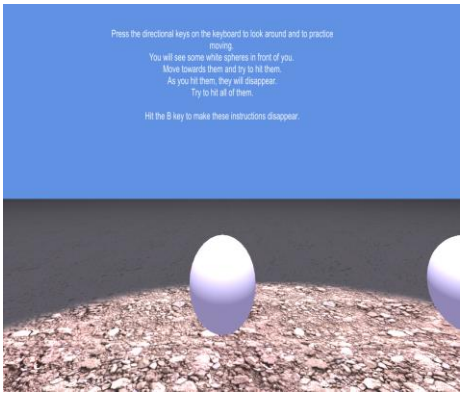
For descriptive purposes we have reported whether participants:

- Felt comfortable using a computer (Very much/Somewhat/Not at all);
- Had difficulty with orientation (Never/Sometimes/Always);
- Were 'creating' a map (mentally) when learning the location of the target item (Y/N);
- Noticed they were in a novel start location (Y/N); and,
- Did anything different when in the novel start location (Y/N).

In order to assess whether the type of strategy outlined above interacted with OMC, an open-ended question used to assess spatial navigation strategies: "*Could you tell me more about how you were trying to find the hidden chest*?" (question 9 in Appendix, Figure A1).

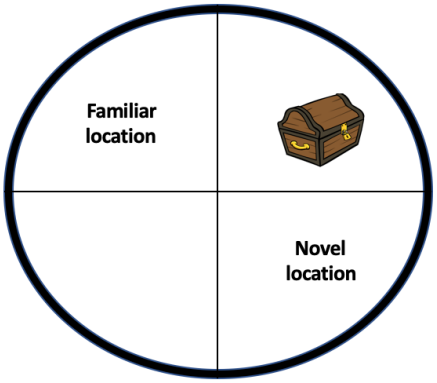
Participant's responses were coded via inter-rater reliability as being one of three strategies:

I. Egocentric (beaconing towards one landmark, following a specific path or vector from the familiar start location, or dead reckoning);
II. Allocentric; or,
III. Random search.



a. Familiarisation phase

b. Learning phase



c. Recall

Figure 4.2. Example of images of the CASNAT including the a) Familiarisation phase, b) Learning phase, and c) Recall phase. Image 4.2.a indicates two of the six white spheres participants are asked to 'hit'. The six spheres are placed in a 360 degree manner. Figure 4.2.b includes the treasure chest at the landmarks to the north of it. Figure 4.2.c illustrates a topographical viewpoint of the arena.

Polysomnography

Polysomnography (PSG, Grael System, Compumedics, Melbourne, Australia) was acquired using a ten-channel electroencephalography (EEG) montage (Fz-M1&M2/2, F3-M2, F4-M1, Cz-M1&M2/2, C3-M2, C4-M1, Pz-M1&M2/2, Oz-M1&M2/2, O1-M2, O2-M1); two electrooculographic (EOG) channels (left and right outer canthi), electromyogram (EMG) (submentalis, left and right leg), flow recording (pressure-based and thermal based), efforts (thoracic and abdominal), electrocardiogram (ECG) and finger oximeter. EEG data were sampled at 512 Hz. Sleep architecture stages were scored manually in 30 second epochs by a sleep technician using the American Association for Sleep Medicine (AASM) 2.2 scoring manual (Berry et al., 2012). A subsample (n = 26) underwent high-density EEG (256-channel) as described in Chapter 5. Electrophysiology data for this subsample was analysed using a 10-channel montage consistent with the methods outlined below.

EEG artefact processing

All night PSG recordings were subjected to automated EEG artefact processing. An algorithm identified artefactual EEG data at a resolution of five second epochs based on previously validated artefact detection threshold parameters (D'Rozario et al., 2015). Contaminated five second epochs were subsequently excluded from EEG analysis. Quantitative EEG (qEEG) measures were derived from all artefact-free sleep EEG recordings.

Power spectral analysis

Artefact-free epochs were analysed using a standard fast Fourier transform (FFT) with a rectangular weighted window for each non-overlapping 5-second epoch of EEG for frontal Fz-M1&M2/2 and parietal Pz-M1&M2/2 channels. We calculated absolute spectral power (μV^2) in the delta, theta, alpha, sigma and beta bands defined as EEG activity in each of the respective frequency ranges 0.5–4.5, 4.5–8, 8–12, 12-15 and 15–32 Hz. The EEG power for each sleep-staged 30-second epoch of the PSG recording was calculated by averaging data from up to six artefact-free five second epochs of EEG that comprised that 30-second recording segment. The weighted-average spectral power within the defined frequency bands was then computed for NREM (N2 and N3) sleep stages.

Spindle event detection algorithm

A spindle identification algorithm developed and written in Java (Version 1.6, Oracle, Santa Clara, CA, USA) automatically identified sleep spindle events during NREM sleep. The algorithm has been previously validated in MCI (Lam et al., 2021). The algorithm computationally performed the following steps: a band-passing Finite-Impulse-Response filter (11 – 16 Hz) was applied to the raw EEG signal yielding a time course of EEG activity in the sigma frequency range. A Hilbert transformation was applied to extract envelopes of the sigma EEG activity using a threshold calculated independently for Fz-M1+M2/2 and Pz-M1+M2/2 derivation. The threshold value for each channel was given by the formula: median amplitude (μV) + 1.0 x standard deviation amplitude of the signal. The duration threshold for spindle events was 0.5 – 3.0 seconds. An index of sleep spindle events per minute of N2 was calculated for overall spindle density (11 – 16 Hz, events per min), slow spindle density (11 – 13 Hz) and fast spindle density (13 – 16 Hz).

Sleep EEG variables of interest

The primary EEG measures of interest were: frontal absolute SO (0.25 – 1 Hz) during N3 (SWS); frontal SWA power (0.5 – 4.5 Hz) during SWS; frontal and parietal slow spindle density during N2 sleep; and, frontal and parietal fast spindle density during N2 sleep. Secondary EEG variables of

interest included overall frontal and parietal spindle density. Relative spectral power was also calculated for SWA during SWS ([N3 SWA/N3 delta+theta+alpha+sigma+beta]*100) and reported alongside absolute SWA power for completeness based on prior literature with spatial navigation OMC (Varga et al., 2016). In addition, based on previous studies with younger adults (Varga et al., 2014) and older adults (Lam et al., 2021; Mullins et al., 2021) we examined obstructive sleep apnoea as a potential confounder, using AHI during total sleep time and REM sleep.

Neuroimaging acquisition and analysis

A subsample of participants underwent magnetic resonance imaging (MRI) within three weeks of their PSG assessment using a 3-Tesla Discovery MR750 (General Electric Healthcare, Milwaukee, WI, USA) scanner at the Brain and Mind Centre (8-channel phased-array head coil (T1: n = 5, T2: n = 25) or 32-channel (T1: n = 46, T2: n = 26).

8-channel MRI. A 3D-T1-weighted BRAVO Spoiled Gradient-Recalled (SPGR) sequence was utilised (phase acceleration factor = 2), acquiring 196 sagittal slices (repetition time = 7.2 milliseconds; echo time = 2.8 milliseconds; flip angle = 12; matrix 256 × 256; 0.9 mm isotropic voxels), acquisition time = 4 minutes, 27 seconds. In addition, a 2D-T2-weighted Fast Spin Echo (FSE-XL) high-resolution hippocampal sequence was also utilised, acquiring 24 coronal slices (repetition time = 3000 milliseconds; echo time = 51.4 milliseconds; flip angle = 111; matrix 512 x 512; 0.25 x 0.25 x 2.0 millimetre voxels).

32-channel MRI. A 3D-T1-weighted BRAVO Spoiled Gradient-Recalled (SPGR) sequence was utilised (phase acceleration factor = 2), acquiring 176 sagittal slices (repetition time = 7.2 milliseconds; echo time = 2.8 milliseconds; flip angle = 12; matrix 256 × 256; 1.0 mm isotropic voxels), acquisition time = 4 minutes, 27 seconds. In addition, a 2D-T2-weighted Fast Spin Echo (FSE - XL) high-resolution hippocampal sequence was also utilised, acquiring 24 coronal slices (repetition time = 3200 milliseconds; echo time = 55.04 milliseconds; flip angle = 111; matrix 512 x 512; 0.25 x 0.25 x 2.0 millimetre voxels).

Automatic segmentation of hippocampal subfields (ASHS). The ASHS software package (v2.0.0; https://sites.google.com/site/hipposubfields/) was used to automatically calculate the volumes of each hippocampal subfield. We selected "UPENN PMC atlas" as the Atlas package since it is suitable for labelling older adult brains in 3 Tesla MRI (Yushkevich et al., 2015). Briefly, as described elsewhere (Wisse et al., 2016), ASHS software applies deformable registration of the T1- and T2-weighted images, multi-atlas joint label fusion and voxel-wise learning-based error correction to calculate

automatically the volumes of each hippocampal subfield. Per ASHS guidelines (https://sites.google.com/site/hipposubfields/), due to substantial differences in the MRI intensity characteristics of our T2-weighted images compared with the intensity characteristics of the T2-weighted images in the atlas package, we used the recommended JLF/CL-lite result (i.e. corr_nogray). Our primary regions of interest for the right hemisphere were delineated: cornu ammonis 1 (CA1), dentate gyrus (DG), and entorhinal cortex (ERC) (Yushkevich et al., 2015) (Figure 4.3). The quality of all the automatic segmentations generated by ASHS was visually checked. Participants with errors in subfield segmentations were either entirely excluded or partially excluded on a subfield-by-subfield basis.

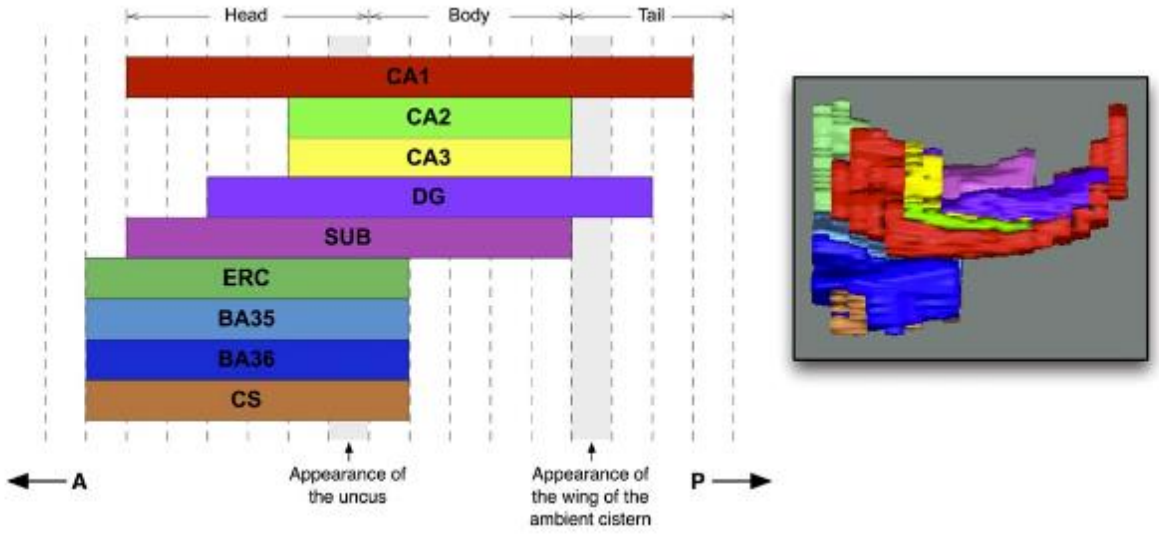


Figure 4.3. Anatomical label of the hippocampaus and its surrounding regions using ASHS software. It shows the extent along the anterior-posterior axis (A-P in the figure) of the different anatomical labels included in the segmentation protocol. Dashed vertical lines outline MRI slices (the number of slices is variable from subject to subject). A 3D rendering of the manual segmentation viewed from a location superior to the hippocampus is shown for reference. Abbreviations: ***CA**: cornuammonis; ***DG**: dentate gyrus; SUB: subiculum; ***ERC**: entorhinal cortex. BA35/BA36: (which together form the perihinal cortex); CS: collateral sulcus. *CA1, DG and ERC used in analysis. Image retrieved from Yushkevich and colleagues (2015) (Yushkevich et al., 2015).

Freesurfer processing

T1-weighted scans were processed using the Freesurfer (Fischl et al., 2002) v6.0 recon-all processing stream, which includes motion correction, skull-stripping, Talairach transformation and cortical parcellation. This pipeline utilised the Desikan-Killiany atlas (Desikan et al., 2006). Our primary region of interest was the medial prefrontal cortex (mPFC) thickness, calculated based on the average

of the medial orbitofrontal cortex, rostral and caudal anterior cingulate cortex (Fuster, 2015) (Figure 4.4). Associations between OMC with mPFC subregions were reported: medial orbitofrontal cortex, rostral and caudal anterior cingulate cortex in the Appendix, Table A8. Data was visually inspected for errors for each region of interest.

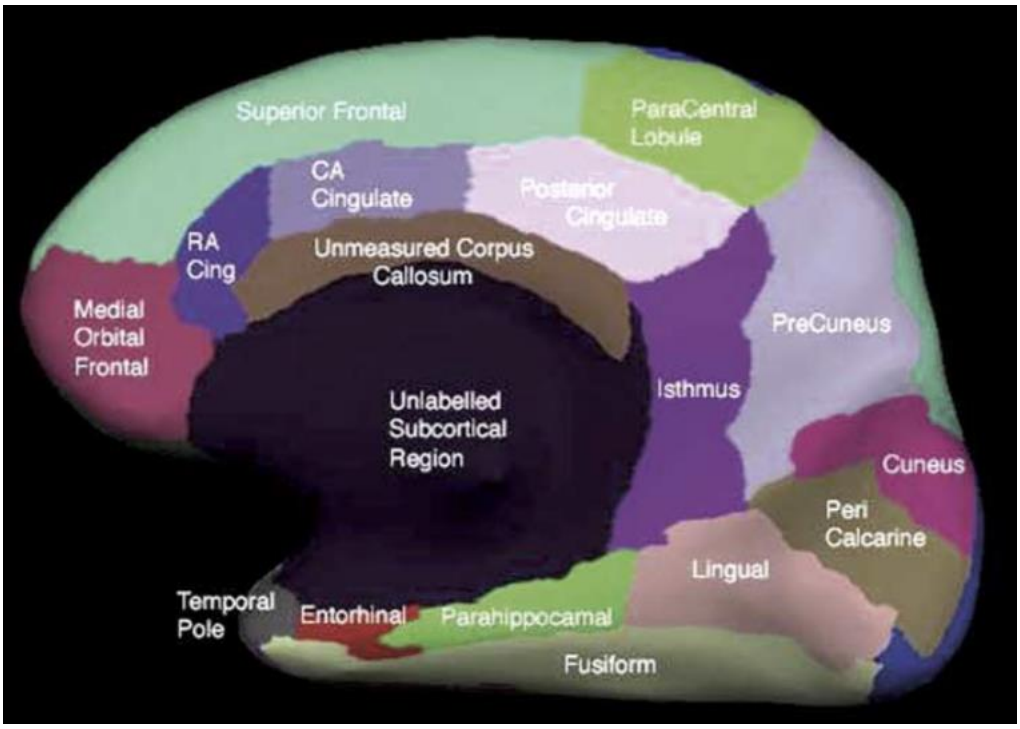


Figure 4.4. Freesurfer v6 automated labelling atlas showing inflated cortical representations of medial view of hemisphere. The medial prefrontal cortex volume (mm) is calculated by mean thickness of the medial orbitofrontal, rostral anterior cingulate and caudal anterior cingulate thickness. Image retrieved from Desikan and colleagues (2006) (Desikan et al., 2006).

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS version 28, IBM Corp. Sydney, Australia) for Macintosh. An independent samples t-test, welch's test and chi-square goodness of fit test was used for two groups (pooled MCI [pMCI], Controls) where applicable, and a one-way analysis of variance (ANOVA) was used for three groups (aMCI, naMCI, Controls) to assess group differences in clinical, sleep and neuroimaging characteristics. Cohen's *d* or hedges *g* was used to measure effect sizes. Cohen's *d* and hedges *g* effect size were calculated as: small = 0.2, medium = 0.5, large = 0.8, and omega^2 were calculated as: small = .01, medium = .06, large = .14 (Brydges, 2019; Cohen, 1988; Lakens, 2013). A univariate general linear model (GLM) was used to assess neuroimaging group differences, controlling for age. An independent samples t-test was used to assess OMC for both recall components (familiar, novel) between Controls and MCI and a one-way ANOVA was used for MCI subtypes. Data transformations were conducted in order to account for extreme outliers for OMC% results. Participants were removed if they did not attempt to move from the start location in either the evening or the morning tests before they hit the 'x' to mark the goal location. A univariate GLM was used to confirm results were not driven by age. This was repeated to assess for an interaction between strategies used and group for familiar and novel OMC% independently for pMCI and Controls only due to small sample size. Spearman's correlations were used to assess associations between sleep microarchitecture and mPFC thickness with OMC% for allocentric spatial navigation (novel location). Spearman's correlations was also used to examine OMC associations with apnoea hypopnea index (a potential confounder). Pearson's correlation was used to assess MTL grey matter volume with OMC%. A partial correlation was used to examine whether MRI or sleep microarchitecture associations with OMC% were related to age, and as well coil type (8 or 32 channel) for MRI. Correlations were conducted for OMC% for novel location only (allocentric spatial navigation memory). Correlations between OMC% and sleep microarchitecture was conducted in Controls and MCI subtypes. For neuroimaging, correlation analysis was conducted in Controls and pooled MCI (pMCI) sample only due to data loss as a subsample completed MRI scans. All analyses were two-tailed and employed an alpha level of 0.05.

4.4. RESULTS

Demographics

A total of 57 participants (males = 24, females = 33) were recruited, of which 25 were cognitively intact Controls (M_{yrs} = 69), and 32 met clinical criteria for MCI (M_{yrs} = 66) according to consensus. Within the MCI group, 10 met criteria for aMCI and 22 for naMCI. The sample included one

participant meeting DSM-IV criteria for major depression. No group differences were found in clinical measures such as age, sex, years of education, predicted IQ (WTAR), body mass index, current depressive symptoms (GDS-15), self-reported sleep disturbance (PSQI and ISI). However, aMCI participants had significantly reduced MMSE scores compared to naMCI and Controls (Table 4.1).

Table 4.1. Demographic, clinical and neuropsychological group differences.

	Controls *M, sd*	pMCI *M, sd*	*t*	*p*	aMCI *M, sd*	naMCI *M, sd*	*F*	*p*
Demographic								
Age, *yrs*[a]	66.4 (9.3)	68.7 (7.5)	-1.0	.318	66.6 (10.6)	69.6 (5.7)	.96	.389
Gender, n % female[b]	14, 56%	19, 59%	.07	.798	5, 50%	14, 44%	.59	.745
Education, *yrs*[a]	14.4 (2.9)	14.8 (2.7)	-.58	.562	15.0 (2.2)	14.7 (2.9)	.20	.819
Body Mass Index (BMI)[a]	27.7 (4.6)	27.7 (4.1)	-.05	.964	26.6 (4.4)	28.1 (4)	.38	.688
Clinical								
Mini mental state examination[a]	29.4 (1.3)	28.6 (2.1)	1.7	.103	27.1 (3.2)	29.2 (.9)	7.2	**.002*[1,2]**
WTAR (Predicted IQ)[a]	104.5 (9)	106.8 (9.7)	-.95	.349	105.3 (11)	107.6 (9.2)	.64	.533
PSQI (Global Score)[a]	6.0 (2.9)	5.6 (3.6)	.46	.649	5.6 (5)	5.6 (2.9)	.10	.903
Insomnia severity index[a]	7.8 (5.6)	8.2 (7.1)	-.24	.814	8.4 (9.8)	8.2 (5.9)	.03	.969
Epworth sleepiness scale[a]	6.5 (3.8)	7.1 (4.4)	-.60	.549	7.7 (4.8)	7.0 (4.3)	.29	.751
Karolinska sleepiness scale (pm)[a]	5.9 (1.4)	6.2 (1.6)	-.73	.471	5.9 (2.1)	6.4 (1.5)	.55	.58
Karolinska sleepiness scale (am)[a]	5.4 (1.5)	4.9 (1.7)	.98	.333	4.6 (1.8)	5.1 (1.7)	.81	.45
Geriatric depression scale-15[a]	2.8 (2.3)	2.1 (2.8)	.93	.358	1.1 (1.2)	2.6 (3.2)	1.5	.242
Neuropsychological								
RAVLT (7/6) z score[c]	.01 (.52)	-.25 (1.2)	1.1	.272	-.14 (1.7)	.12 (.4)	7.5	**.001*[1,2]**
Logical Memory ASS[a]	13.0 (2.1)	10.9 (3)	2.0	.056	9.1 (4.4)	11.7 (1.6)	5.9	**.005*[1,2]**
ROCFT (3min) z score[a]	65.0 (26.3)	57.7 (32.7)	.89	.377	52.9 (36.7)	59.9 (31.3)	.58	.566
Trials A z score[a]	.97 (.6)	.58 (.8)	2.1	**.045***	.65 (.73)	.55 (.8)	2.1	.128
Trials B z score[a]	.49 (.61)	.43 (.5)	.38	.705	.64 (.44)	.35 (.5)	1.0	.376

Note. ***p<.05. ****p<.01.** [a]Independent samples t-test to compare Controls and pMCI. [b]Chi-square goodness of fit test. [c]Welch's t-test to compare Controls and MCI. One-way ANOVA to compare all Controls and MCI subtypes. [1]Significant group difference between Controls and aMCI. [2]Significant group difference between naMCI and aMCI. WTAR = Wechsler Test of Adult Reading. PSQI = Pittsburgh Sleep Quality Index. RAVLT = Rey Auditory Verbal Learning Test. ROCFT = Rey-Osterrieth Complex Figure Test

Sleep macroarchitecture and microarchitecture group differences

Group differences in sleep microarchitecture and microarchitecture presented for descriptive purposes only. No group differences were found on any sleep macroarchitecture or spindle measures between Controls and MCI or their subtypes. Although not statistically significant, pMCI participants showed a trend towards reduced absolute SWA power compared to Controls (p = .058, Cohen's d = -.562) (Table 4.2.a). No significant differences in SWA were found when examining MCI subtypes (Table 2.b).

Neuroimaging group differences

Of the 57 participants, 51 completed neuroimaging. Group differences presented for descriptive purposes only. As shown in Table 4.2.a, pMCI participants had significantly reduced mPFC thickness compared to Controls, and when examining subtypes, this was significantly reduced in naMCI compared to Controls (Table 4.2.b). No significant group differences were found between Controls and pMCI on the right CA1 GMV, however they demonstrated reduced right DG GMV compared to Controls. Similar results were found for right ERC GMV, however this did not reach significance (p = .055, hedges g = .594) (Table 4.2.a). No group differences were found in MCI subtypes for right CA1, DG or ERC GMV. Results remained unchanged after controlling for age. Left CA1, DG and ERC GMV group differences are reported in the Appendix, Table A2 and A3.

Table 4.2.a. Sleep macroarchitecture, microarchitecture and neuroimaging group differences between Controls and pMCI.

	Controls *M, sd*	pMCI *M, sd*	*t*	*p*	*Cohen's d*
Macroarchitecture					
Total sleep time, *mins*[a]	367.6 (78.0)	350.4 (54.0)	.98	.331	.26
Sleep onset latency, *mins*[b]	29.8 (56.9)	15.7 (14.7)	1.2	.239	.36
REM onset latency, *mins*[a]	148.9 (77.7)	127.5 (69.5)	1.1	.285	.29
Wake after sleep onset, *mins*[a]	93.6 (72.4)	78.0 (54)	.18	.357	.25
Sleep efficiency %[a]	76.2 (16.9)	78.4 (12.4)	-.56	.580	-.15
Stage N1, *mins*[a]	61.0 (25.3)	48.8 (26.9)	1.7	.087	.47
Stage N2, *mins*[a]	160.0 (49.5)	153.8 (46.1)	.48	.629	.13
Stage N3, *mins*[a]	83.0 (37.7)	91.6 (27.7)	-.99	.327	.13
Slow wave sleep %[a]	23.0 (9.3)	26.2 (6.9)	-1.5	.135	-.41
Rapid eye movement (REM) %[a]	15.7 (5.8)	15.9 (5.6)	-.14	.893	-.04
AHI REM[a]	26.3 (20.4)	25.6 (21.2)	.13	.895	.04
AHI total sleep time[a]	17.5 (12.3)	14.2 (16.6)	.83	.409	.22
Arousal index[a]	22.1 (8.4)	18.1 (11.1)	1.4	.165	.40
Microarchitecture					
Absolute slow oscillations(*f*)[b]	458.4 (277.6)	359.3 (155.4)	1.6	.126	.46
Absolute slow wave activity(*f*)[b]	642.0 (312.0)	499.6 (197.1)	2.0	.058	.56
Relative slow wave activity (*f*)	90.4 (3.3)	89.7 (3.5)	.79	.433	.21
Fast spindle density(*f*)[a]	.21 (.5)	.26 (.4)	-.38	.708	-.10
Slow spindle density(*f*)[a]	.91 (.5)	.96 (.7)	-.30	.763	-.08
Overall spindle density(*f*)	1.1 (.8)	1.2 (.8)	-.45	.656	-.12
Fast spindle density(*p*)[a]	1.8 (1.2)	1.7 (1.4)	.07	.945	.02
Slow spindle density(*p*)[a]	.57 (.8)	.48 (.7)	.48	.635	.13
Overall spindle density(*p*)	.8 (.6)	.7 (.6)	.31	.755	.09
Neuroimaging					*hedges g*
Medial prefrontal cortex (mm)[a, c]	2.70 (.1)	2.62 (.1)	2.1	**.045***	.58
Right Hippocampal CA1(mm^3)[a, d]	1393.2 (160.6)	1270.8 (232.5)	1.5	.132	.57
Right Dentate gyrus right (mm^3)[a, d]	828.1 (134.1)	739.3 (145.8)	2.1	**.046***	.62
Right Entorhinal cortex (mm^3)[a, d]	444.7 (63.2)	403.5 (72.3)	2.0	.055	.59

Note. ***p<.05. ****p<.01.** [a]Student t-test. [b]Welch's t-test. REM = Rapid eye movement. AHI = Apnoea hypopnea index. Arousal index = Events p/hr (Controls n = 23, pMCI n = 28). [c]Thickness measured in mm. [d]Grey matter volume measured in mm^3. *f* = frontal**,** *p* = parietal. Slow oscillations and slow wave activity absolute power calculated for slow wave sleep (N3). Spindle density = events per hour, calculated for N2. Relative slow wave activity calculated as ([N3 delta/N3 delta+theta+alpha+sigma+beta]*100).

Table 4.2.b. Sleep macroarchitecture, microarchitecture and neuroimaging group differences between Controls and MCI subtypes.

	aMCI *M, sd*	naMCI *M, sd*	*F*	*p*	*omega*^{2}
Macroarchitecture					
Total sleep time, *mins*	373.0 (45.9)	340.2 (55.2)	1.4	.266	.01
Sleep onset latency, *mins*	12.2 (7.9)	17.3 (16.9)	.9	.395	<-.00
REM onset latency, *mins*	109.9 (47.7)	135.5 (77.1)	1.0	.373	<.00
Wake after sleep onset, *mins*	70.2 (47.7)	81.6 (57.3)	.5	.597	-.02
Sleep efficiency %	81.5 (9.8)	76.9 (13.3)	.5	.616	-.02
Stage N1, *mins*	52.3 (27.9)	47.2 (27.0)	1.6	.206	.02
Stage N2, *mins*	165.8 (46.9)	148.4 (45.8)	.6	.567	-.02
Stage N3, *mins*	97.6 (34.6)	88.8 (24.3)	.7	.485	-.01
Slow wave sleep %	26.0 (7.7)	26.3 (6.7)	1.1	.329	.01
Rapid-eye movement (REM) %	15.4 (4.8)	16.2 (6.0)	.1	.926	-.03
AHI REM	27.3 (20.1)	24.8 (22.1)	.1	.946	-.03
AHI total sleep time	18.6 (20.2)	12.1 (14.8)	.1	.373	<.00
Arousal index	19.4 (15.9)	17.5 (8.4)	1.1	.348	<.00
Microarchitecture					
Absolute slow oscillations(*f*)	372.0 (158.6)	353.2 (157.5)	1.4	.254	.02
Absolute slow wave activity(*f*)	509.7 (196.5)	494.8 (202.1)	2.1	.132	.04
Relative slow wave activity (*f*)	88.7 (4.1)	90.1 (3.1)	.9	.399	-.01
Fast spindle density(*f*)	.24 (.4)	.26 (.4)	1.0	.924	-.04
Slow spindle density(*f*)	.91 (.5)	.99 (.8)	.1	.900	-.03
Overall spindle density(*f*)	1.1 (.8)	1.3 (.9)	.2	.857	-.02
Fast spindle density(*p*)	1.7 (1.1)	1.7 (1.5)	.1	.998	-.04
Slow spindle density(*p*)	.38 (.4)	.53 (.8)	.3	.770	-.03
Overall spindle density(*p*)	2.1 (1.2)	2.3 (1.6)	.1	.929	-.02
Neuroimaging					
Medial prefrontal cortex (mm)[a]	2.68 (.1)	2.58 (.1)	3.7	**.032*[1]**	.10
Right Hippocampal CA1 (mm^3)[b]	1191.5 (340.8)	1313.6 (147.8)	2.0	.154	.06
Right Dentate gyrus right (mm^3)[b]	699.8 (196.9)	760.2 (111.8)	2.6	.083	.07
Right Entorhinal cortex (mm^3)[b]	394.9 (100.2)	407.2 (59.9)	2.0	.149	.04

Note. ***p< .05.** One way ANOVA. REM = Rapid eye movement. AHI = Apnoea hypopnea index. Arousal index = Events p/hr (Controls n = 23, MCI n = 28)· [a]Thickness measured in mm.[b]Grey matter volume measured in mm^3. *F* = frontal, *p* = parietal. Slow oscillations and slow wave activity absolute power calculated for slow wave sleep (N3). Spindle density = events per hour, calculated for N2. Relative slow wave activity calculated as ([N3 delta/N3 delta+theta+alpha+sigma+beta]*100). [1]Significant group differences between Controls and naMCI.

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Learning

Upon visual inspection across the five learning trials, Controls and aMCI improved from trial one to two, whereas naMCI performed worse. From trial one to five (final trial), Controls improved from their baseline score, naMCI performance remained the same as baseline score, and aMCI performed worse compared to their baseline score (Figure 4.5.a).

Of the average error score across the five trials, pMCI participants performed significantly worse than Controls with moderate effect sizes (omega^2 = .08, p = .047), however this difference was attenuated when controlling for age (p = .063). A post-hoc analysis revealed that aMCI participants performed significantly worse compared to Controls across the average of the five trials (p = .039). Results remained unchanged after controlling for age (p = .042) (Table 4.3.a).

Overnight memory consolidation (OMC)

MCI *vs.* Controls: In the familiar location test, pMCI participants performed significantly worse in remembering the location of the target item overnight compared to Controls with moderate – large effect sizes indicated (Cohen's d = -.67, p = .016), however no group differences were found when participants were placed in a novel start location, although moderate effect sizes were indicated (Cohen's d = -.54, p = .055). Results remained unchanged when controlling for age (Table 4.3.a). Two extreme outliers that were significantly skewing results were removed for the familiar location test, and three were removed in the novel location test.

MCI subtypes: No group differences were found with Bonferroni-adjusted post-hoc pairwise contrasts when participants were placed in a familiar start location (overall model: omega^2 = .07, p = .052). When examining the novel start location with Bonferroni-adjusted post-hoc pairwise contrasts (overall model: omega^2 = .09, p = .032), aMCI performed significantly worse in remembering the location of the target item compared to Controls (p = .027), however there were no significant differences between Controls and naMCI or between naMCI and aMCI (Figure 5.b). Results remained unchanged after controlling for age (p = .031) (Table 4.3.a).

Table 4.3.a. Spatial Navigation Task: Quantitative measure of learning and memory consolidation from a learnt and novel location.

	Controls *M, sd*	pMCI *M, sd*	*t, F*	*p*	*cohens d*	aMCI *M, sd*	naMCI *M, sd*	*F*	*p*	*omega*^{2}
Learning (PM)[b,c]	25.4 (13.7)	34.8 (20.7)	-2.0	**.047***	-.518	42.5 (24.9)	31.3 (18.0)	3.3	**.044***[1]	.08
Familiar										
PM error score[a]	66.5 (34.0)	66.8 (38.0)	-.03	.977	-.008	60.5 (39.7)	69.6 (37.7)	.2	.809	-.03
AM error score[a]	65.2 (39.3)	76.8 (35.9)	-1.2	.250	-.310	72.2 (41.1)	78.8 (34.1)	.8	.466	-.01
OMC %[a]	94.0 (44.7)	127.9 (54.2)	-2.5	**.016***	-.673	133.1 (52.7)	125.1 (60.7)	3.1	.052	.07
OMC % (age)[d]	-	-	7.1	**.010***	-	-	-	3.5	**.037***[2]	-
Novel										
PM error score[a]	73.2 (40.7)	69.4 (35.4)	.4	.709	.100	68.1 (37.3)	70.0 (35.5)	.1	.926	-.03
AM error score[a]	68.3 (42.2)	74.0 (36.4)	-.6	.586	-.146	79.2 (33.0)	71.7 (38.5)	.3	.76	-.03
OMC %[a]	88.7 (37.5)	120.3 (69.8)	-2.0	.055	-.541	147.3 (90.1)	107.4 (55.8)	3.7	**.032***[3]	.09
OMC % (age)[d]	-	-	3.5	.066	-	-	-	3.6	**.036***[3]	-

Note. ***p<.05.** PM= pre-sleep, AM= post-sleep. OMC= overnight memory consolidation calculation by: ([AM error score/PM error score]*100). Greater OMC% = worse performance. [a]Student t-test to compare Controls and MCI. [b]Welch's t-test to compare Controls and MCI. One-way ANOVA to compare Controls and MCI subtypes. [c]Error score average over five trials in the evening. [d]Univariate GLM to compare OMC % between groups whilst controlling for age. [1]Significant group difference indicated in Bonferonni post-hoc analysis between Controls and aMCI (p = .039).[2]No significant group differences in post-hoc analysis. [3]Significant group difference between Controls and aMCI (p = .027, controlling for age: p= .031).

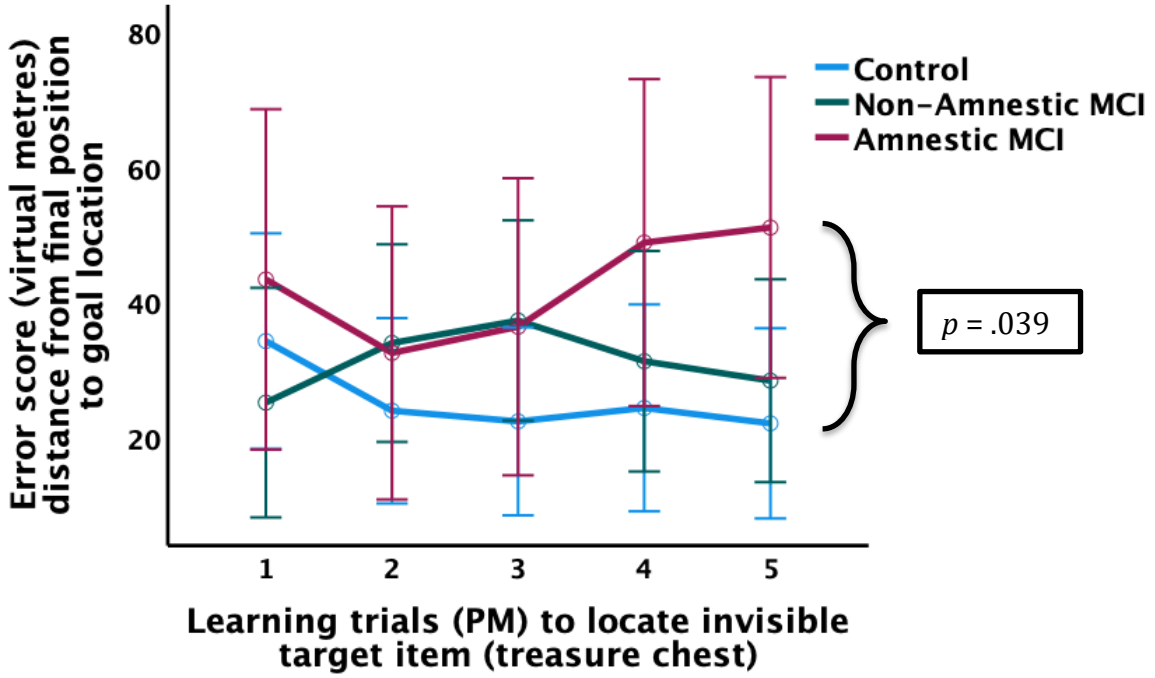

Figure 4.5. Spatial navigation learning trials in the evening (PM, pre-sleep) from the same start location (see Figure 2.c). All participants are given five trials in the evening to find an invisible target item, up to four minutes per trial. The error score is calculated in virtual metres as the distance from the final position to the goal location. Post-hoc analysis indicates significant group differences between Controls and aMCI participants.

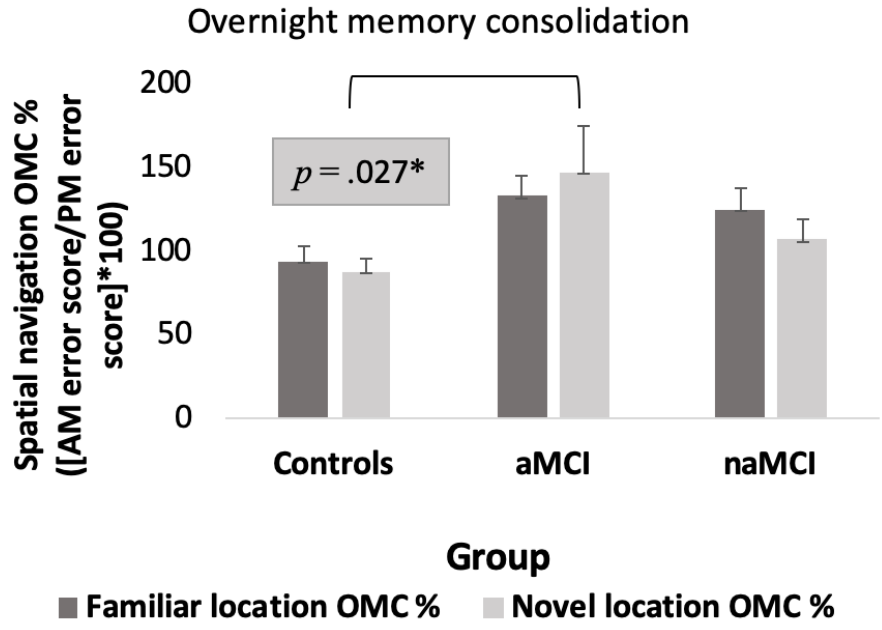

Figure 4.6. Spatial navigation overnight memory consolidation (OMC) error score %. OMC% calculated by ([PM error score/AM error score]*100) for both familiar and novel locations. Greater OMC% = worse performance. AM= post-sleep, PM= pre-sleep. Post-hoc analysis indicates significant group differences between Controls and aMCI participants for OMC % that remained significant even after controlling for age. *Note.* Greater OMC% (error score) = worse overnight memory consolidation.

Spatial Navigation Questionnaire

Two participants from our sample did not complete the SN-Q. All but one MCI participant reported feeling '*very much'* (63%) or '*somewhat*' (35%) comfortable using a computer. When asked about trouble with spatial orientation, 40% reported '*never*', 53% '*sometimes*' and 7% '*always*'. Over half of participants (55%) reported trying to create a map in their head when learning the location of the target item. When asked whether they recognised if they were in a different start location, 68% reported they did, however only 33% indicated they performed differently in a novel location. The breakdown of responses for Controls and pMCI is reported in Table 3.b. The majority of participants used simple egocentric strategies (71%), notably path and beaconing. No participants used route learning, which is not unexpected given the nature of the task, 22% used allocentric strategies, and 7% used random search. When accounting for strategies used for the familiar location test OMC%, no interaction was found between strategy used and group (Controls, pMCI) ($F(1, 48) = .35$, $p = .559$), and similarly for novel location test OMC% ($F(1, 47) = .09$, $p = .769$). However, numerical observation of OMC% by strategy and group indicated that Control participants performed better when using allocentric strategies on both familiar and novel locations, whereas pMCI participants performed better using allocentric strategies for the novel location (Table 4.3.b).

Table 4.3.b. Spatial Navigation Questionnaire. Qualitative measure of spatial strategies.

	Controls n=24	**pMCI** n=31
Do you feel comfortable using a computer?[a]	54% very much 46% somewhat	70% very much 27% somewhat
Do you have trouble orientating yourself in an unfamiliar environment?[b]	33% never 63% sometimes 3% always	45% never 45% sometimes 10% always
When you were learning the location of the target item over the 5 trials, were you trying to create a map in your head while looking for the target item?[c]	54% yes 46% no	55% yes 45% no
Did you recognise in the second recall test that you started from a different location?[c]	77% yes 33% no	61% yes 39% no

Did you do anything differently to the first recall test starting from the same location you learnt?[c]	25% yes 75% no	39% yes 61% no
Could you tell me more about how you were trying to find the hidden chest? (Strategies used)[d]	79% egocentric 21% allocentric 0% random search	65% egocentric 22% allocentric 13% random search
	M, sd	*M, sd*
Familiar location OMC%	Egocentric: 96% (46.7) Allocentric: 77% (40.5)	Egocentric: 127% (60.4) Allocentric: 129% (34.7) Random search: 136 (68.9)
Novel location OMC%	Egocentric: 92% (38.1) Allocentric: 66% (35.8)	Egocentric: 125% (80.8) Allocentric: 111% (50.4) Random search: 134% (40.8)

Note. ***p<.05.** [a]n = 1: not at all (MCI). [b]n = 1: always (Control). [c]Yes/No. Mean OMC% based on strategies used indicates Control participants using allocentric strategies had better consolidation of both familiar and novel locations. On the familiar location pMCI participants performed similarly across the three strategies, however performed better on the novel location when using the allocentric strategy. No interactions were found between strategy used and group for familiar and novel location OMC independently.

Sleep microarchitecture associations with spatial navigation OMC

The associations between sleep microarchitecture variables of interest and OMC% are displayed in Table 4.4. In order to account for potential confounders, associations between OMC% and apnoea hypopnea index (measure of OSA) during total sleep time or REM within both groups were examined. No significant correlations were found in either group (results provided in appendix, Table A4). As OMC% is calculated as an error score, a negative rho indicates better memory performance.

- *Slow oscillations*: No significant associations were found between absolute SO and OMC% in Controls or those naMCI. Although non-significant, moderate effect sizes were found between reduced SO power with worse OMC% in aMCI (*rho* = -.527, *p* = .117).
- *Slow wave activity*: No significant associations were found between absolute or relative SWA and OMC % in any of the groups.
- *Slow spindles*: There were no significant associations between slow spindle density with OMC% in Controls or those with naMCI. In the aMCI group, significant large effect sizes

were found between reduced frontal slow spindle density and worse OMC% (*rho* = -.782, *p* = .008) (Figure 4.6.a). Results remained unchanged after controlling for age.

- *Fast spindles*: No significant associations were found between fast spindle density and OMC in Controls or those with naMCI. Although non-significant, moderate effect sizes were found between parietal fast spindle density and worse OMC% in aMCI (*rho* = -.576, *p* = .082) (Figure 4.6.b), results remained unchanged after controlling for age.
- *Overall spindles*: Reduced frontal overall spindle density was associated with worse OMC % in Controls (*rho* = -.451, *p* = .035) and aMCI (*rho* = -.794, *p* = .006), but not in naMCI (*rho* = .065, *p* = .787). No significant associations found with parietal overall spindle density within any groups.

Table 4.4. Correlations between sleep microarchitecture and OMC.

	Controls *rho* n= 22	*p*	aMCI *rho* n= 10	*p*	naMCI *rho* n= 20	*p*
Frontal						
Absolute slow oscillations (0.25-1 Hz)	.151	.503	-.527	.117	-.086	.719
Absolute slow wave activity (0.5-4.5 Hz)	.103	.647	-.406	.244	.098	.682
Relative slow wave activity (0.5-4.5 Hz)[a]	.046	.840	-.236	.511	.146	.539
Fast spindle density (13-16 Hz)	-.361	.098	-.127	.726	.096	.686
Slow spindle density (11-13 Hz)	-.361	.099	-.782	**.008***	-.039	.870
Overall spindle density (11-16 Hz)[a]	-.451	**.035***	-.794	**.006***	.065	.787
Parietal						
Fast spindle density (13-16 Hz)	-.230	.304	-.576	.082	-.203	.378
Slow spindle density (11-13 Hz)	-.228	.308	.200	.580	.040	.862
Overall spindle density (11- 16 Hz)[a]	-.312	.157	-.515	.128	-.035	.870

Note. ***p<.05.** Univariate spearman's correlation analysis. Slow oscillations and slow wave activity absolute power calculated for slow wave sleep (N3). Spindle density = events per hour, calculated for N2. Relative slow wave activity calculated as ([N3 delta/N3 delta+theta+alpha+sigma+beta]*100). No significant correlations when MCI sample was pooled. [a]Secondary measures.

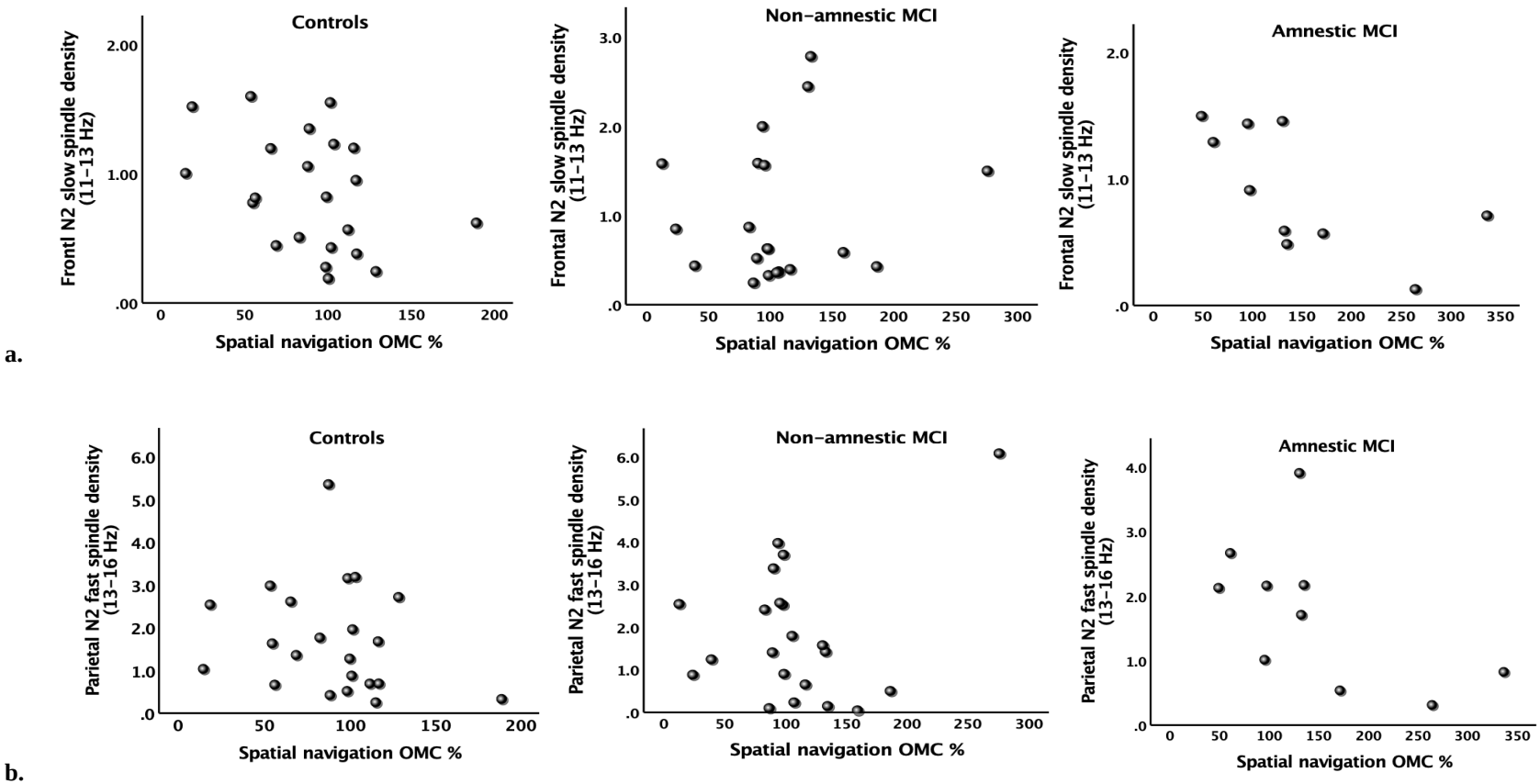

Figure 4.7. Scatterplots on top row (panel a) shows associations between spatial navigation OMC% and frontal N2 slow spindle density. A greater OMC% score (error score) = worse overnight memory consolidation. Significant associations indicated in aMCI subgroup between reduced OMC% and reduced slow spindles (rho = -.782, p = .008). Bottom row (panel b) shows associations between OMC% and parietal N2 fast spindle density. Results indicate reduced OMC% was associated with reduced parietal fast spindle density in aMCI; although not significant, moderate-large effect sizes were observed (rho = -.576, p = .082). Spearman's correlations analysis used. Results remained unchanged when controlling for age.

Neuroimaging associations with spatial navigation OMC

The associations between neuroimaging variables of interest and OMC% are displayed in Table 4.5.a and 4.5.b. Note, figure 4.9 uses trend lines for Pearson's correlation analysis and figure 4.8 does not include trend lines as Spearman's correlation analysis is used. As OMC% is calculated as an error score, a negative rho or r indicates better memory performance.

Controls:

a) *Medial prefrontal cortex*: Greater mPFC thickness was significantly associated with worse OMC % performance (*rho* = .477, *p* = .029) (Figure 4.7). When controlling for age, results did not remain significant for mPFC (*rho* = .338, *p* = .145). As five participants had a T1 8-channel type coil, analysis was conducted controlling for coil type, and results trended towards significance (*rho* = .441, *p* = .052).

b) *Medial temporal lobe*: No significant associations were found between right CA1 or ERC with OMC%. Associations with right DG were of moderate magnitude, however not significant (*r* = -.406, *p* = .119) and remained unchanged when controlling for coil type (*r* = -.398, *p* = .142), however when controlling for age there was no trend association (*r* = -.081, *p* = .775).

Pooled MCI:

a) *Medial prefrontal cortex*: No significant associations were found between mPFC thickness and OMC% (Table 4.5.a).

b) *Medial temporal lobe*: Associations between right CA1 volumes and OMC% were of moderate magnitude but were not significant (*r* = -.426, *p* = .069), except when controlling for age (*r* = -.542, *p* = .020) (Figure 4.8.a). Results were essentially unchanged when controlling for coil type (*rho* = -.400, *p* = .100). Reduced right DG volume was significantly associated with worse OMC % (*r* = -.453, *p* = .020). Results remained unchanged when controlling for age (*r* = -.475, *p* = .017) and coil type (*r* = -.475, *p* = .017) (Figure 4.8.b). No significant associations were found with right ERC volume with OMC%, and results remained unchanged when controlling for age and coil type respectively.

Given MRI subsamples were small for the MCI subtypes, notably aMCI (aMCI: n= 7-9, naMCI: n= 12-16), analyses between OMC% and neuroimaging outcomes were not included (see Appendix, Table A7). As this study focused on the right hemisphere, associations with left hemisphere are reported in the Appendix Table A8 and A9. Results for associations between

mPFC sub-regions (medial orbitofrontal cortex, rostral and caudal anterior cingulate cortex) and OMC% presented in the Appendix, Table A8 and A9.

Table 4.5.a. Correlations between neuroimaging and OMC.

	Controls n= 9-21	*p*	pMCI n= 19-25	*p*
Medial prefrontal cortex (mm)	.477	**.029***	.210	.314
Right Hippocampal CA1 (mm^3)	-.296	.439	-.426	.069
Right Dentate gyrus (mm^3)	-.406	.119	-.453	**.023***
Right Entorhinal cortex (mm^3)	.282	.241	-.299	.176

Note. ***p<.05.** Univariate spearman's correlation used for mPFC.

Univariate pearson's correlations used for CA1, dentate gyrus and entorhinal cortex.

MCI subtypes not included due to small sample size.

Numbers in Controls: mPFC = 21, CA1 = 9, DG = 16, ERC = 19.

Numbers in pMCI: mPFC = 25, CA1 = 19, DG = 25, ERC = 22.

Significant results remained for dentate gyrus but not medial prefrontal cortex when controlling for age.

Table 4.5.b. Neuroimaging and OMC correlations (controlling for age and coil type).

	AGE				**COIL**			
	Controls	*p*	pMCI	*p*	Controls	*p*	pMCI	*p*
Medial prefrontal cortex (mm)	.338	.145	.203	.340	.441	.052	.200	.348
Right CA1 (mm^3)	.251	.549	-.542	**.020***	-.512	.195	-.400	.100
Right Dentate gyrus (mm^3)	-.081	.775	-.475	**.019***	-.398	.142	-.475	**.019***
Right Entorhinal cortex (mm^3)	.341	.166	-.352	.118	.291	.241	-.249	.277

Note. ***p<.05.** Univariate spearman's correlation used for mPFC.

Univariate pearson's correlations used for CA1, dentate gyrus and entorhinal cortex.

MCI subtypes not included due to small sample size.

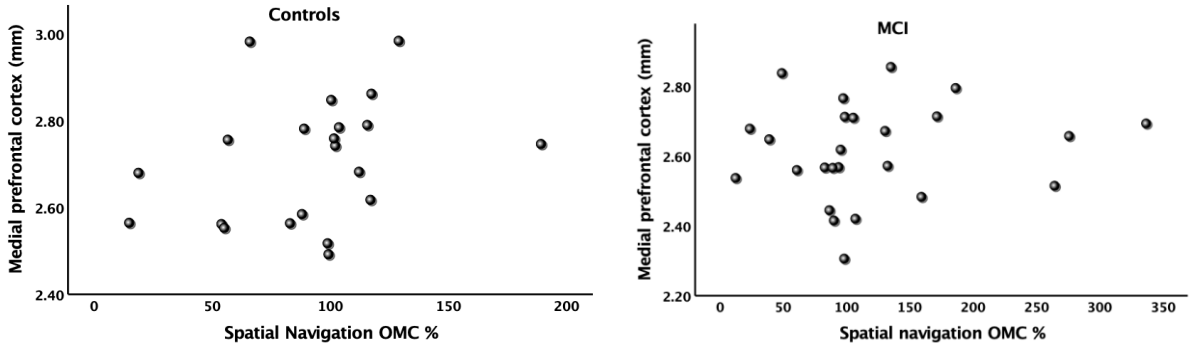

Figure 4.8. Scatterplots show associations between spatial navigation OMC% and medial prefrontal cortex (mPFC) thickness (mm). A greater OMC% score (error score) = worse overnight memory consolidation. Significant associations indicated in Controls between greater OMC% and reduced mPFC thickness (rho = .477, p = .029) (left). No significant associations indicated in pooled MCI group (right) (rho = .210, p = .314). Spearman's correlations analysis used. Results did not remain significant in Controls after controlling for age (rho = .338, p = .145).

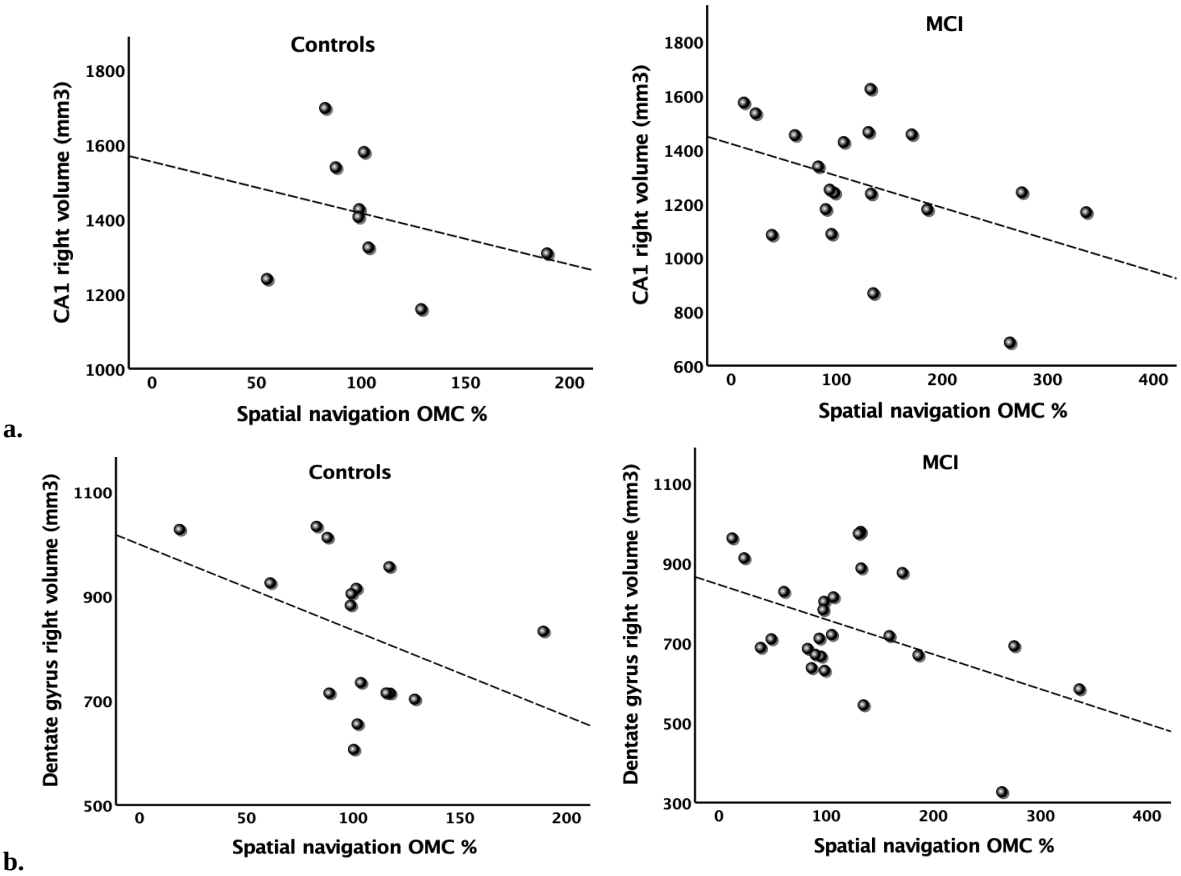

Figure 4.9. Scatterplots on top row (panel a) shows a trend significance between worse OMC% and reduced CA1 volume in pooled MCI (r = -.412, p = .069), but not in the Control group. Bottom row (panel b) shows worse OMC% significantly associated with reduced dentate gyrus volume (r = -.512, p = .023), but not in the Control group. A greater OMC% score (error score) = worse overnight memory consolidation. Pearson's correlations analysis used. Results presented are not controlling for age or coil type. When controlling for age, associations between OMC% and right CA1 in MCI are significant (p < .05), and remain unchanged with right dentate gyrus.

4.5. DISCUSSION

This novel study examined the overnight consolidation of spatial navigation memory in clinical MCI and its subtypes. Using a newly developed task (CASNAT), it employed two well categorised components of SN; egocentric (target item located from a familiar start location) and allocentric (target item located from a novel start location) spatial memory built upon the gold standard MWMT of SN. For the first time, this study has shown that people with MCI demonstrate poorer OMC for SN memory. In people with aMCI, sleep spindles are pertinent for optimal OMC, with reduced frontal slow spindle density associated with decrements in consolidation. Frontal SO and parietal fast spindle density may be important for OMC with a moderate trend between reduced SO and fast spindles and poorer OMC in aMCI. By contrast, in Controls, this relationship was only evident for the total range of spindles (11-16 Hz). Reduced CA1 and DG volume in MCI was associated with worse OMC, and greater mPFC thickness was associated with worse OMC in Controls. Whilst moderate effect sizes were indicated with right DG and worse OMC in Controls, age had a significant negative influence and attenuated this relationship.

A key finding of this study was that MCI is not only associated with more marked decrements in overnight consolidation of spatial material, in contrast to cognitively intact older people, for whom benefit from sleep on OMC, reduced learning of new spatial information is observed; potentially compounding the memory impairments. Specifically, when placed in a familiar start location, whereby the target location can be ascertained using egocentric SN, people with MCI had compromised recall of the target location following sleep compared to Controls. This was not apparent when allocentric SN was required (i.e. tested when the subject was required to navigate from a novel start location). However, only when the MCI subtypes was examined, those with the amnestic subtype had significantly reduced allocentric SN OMC compared to Controls. As an exploratory analysis, we examined spatial strategies used. No interaction was found between OMC and SN strategies, likely due to the lack of spread in the strategies used in both groups. Numerical observation indicated both groups had greater OMC in the familiar location when using allocentric strategies, however in the novel location, this was only evident for the Control group.

The above cognitive results are aligned with prior work that has demonstrated that allocentric SN tested during daytime, is significantly more impaired in aMCI compared to healthy Controls (Laczo et al., 2017; Laczo et al., 2010; Laczo et al., 2009; Tuena et al., 2021; Weniger et al., 2011) and in comparison to the naMCI subtype (Rusconi et al., 2015). Previous studies have also found that during

spatial encoding, aMCI participants are not able to improve scores over five learning trials, compared to Controls (Weniger et al., 2011) and similarly in preclinical AD (Allison et al., 2016). The novel location at test requires participants to come up with a new strategy that relies on the hippocampus, taking into account positions of landmarks and distances between landmarks (Lithfous et al., 2013), whereas a familiar location allows participants to use more simple, egocentric strategies, as this reference relies on well-learned stimulus-response associations (Lithfous et al., 2013). Our overall sample described using mostly egocentric strategies, typical in ageing (Rodgers et al., 2012; Wiener et al., 2013), particularly the beaconing strategy (Wiener et al., 2013), although it is noted that 39% of MCI participants reported not realising that they were in a novel start location. Here it may be that MCI participants are failing to learn or apply simple strategy, and/or having difficulty acquiring the environment information (Allison et al., 2016).

Although we assessed allocentric and egocentric SN independently, designing SN tasks that purely measure egocentric and allocentric processes are near impossible (Ekstrom et al., 2014). The varying forms of SN tasks (Laczo et al., 2009; Laczo et al., 2021; Mokrisova et al., 2016; Tu et al., 2015; Varga et al., 2016; Wood et al., 2016) shed light of the neural complexity of the navigational system. It has been suggested that egocentric and allocentric memory can be considered on a continuum, whereby we switch between the two, instead of these references being completely dichotomous (Ekstrom et al., 2017). This study provides evidence for still measuring these independently, but potentially future studies could consider using metrics to assess switching between two frames of reference; a strategy known to be impaired in AD (Morganti et al., 2013; Ruggiero et al., 2018). One suggestion in quantitatively capturing the use of egocentric and allocentric SN and the switching between these frames of references is the use of eye-tracking devices (de Condappa & Wiener, 2016; Segen et al., 2021). Whilst criticisms of the MWMT in over-emphasising the allocentric representation have been stated (Ekstrom et al., 2014; Wolbers & Wiener, 2014), it has been unclear to date whether memory recall based on differing SN representations, are affected by sleep or even after long delay recall (12 hours~).

With regard to sleep, it is noted that there were no between group differences in NREM neurophysiology in this sample. However, the findings do indicate moderate effect size decrements in SWA in the pMCI group compared to Controls. Upon examining how sleep microarchitecture may relate to OMC in this sample, the findings of this study revealed that in aMCI, reduced frontal slow spindle density was associated with worse OMC, and there was also a moderate (yet non-significant) magnitude correlation between frontal slow oscillations and parietal fast spindle density with worse

OMC. The beneficial role of greater relative SWA has been evidenced in a pooled sample of healthy older and younger adults with better performance on SN OMC (Varga et al., 2016), however results were no longer significant when accounting for age. Our findings are not consistent with those that found significant associations between absolute SWA and verbal OMC in healthy older adults (Mander et al., 2013; Westerberg et al., 2012). Rather, our results aligned with Lam and colleagues who found no associations between slow waves (SO and SWA) and OMC in either Controls or MCI (Lam et al., 2021). Whilst associations have been found between fast spindles (12-15 Hz) and SN OMC in younger adults during a nap (Shimizu et al., 2018), spindle associations with SN OMC have not been examined in older adults. Our lack of findings between NREM EEG and OMC in Controls may be due to the heterogeneity within this sample, as participants with subjective cognitive decline were included. Although the Control sample was cognitively homogenous on neuropsychological assessment, we cannot confirm that they were homogenous with respect to AD pathology such as underlying tau or amyloid-beta (Aβ), which has been linked with verbal OMC (Mander et al., 2022; Mander et al., 2015). Other factors that could have influenced the relationships observed within the Control group include sleep disordered breathing (Haba-Rubio et al., 2017; Mubashir et al., 2019), though notably few studies have examined this in relation to OMC. Of those that have, greater obstructive sleep apnoea has been associated worse OMC in healthy older Controls (Lam et al., 2021), and with SN OMC in younger adults during REM (Varga et al., 2014). In this study, however, the associations between obstructive sleep apnoea (as measured by apnoea hypopnea index) and OMC during total sleep time or REM were not significant. However, given the association between sleep apnoea and increased risk of dementia, notably in AD (Guay-Gagnon et al., 2022), and higher incidence of adverse driving behaviours (independent of positive AD biomarkers) (Doherty et al., 2022), future studies still warrant the examination of its effects on SN memory.

Of note, NREM neurophysiology (spindle) associations with OMC were identified only in the aMCI subtype in this study. While it is unclear why these specific findings occurred, some considerations are worthy of mention. First, evidence indicates a stronger association between slow oscillation and spindle cross-frequency coupling and verbal OMC in older adults (Helfrich et al., 2018; Muehlroth et al., 2019), and SN memory consolidation during a nap in younger adults (Bastian et al., 2022). Second, it may be that the NREM-REM interaction may better explain OMC (Hoedlmoser et al., 2022; Llewellyn & Hobson, 2015; Scullin & Gao, 2018). For example, greater memory consolidation has been associated with SWS followed by REM (Batterink et al., 2017; Diekelmann & Born, 2010) and with spindles followed by REM (Strauss et al., 2022). Third, the role of lighter sleep (N1 and N2) has been suggested in spatial memory loss in younger adults (Lacaux et al., 2022). Finally, given our

sample did not differ on any key sleep features such as SWS or OSA, or NREM neurophysiology, it may be that OMC and NREM EEG associations are mediated by underlying brain pathology (Mander et al., 2015; Mander, Zhu, et al., 2017). Evidence for this is indicated in a recent finding in cognitively normal, tau and Aβ pathology-free older adults, showing greater microglia activation via association with tau and synaptic degeneration was associated with impaired fast spindles (Mander et al., 2022). In turn, spindles in the regions where greater tau pathology was indicated (frontal), was associated with reduced verbal episodic OMC. Given our findings with spindles in aMCI and Controls (overall spindle density only) but not naMCI, the mechanisms of spindles may differ between groups, or rather, may potentially be dependent upon level of Aβ or tau pathology.

This study was unique in also examining how OMC of spatial material relates to markers of prefrontal cortex and hippocampal subfield integrity, and findings revealed differential associations depending on subgroup. Contrary to our hypothesis, for Controls, greater mPFC thickness was linked with reduced OMC for spatial material. When controlling for age, such results were no longer significant, suggesting that this finding should be interpreted with caution and results are still require further replication. Our findings are discordant with those reported in a pooled sample of healthy younger and older people whereby no associated were indicated between mPFC and SN OMC (Varga et al., 2016), and those indicating positive association between mPFC and verbal episodic OMC (Frase et al., 2020). However, aligned with our findings, prior studies have also failed to find associations between OMC and mPFC thickness in MCI (Lam et al., 2021). It is possible that this region has a greater association with NREM neurophysiology (Helfrich et al., 2018; Varga et al., 2016) and functions to moderate the relationship between sleep and OMC (Mander et al., 2013). While further replication is certainly necessary, these preliminary findings would suggest that mPFC thickness is unlikely to solely underpin decrements in OMC of spatial material in MCI and that perhaps a more diffuse or distributed neural network is implicated. Indeed, the white matter connectivity (Palmer et al., 2022) and functional connectivity (Liu et al., 2018; McKinnon et al., 2016; Ujma et al., 2019) may be key factors to examine in future studies; with white matter tracts (using diffusion tensor imaging) being associated with NREM spindles and slow waves.

Upon examination of the hippocampal subfields, for those with MCI, reduced OMC was significantly associated with reduced right dentate gyrus volume. Associations between OMC and right CA1 were of moderate magnitude but was only significant in the presence of age. This is aligned with prior work showing that the DG is crucial and likely underpins key components of SN (Brown et al., 2014; Gothard et al., 2001). It differs, however, from prior work showing that the CA1 but not DG region is

linked to verbal episodic OMC in MCI (Lam et al., 2021), but notably we observed moderate sized correlations and it is likely this study was underpowered to detect this association significantly. Concordant with our hippocampal findings, previous studies have also indicated no associations with left or right hippocampal volume with allocentric SN in Controls (Laczo et al., 2017). Given the nature of our task, it is expected that MTL rather than mPFC would have a stronger association with OMC, notably in MCI, due to greater hippocampal atrophy (Broadhouse et al., 2019). To summarise, it appears that poorer OMC of spatial material in MCI is linked closely to the size of the right DG.

As noted above, mechanistic pathways involved in SN OMC and their association with sleep neurophysiology in ageing may be further delineated or even better characterised by using resting-state functional MRI during sleep (Deantoni et al., 2021) and functional MRI during pre- and post-sleep (Mander et al., 2013). Differential cortical activity during post-sleep retrieval (Deantoni et al., 2021) may determine if indeed reduced allocentric OMC is a result of MTL atrophy, or dependent on a wider network disruption. It may be that in Controls different MTL regions are utilised such as the CA2 and CA3 (Peter et al., 2018), or that differing networks are utilised for post-sleep retrieval (Bastian et al., 2022; Mander et al., 2013). Given the suggestion that egocentric and allocentric representations could be considered a "combined" representation (Ekstrom et al., 2014), it is difficult to pin point one particular brain region for allocentric SN memory. Although not measuring hippocampal subfields, previous studies found that both left and right hippocampal volumes are associated with allocentric SN in aMCI (Laczo et al., 2017), however using regression analysis, after accounting for age, gender and education, right hippocampal volume accounted for 26% of the variance compared to 12% for the left CA1 (Laczo et al., 2017). Our results may suggest a general weakening of the MTL in MCI in impairing allocentric SN memory consolidation. Furthermore, given participants with the naMCI subtype (but not aMCI) had a reduction in mPFC thickness compared to Controls, it is possible that the mPFC reductions in naMCI may partially account for differences in OMC and sleep associations between MCI subtypes.

Of significance, given the clinical relevance of allocentric SN in characterising those at greater risk of cognitive decline and AD (Allison et al., 2016; Wood et al., 2016) and with evidence pointing to allocentric SN performance as a predictor of greater risk of dementia, with a stronger predictive value above tests of episodic memory, verbal fluency, or executive functioning (Ritchie et al., 2018), this novel computerised SN test could be used as a digital tool to screen for and phenotype MCI. Large correlations have also been identified between 'real space' measurements of allocentric SN with

computerised tests of SN in aMCI (Laczo et al., 2012) suggesting that computerised SN tests have ecological validity.

Study limitations

Whilst the sample was very well phenotyped from a cognitive, medical, sleep and mental health perspective, the sample did not have AD biomarkers measured, which would have led to superior characterisation in terms of underlying aetiology of cognitive impairment. Notably, however, studies have shown that for those with MCI, around 60% of participants would have underlying Aβ on PET scanning (Jansen et al., 2022). Secondly, our aMCI sample was small which may potentially result in both type I and type II errors when examining OMC associations with MCI and EEG. With an overall larger sample size, the interaction between brain atrophy and NREM neurophysiology on OMC could have been more thoroughly investigated. This study, however was the first known to examine hippocampal subfields, whereas previously hippocampal volumes have been examined as whole when assessing allocentric SN in MCI subtypes (Laczo et al., 2017; Laczo et al., 2012; Laczo et al., 2014; Laczo et al., 2009), and these prior studies in MCI also did not examine egocentric and allocentric memory in relation to sleep. Whilst previous SN studies have assumed the use of egocentric or allocentric SN, here we included a novel component by asking participants what SN strategies they used. Future studies could extend this work by devising appropriate ways to quantitatively measure SN strategies, which may provide evidence for clinicians incorporating spatial strategies in cognitive training programs (Lovden et al., 2012), and understanding how sleep influences daytime SN function. As our results rely on one single frontal sensor and one parietal sensor, this limits the ability to capture regional specificity of NREM neurophysiology abnormalities as has been identified in older adults using high-density EEG (Sprecher et al., 2016), and future studies are required to address this knowledge gap.

Future directions and conclusions

Future studies should now be designed in MCI to understand if increasing slow waves and spindles enhances SN OMC. Also, future work may wish to investigate the role of slow oscillation and spindle cross-frequency coupling and determine if targeting these neurophysiological processes could alleviate changes that may occur in OMC with ageing generally and neurodegeneration specifically. For example, techniques such as acoustic stimulation (Papalambros et al., 2019; Westerberg et al., 2015; Wunderlin et al., 2021), brain stimulation (Ladenbauer et al., 2017) or pharmacological manipulation using zolpidem (Mednick et al., 2013; Zhang et al., 2020), may be worth pursuing. Results from these

studies may determine the unique characteristics of those who may benefit from sleep interventions and more importantly, how such treatments may result in improved daytime cognition and functioning.

In conclusion, this novel study utilised the gold standard task for measuring hippocampal-dependent allocentric SN memory, specifically the virtual MWMT in a clinical sample of patients with MCI and Controls. It extends the limited studies examining OMC in MCI (Lam et al., 2021; Westerberg et al., 2012) by assessing an unexplored memory domain, which is of clinical significance in MCI and AD, likely to underpin early changes such as getting lost, difficulties recalling the location of a parked car, and remembering their route home. For the first time, this thesis presents the results of a newly developed SN task and shows that it is sensitive to both new learning deficits in MCI, as well as to additional decrements in overnight consolidation of spatial material, potentially compounding the memory impairments. This study also highlights that both sleep spindle and hippocampal integrity are integral to allocentric SN OMC in MCI. Whereas for Controls, prefrontal (medial) cortex thickness may be more pertinent, age appears to significantly influence this relationship. It provides the foundation for further work now seeking to delineate the broader neural networks fundamental for sleep-memory relationship and how these may differ along the cognitive spectrum in ageing and neurodegenerative disease. Finally, testing of allocentric SN may be worth considering further in neuropsychological examinations and in response to clinical trials targeting sleep neurophysiology.

Chapter 5

Regional specificity of sleep EEG and allocentric spatial navigation memory correlates in older adults with and without MCI: A high-density EEG study.

5.1. ABSTRACT

Objective: The primary aim of this study was to identify the regional specificity of associations between slow waves and spindles during non-REM sleep with allocentric spatial navigation (SN) overnight memory consolidation (OMC). This study also aimed to explore how sigma power is associated with key medial temporal lobe regions.

Methods: Healthy older adults (n= 18) and those with multiple-domain MCI (n= 8) underwent assessments of overnight polysomnography using high-density EEG (hdEEG) and memory testing. Participants were trained on a novel clinical allocentric SN task (CASNAT) pre-sleep and assessed post-sleep. Overnight allocentric SN memory was assessed by the % change in error scores when tested from a novel start location ([morning score – evening score]*100). NREM EEG power for slow oscillations (SO; 0.25-1 Hz), slow wave activity (SWA; 0.5-4.5 Hz), sigma power (12-15 Hz), and slow (11-13 Hz) and fast (13-16 Hz) spindle frequency activity (SFA) were derived. Grey matter volumes of the right CA1, dentate gyrus and entorhinal cortex regions were computed using ASHS software.

Results: In the MCI group, lower sigma EEG power (*rho*= -.929, *p*= .001) and slow and fast SFA in the right central, parietal and occipital regions were correlated with worse OMC. Lower fast SFA in the left central, parietal, occipital, and lateral frontal regions was also related to worse OMC in MCI. No associations between SO or SWA and OMC were observed in either group. Lower sigma power in lateral frontal and central regions was associated with lower hippocampal CA1 volumes in the pooled sample only (*rho*= .593, *p*= .020), but did not remain after multiple corrections. No significant associations were found between sigma power and right dentate gyrus or entorhinal cortex.

Conclusion: This study highlights the role of spindles, in particular fast SFA; indicating more widespread associations with SN memory in MCI. Future studies in larger MCI samples could further examine how brain structure and connectivity may mediate or moderate the relationships between OMC and spindles MCI and neurodegeneration.

Key words: High-density EEG, Hippocampus, Mild Cognitive Impairment, Sleep, Spindles

5.2. INTRODUCTION

Mild cognitive impairment (MCI) is considered a prodromal or 'at risk' stage of Alzheimer's disease (AD) (Levey et al., 2006; Yaffe et al., 2005). Impairments in cognition commonly seen in the early stages of MCI include episodic (van Geldorp et al., 2015) and visuospatial memory (Mitolo et al., 2013) as well as in spatial navigation (Lithfous et al., 2013). Spatial navigation abilities are considered to be one of the first functional impairments in early AD (Coughlan et al., 2018), in particularly hippocampal-dependent allocentric spatial navigation tasks which have shown to predict the progression of MCI to AD (Wood et al., 2016).

Of significance, up to 40% of risk factors for AD are modifiable (Livingston et al., 2020). Based on converging studies over the last two decades, sleep is now considered a possible modifiable risk factor and biomarker for neurodegeneration (Livingston et al., 2020; Lucey et al., 2021; Mander et al., 2016). In older adults with confirmed MCI, significant sleep abnormalities based on overnight polysomnography have been identified compared to cognitively healthy older adults (Brayet et al., 2016; D'Atri et al., 2021; D'Rozario et al., 2020; Gorgoni et al., 2016; Westerberg et al., 2012). However, sleep studies remain scarce in MCI despite the links between altered sleep and accelerated cognitive decline (Shi et al., 2018).

In healthy older adults, reduced frontal, central and parietal spindle density has been associated with worse overnight memory consolidation (OMC) (Fogel et al., 2017; Mander et al., 2014; Mander, Zhu, et al., 2017; Tamminen et al., 2010). Similarly, reduced frontal SWA has been associated with worse verbal OMC in healthy older adults (Mander et al., 2013), and spatial navigation (SN) OMC in a combined younger and older sample (Varga et al., 2016). However, only two studies to date have examined verbal OMC in MCI sample (Lam et al., 2021; Westerberg et al., 2012), as outlined in Chapter 1, 3 and 4. Data from healthy older adults suggests that increased prefrontal cortex thinning is related to reduced SWA (Dube et al., 2015; Varga et al., 2016) and poorer verbal episodic OMC via its disruption to SWA (Mander et al., 2013). In those with MCI, smaller hippocampal CA1 and CA3 subfield volumes have been shown to correlate with poorer verbal episodic OMC (Lam et al., 2021), although no associations were found with medial prefrontal cortex (mPFC) thickness in MCI or Controls. Given the associations between sleep microarchitecture, brain structure and OMC in ageing, and structural changes in in MCI, namely the entorhinal cortex and hippocampal subfields CA1, CA3 and dentate gyrus, (Broadhouse et al., 2019; Csukly et al., 2016; Du et al., 2001; Zhang et al., 2013), underlying brain pathology is a potential contributor to the sleep-memory relationship in MCI.

Relative to verbal episodic memory consolidation, there is less known about consolidation of SN memory. Given the significant role of the medial temporal lobe (MTL) in SN memory (Bartsch et al., 2010; Eichenbaum & Lipton, 2008; Qasim et al., 2019), notably the right hemisphere in MCI (Laczo et al., 2014), it is plausible that MTL atrophy and changes in sleep microarchitecture may underpin or mediate decrements in SN OMC in older adults. Research has shown reduced hippocampal atrophy relates to reduced spindles and worse motor memory performance in an older sample; although causation cannot be ascertained, it is possible that age-related changes in the hippocampus impact spindles, and in turn, motor memory consolidation (Fogel et al., 2017). Overall, our understanding of the inter-relationships between changes in sleep, memory and brain atrophy in ageing and early neurodegeneration remains embryonic and warrants further attention.

One of the gaps in understanding the changes in sleep neurophysiology with age, and its relationship with cognitive decline and neurodegeneration, is the identification of localised neurophysiological changes. The use of limited channel EEG sensors (typically 6 scalp electrodes during polysomnography) to measure brain activity during sleep is one of the methodological pitfalls of prior work due to limited spatial resolution, and inability to identify localised abnormalities (Muehlroth & Werkle-Bergner, 2020). Whilst sleep studies using hdEEG have been used to examine travelling brain waves (Massimini et al., 2004), in mental health (Ferrarelli et al., 2007; Plante et al., 2013; Wang et al., 2020) and sleep disorders (Jones et al., 2014; Valomon et al., 2021), no studies have used this technology to examine regional EEG sleep activity in MCI and explore associations between OMC and NREM sleep EEG oscillations. Two studies have used hdEEG in a healthy older sample (Mander et al., 2022; Sprecher et al., 2016). The first study revealed that that global SWA is diminished in older adults compared to younger, and reduced frontal sigma and parietal fast spindles were correlated with increased age (Sprecher et al., 2016). The second study revealed tau in frontal region overlapped with spindle decrements in the same region, and these spindle decrements were associated with verbal OMC (Mander et al., 2022). Overall, evidence points to impaired NREM frontal slow waves and frontal and parietal spindles in ageing, it is unclear however, whether these specific regional decrements are associated with OMC in MCI.

Therefore, hdEEG represents a viable tool to examine neurophysiological correlates of SN OMC in MCI, particularly in when using tasks well suited to older clinical samples. In order to address this gap in the literature we have utilised: 1) all-night hdEEG and, 2) a validated allocentric SN OMC task sensitive to detect impairment in cognitively impaired older adults (see Chapter 4). Given the greater

reversion rate of the single-domain MCI compared those with multiple-domain MCI (Overton, 2019), this study included only the latter subtype. The primary aim of this study was to examine, 1) the regional specificity of associations between NREM slow waves (slow oscillations and SWA) and, 2) spindle frequency activity (sigma power, slow SFA, fast SFA) using hdEEG, with allocentric SN OMC in those with and without MCI. It was hypothesised that reduced frontal slow waves, and frontal and parietal sigma would be associated with worse SN OMC. As an exploratory aim, any significant associations from the primary aims would be used to conduct further analysis between EEG and brain structure, specifically the mPFC and right MTL (CA1, dentate gyrus, and entorhinal cortex).

5.3. METHOD

Participants

Participants were recruited from the community and from the Healthy Brain Ageing Clinic, Brain and Mind Centre, Sydney, Australia, which specialises in early assessment and intervention for individuals experiencing cognitive and/or mood concerns. Inclusion criteria: cognitively intact older adults or with multiple-domain MCI according to Winblad's criteria (Winblad et al., 2004); indicated by scores 1.5s*d* below age and education matched on two or more memory and/or non-memory neuropsychological tests. Exclusion criteria were: history of stroke; neurological disorder; dementia; Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score < 24; head injury with loss of consciousness > 30min; medical conditions known to affect cognition (e.g. cancer); shift-workers; transmeridian travel within the last 60 days; mental health or psychiatric disorders including depression, bipolar and schizophrenia; sleep-affecting medications including anti-depressant medications. Participants from this sub-study were also required to have undergone polysomnography with 256 channel high-density EEG and to have completed the overnight SN task, as detailed in Chapter 4. The University of Sydney Ethics Committee approved this study, and all participants gave written and verbal consent.

Clinical assessment

Medical and neuropsychological assessment

As described in Chapter 4, all participants received a medical assessment by an medical specialist using a semi-structured interview including measurement of body mass index, medication use, sleep disorders, and depression, as per the affective component of the Structured Clinical Interview for DSM-IV-R (Kübler, 2013). Self-reported sleep quality measures were reported for descriptive purposes using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and the Insomnia Severity Index Scale (ISI) (Bastien et al., 2001). A comprehensive standardised neuropsychological assessment was conducted by a clinical neuropsychologist and a clinical classification of multiple-domain MCI was obtained via consensus of two neuropsychologists and the medical specialist using Winblad's criteria (Winblad et al., 2004). Criteria for multiple-domain MCI was met if performance was 1.5SD below age and education-matched norms on two or more neuropsychological test and in reference to pertinent clinical criteria (Winblad et al., 2004). Premorbid intellectual ability was estimated using the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) and global cognition was measured using the MMSE (Folstein et al., 1975).

Sleep study visit

Participants attended the Woolcock Institute of Medical Research, Glebe, NSW prior to their full overnight sleep study for a screening assessment, to ascertain their suitability for hdEEG. This entailed them wearing the 256-channel hdEEG cap and a 1.5 hour nap opportunity within two weeks of the sleep study to become familiar with the cap. An overnight full polysomnography (PSG) sleep study was then scheduled. All participants who completed the nap completed the sleep study. For this, participants arrived at the sleep laboratory by 6pm, after which they completed questionnaires, had a consultation with the sleep physician and then had an evening meal. Following this, the hdEEG was set up on participants by sleep technicians and researchers, and three hours prior to sleep memory test was administered. In the morning, one hour after wake, participants completed the morning recall test. Participants were asked to abstain from caffeinated beverages and alcohol at least three hours before evening testing and prior to morning testing.

Clinical allocentric spatial navigation task (CASNAT)

As described in Chapter 4, a spatial navigation task was administered before and after sleep In the evening (pre-sleep), participants were required to learn the location of a target item (a hidden treasure chest) over five trials. After 30 minutes, participants were instructed to recall where the location of the target item was by pressing the letter 'x' on the keyboard. Immediately following this, participants began a second test trial beginning from a novel start location. In the morning (post-sleep), participants were asked to repeat the recall tests one hour after wake. The detailed description and procedure of the CASNAT is outlined in Chapter 4. For the purposes of this study, allocentric spatial navigation OMC % (novel start location) will be the primary variable, measured by an error score % ([morning error score/evening error score] * 100). Scores above 100% indicate participants performed worse in the morning in locating the target item compared to evening.

Polysomnography

High-density EEG was conducted using GES400 amplifier and NetStation software (PhilipsNeuro EGI, Eugene, Oregon, USA). PSG included 256-channel EEG (Geodesic Sensor Net), electrocardiogram (ECG), nasal airflow pressure (nasal cannula), thoracic and abdominal respiratory effort, finger pulse oximetry (SpO_2%), body position, and leg electromyogram (EMG) measurements.

Polysomnpgraphy recordings were exported into standardised digital European Data Format (EDF) and imported into Compumedics Profusion 4 software for sleep staging and scoring using a ten-channel EEG montage and standardised assessment criteria by one experienced and board registered sleep technologist (Berry et al., 2012). Electrodes at (Fz-M1&M2/2, F3-M2, F4-M1, Cz-M1&M2/2,

C3-M2, C4-M1, Pz-M1&M2/2, Oz-M1&M2/2, O1-M2, O2-M1) were used for sleep staging. Two electrooculographic (EOG) channels (left and right outer canthi), EMG (submentalis, left and right leg), flow recording (pressure-based and thermal based), efforts (thoracic and abdominal), ECG and finger oximeter.

Macroarchitecture measures are provided for descriptive purposes which include: total sleep time (minutes), percentage of time spent in slow wave sleep (N3), and apnoea hypopnea index events per hour during total sleep time.

High-density EEG recordings

Electrophysiology data were collected with a 256-channel geodesic EEG system with HydroCell Sensor Nets (Electrical Geodesics, Eugene, OR). Each electrode was filled with gel electrolyte to ensure the good quality of signals during overnight recording. The EEG signals were amplified by using NetAmps 300 amplifier and were digitized at 500 Hz with a 16-bit analog-to-digital converter. Impedances was maintained below 10 kΩ. The signals were filtered with high pass filter at 0.3 Hz, a low pass filter at 70 Hz, and notch filter at 50 Hz. The recordings were initially referenced to vertex and then re-referenced to the average across all the electrodes in the NetStation.

EEG processing

Artefacts and arousals in the EEG signals were identified by semi-automatic algorithms and then visualised by sleep experts. Sleep EEG signals were averaged for 30 seconds after removing artefacts by using Fast Fourier Transform with a Hanning filter function and 50% segment overlap. The frequency resolution of EEG was 0.25 Hz. In order to increase signal-to-noise ratio, analyses were restricted to 164 electrodes that excludes channels on the neck and face (those electrodes falling within a plotting radius of 0.57 specified in the topographical plot function of EEGLAB). Each channel was plotted and visually inspected. Poor quality channels with artefact throughout most of the recording was removed. The signal from limited electrodes (2.5 ± 1.4% of all 164 channels were interpolated) was replaced with interpolated signal using spherical spline interpolation algorithm (Perrin et al., 1987). EEG spectral power density (uV^2/Hz) was quantified between 0.5 Hz and 45 Hz and frequency ranges of interest were computed during NREM (N2 + N3).

The primary variables of interest were slow wave measures: absolute slow oscillations (0.5 – 1 Hz), slow wave activity (1 – 4.5 Hz); and spindle measures: absolute sigma (12 – 15 Hz), slow spindle frequency activity (11 – 13 Hz) and fast spindle frequency activity (13 – 16 Hz).

Analyses were performed using MATLAB (Mathworks, Natick, MA, USA). Within each sleep stage, the EEG power of each electrode within each frequency band was projected to the scalp using the MATLAB EEGLAB toolbox (Delorme & Makeig, 2004).

Threshold-free cluster enhancement (TFCE)

The Threshold-free cluster enhancement technique with permutation-based statistics was used to measure all NREM EEG variables of interest. This takes the data for the selected frequency range of each channel during the specific timepoint while controlling for multiple comparisons. The permutation approach determines the p-value by comparing the original statistic to a data-driven distribution (Smith & Nichols, 2009).

Neuroimaging acquisition and analysis

All participants in the study underwent magnetic resonance imaging (MRI) within three weeks of their PSG assessment using a 3-Tesla Discovery MR750 (General Electric Healthcare, Milwaukee, WI, USA) scanner at the Brain and Mind Centre 8-channel (T2: n = 12) and 32-channel (T2: n = 14, T1: n = 26 [all participants]) phased-array head coil. Complete details of acquisition and analysis process outlined in Chapter 4.

Medial temporal lobe volume

Automatic Segmentation of Hippocampal Subfields (ASHS): As detailed in full in Chapter 4, the ASHS software package (v2.0.0; https://sites.google.com/site/hipposubfields/) was used to automatically calculate the volumes of each hippocampal subfield. Primary variables of interest for this analysis within the medial temporal lobe were right CA1, dentate gyrus and entorhinal cortex grey matter volume.

Medial prefrontal cortex thickness

Freesurfer Processing: As detailed in Chapter 4, T1-weighted scans were processed using the Freesurfer (Fischl et al., 2002) v6.0 recon-all processing stream, which includes motion correction, skull-stripping, Talairach transformation and cortical parcellation. This pipeline utilised the Desikan-Killiany atlas (Desikan et al., 2006). Our primary variable of interest for this analysis was the medial prefrontal cortex thickness. This was calculated by taking the average of the medial orbitofrontal cortex, rostral and caudal anterior cingulate cortices (Fuster, 2015) provided by the Desikan-Killiany atlas. Total thickness (in millimetres) were calculated by the sum of left and right hemispheres. Data was visually inspected for errors for each region of interest.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS version 28, IBM Corp. Sydney, Australia) for Macintosh. Independent samples t-test was used to compare clinical characteristics, global NREM EEG power (slow waves and spindle frequency) and neuroimaging between MCI and Control groups, and hedges *g* was used to indicate effect sizes. Hedges *g* effect size were calculated as; small = 0.2, medium = 0.5, large = 0.8, as per convention (Brydges, 2019; Lakens, 2013). Spearman's correlations were used to assess associations between sleep hdEEG variables of interest (slow wave and spindles) with OMC% on the CASNAT within in the Control and MCI groups. For clusters of significant associations, a representative channel was selected to control for age and AHI, separately, as possible confounding variables. A sensitivity analysis was run for clusters of significant associations using a representative channel, removing seven of the eighteen controls participants who have subjective cognitive decline. As an exploratory analysis, spearman's rho was also calculated to assess relationships between sleep hdEEG variables of interest and neuroimaging (mPFC thickness, and right CA1, dentate gyrus and entorhinal cortex volumes). Correlations were chosen in a data guided approach. If significant associations were indicated between slow waves and OMC, correlation analysis would be conducted between slow waves and mPFC thickness. Similarly, if significant associations were indicated between spindles and OMC%, correlation analysis would be conducted between spindles and MTL volumes. Given data loss in neuroimaging due to medial temporal lobe regions not passing quality check, correlations were also conducted on the pooled sample of Controls and MCI. As noted, a threshold-free cluster enhancement (Smith & Nichols, 2009) test was used to correct for multiple comparisons for hdEEG correlation analyses. All analyses were two-tailed and employed an alpha level of 0.05.

5.4. RESULTS

Participant characteristics, polysomnography, global spectral power in hdEEG and neuroimaging

Eighteen cognitively intact Controls and eight multiple-domain MCI participants were included in this study. Of the eight MCI participant, five were classified as amnestic-MCI and 3 as non-amnestic MCI. There were no between group differences in age, sex, MMSE, predicted IQ scores, body mass index, total sleep time, the proportion of time spent in slow wave sleep %, or in the degree of sleep disordered breathing measured by apnoea hypopnea index (Table 5.1). There were no differences between Control and MCI groups in global absolute SO (p = .961), SWA (p = .998) or sigma (p = .567) EEG power during NREM (Table 5.2). Neuroimaging of the medial prefrontal cortex indicated no group differences between Controls and MCI (p = .760). Medial temporal lobe volume indicated Controls had greater grey matter volume than MCI in the right CA1 (p = .045) and entorhinal cortex (p = .008), however no group differences were found in the right dentate gyrus (p = .140) (Table 5.2).

Table 5.1. Demographic, clinical and sleep microarchitecture descriptives.

	Controls *M, sd*	MCI *M, sd*	*p*
	n= 18	n= 8	
Age, *yrs*	67.2 (9.1)	67.0 (9.8)	.955
Gender[a] % female[1]	59%	63%	.946
Mini mental state examination	29.4 (1.4)	27.8 (2.7)	.146
Wechsler testing of adult reading	105.8 (9.1)	111.1 (9.0)	.184
Body mass index	27.0 (4.7)	26.8 (4)	.939
Pittsburgh sleep quality index	5.7 (2.7)	5.7 (2.1)	.994
Insomnia severity scale	7.5 (5.0)	8.8 (7.5)	.676
Total sleep time, *mins*	359.9 (84.2)	336.4 (76.1)	.506
Slow wave sleep %	22.4 (9.6)	24.6 (7)	.569
Apnoea hypopnea index events/hr	20.7 (12.5)	18.0 (17.8)	.657

Note. ***p<.05.**

Independent samples t-test.

[1]Chi-square goodness of fit test.

Table 5.2. Global EEG power during NREM sleep and MRI GMV.

	Controls *M, sd*	MCI *M, sd*	Whole group *M, sd*	*t*	*p*	*hedges g*
EEG ($\mu V^2/Hz$)	n= 17	n= 8	n= 26			
Slow oscillation absolute global power (NREM)	34.6 (14.4)	34.9 (13.2)	34.7 (13.8)	-.1	.962	-.02
Slow wave activity absolute global power (NREM)	12.4 (5.0)	12.4 (4.5)	12.4 (4.8)	<.0	.998	.01
Sigma global absolute power (NREM)	.48 (.2)	.55 (.3)	.50 (.2)	-.7	.473	-.30
Neuroimaging	n= 9-16	n= 6-8				
Medial prefrontal cortex (mm)	2.7 (.2)	2.7 (.1)	2.7 (.14)	.3	.760	.13
Right Hippocampal CA1 volume (mm^3)	1375.4 (170.9)	1163.2 (198.1)	1290.5 (205.6)	2.2	**.045***	1.10
Right Dentate gyrus volume (mm^3)	804.9 (126.6)	727.4 (105.7)	776.7 (122.9)	1.5	.160	.62
Right Entorhinal cortex volume (mm^3)	447.0 (68.0)	358.2 (53.6)	422.8 (75.0)	2.8	**.010***	1.32

Note. ***p<.05.** Independent samples t-test. Whole group = combined Control and MCI. NREM= non-rapid eye movement.

Neuroimaging numbers in Controls: medial prefrontal cortex = 18, CA1 = 9, dentate gyrus = 13, entorhinal cortex = 15.

Neuroimaging numbers in MCI: medial prefrontal cortex = 7, CA1 = 6, dentate gyrus = 8, entorhinal cortex = 6.

CASNAT: pre-sleep learning and overnight memory consolidation

The hdEEG subsample were representative of the larger sample of 57 participants, whom had completed the CASNAT described in Chapter 4 in terms of age, MMSE and WTAR scores. In this subsample, no significant group differences were found between Controls and MCI for evening learning across five trials, or for allocentric SN OMC% (Table 5.3).

Table 5.3. CASNAT descriptives: pre-sleep learning and overnight memory consolidation.

	Controls		MCI			
	M	*sd*	*M*	*sd*	*t*	*p*
Learning (PM)[1,a]	24.1	10.7	43.5	27.8	-1.9	.094
OMC %[2, b]	103%	58.3	87%	36.0	.7	.511

Note. ***p<.05.** [1]Welch's t-test. [2]Student t-test.

OMC % calculated by: ([evening error score/morning error score] * 100).

[a]Greater average error score across 5 trials on evening learning trials = worse overall learning.

[b]Greater error score % = worse overnight memory consolidation when placed in a novel start location.

NREM associations with overnight memory consolidation on the CASNAT

Slow wave measures:

a) *Slow oscillations*: There were no statistically significant associations between slow oscillation EEG power and OMC% within Controls or MCI (uncorrected $p > .05$) (Figure 5.1). After removing the eight participants with subjective cognitive decline from the Control group, associations remained non-significant.
b) *Slow wave activity*: There were no statistically significant associations between SWA and OMC% in Controls ($p > .05$). In those with MCI, reduced SWA was associated with worse OMC% with large effect sizes in four electrodes in lateral frontal, and right occipital region (uncorrected $p < .05$) (close to known reference O2 based on 10-20 placement: rho = -.762, $p = .028$, and F4: rho = -.738, $p = .037$), however these associations did not remain significant after TFCE analysis (indicated by black dots in Figure 5.2). After removing the eight participants with subjective cognitive decline from the Control group, associations remained non-significant.

Spindle measures:

a) *Sigma power*: No significant associations between sigma power and OMC% were observed in Controls. Lower sigma power in the lateral frontal, central, parietal and occipital regions was associated with worse OMC% in the MCI group (uncorrected $p = < .05$). After TFCE analysis, 30 channels remained significant in the right central, parietal and occipital regions (Figure 5.3). A single channel representative EEG was used to illustrate significant associations with large effect sizes between reduced sigma power and worse OMC% within the MCI group in the right central region (close to known reference C4 based on 10-20 placement: *rho* = -.929, $p = .001$) and right parietal region (channel close to P4 and P8: *rho* = -.833, $p = .010$) (Figure 5.4). Results remained significant for OMC% associations with right central region when controlling for age (*rho* = -.765, $p = .045$) and AHI (*rho* = -.841, $p = .018$), and similarly for OMC% associations with right parietal region when controlling for age (*rho* = -.861, $p = .013$) and AHI (*rho* = -.878, $p = .009$). After removing the eight participants with subjective cognitive decline from the Control group, associations remained non-significant.

b) *Slow SFA*: No significant associations between slow SFA with OMC% were observed in Controls. For MCI, the location of significant associations were similar to those observed between OMC% and sigma power in MCI showing significant associations between reduced right central, parietal and occipital regions with worse OMC%. After TFCE analysis, 27 channels remained significant (Figure 5.5). Large effect sizes were indicated for the same single representative channel as used for sigma power associations in the right central region (close to known reference C4 based on 10-20 placement: *rho* = -.810, $p = .015$) and right parietal region (channel close to P4 and P8: *rho* = -.810, $p = .015$). Results did not remain significant for OMC% associations with right central region when controlling for age (*rho* = -.722, $p = .067$) although large effect sizes remained stable, and when controlling for AHI associations remained significant (*rho* = -.810, $p = .027$). Similarly, results remained significant for OMC% associations with right parietal region when controlling for age (*rho* = -.849, $p = .016$) and AHI (*rho* = -.855, $p = .014$). After removing the eight participants with subjective cognitive decline from the Control group, associations remained non-significant.

c) *Fast SFA*: No significant associations between fast SFA with OMC% were observed in Controls. In the MCI group, significant associations were observed indicating worse OMC% to be associated with reduced fast SFA the lateral frontal, central,

occipital and parietal regions (Figure 5.5). Results did not significantly change after TFCE analysis, with 52 channels remaining significant. Large effect sizes were indicated for the same single representative channel as used for sigma power and slow SFA associations in the right central region (close to known reference C4 based on 10-20 placement: *rho* = -.929, *p* = <.001) and right parietal region (channel close to P4 and P8: *rho* = -.810, *p* = .015). Results remained significant for OMC% associations with right central region when controlling for age (*rho* = -.826, *p* = .022) and AHI (*rho* = -.869, *p* = .011), and similarly for OMC% associations with right parietal region when controlling for age (*rho* = -.873, *p* = .010) and AHI (*rho* = -.891, *p* = .007). In addition, large effect sizes were also indicated in the right frontal region (close to known reference F4: rho = -.881, *p* = .004), left central region (close to known reference C3 and T7: *rho* = -.905, *p* = .002) and left parietal region (channel close to P3 and P7: *rho* = -.810, *p* = .015) (Figure 5.5). Results remained moderate-large in effect size but no longer remained significant for OMC% associations with right frontal region when controlling for age (*rho* = -.494, *p* = .260) nor when controlling for AHI (*rho* = -.669, *p* = .100). Similarly, results were large in effect size but no longer remained significant for OMC% associations with left central region when controlling for age (*rho* = -.610, *p* = .146), although remained significant when controlling for AHI (*rho* = -.761, *p* = .047). Finally, results were moderate in effect size but no longer remained significant for OMC% associations with left parietal region when controlling for age (*rho* = -.332, *p* = .467) nor when controlling for AHI (*rho* = -.585, *p* = .168). After removing the eight participants with subjective cognitive decline from the Control group, associations remained non-significant.

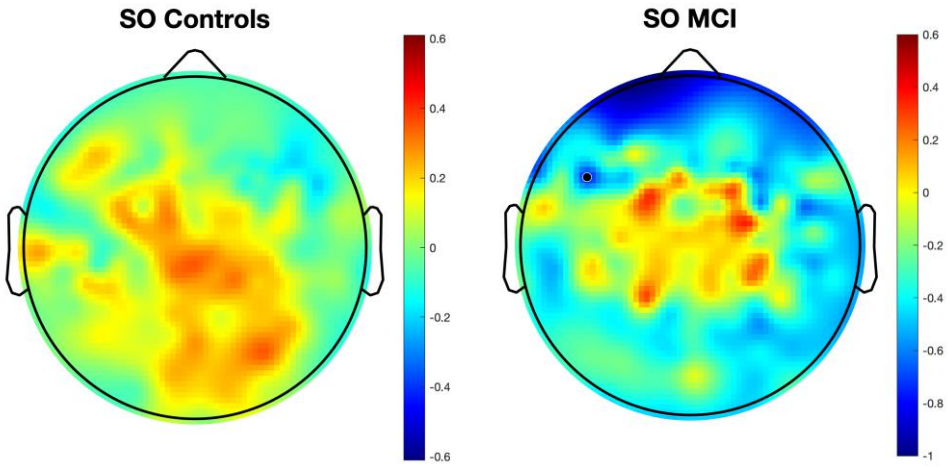

Figure 5.1. Topographical head plots showing the associations between absolute slow oscillations uV^2/Hz (0.5 – 1 Hz) during NREM (N2 + N3) and allocentric spatial navigation OMC%. No significant associations were found between slow oscillations and OMC% in Controls (left image) or MCI participants (right image).

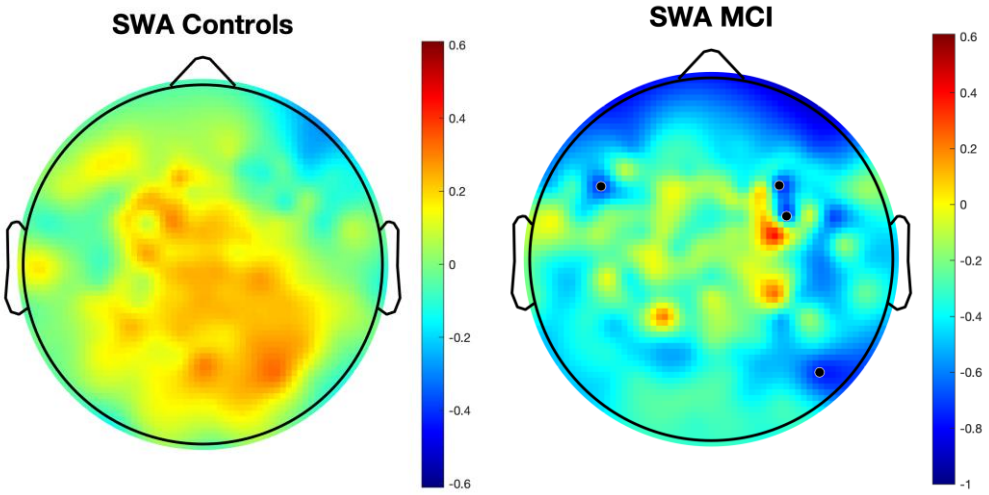

Figure 5.2. Topographical head plots showing the associations between absolute slow wave activity (SWA) uV^2/Hz (1 – 4.5 Hz) during NREM (N2 + N3) and allocentric spatial navigation OMC%. No significant associations were found between SWA and OMC % in Controls (left image) or MCI participants (right image).

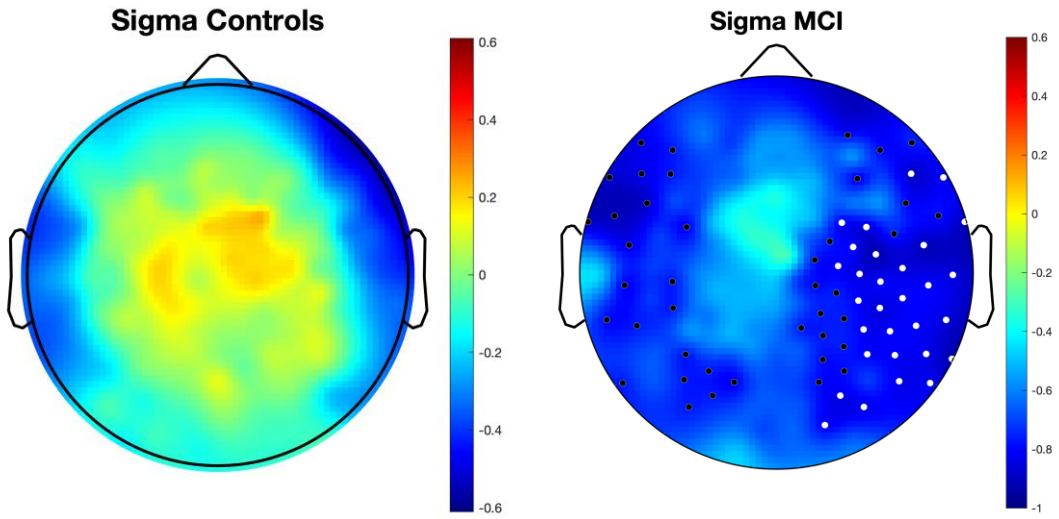

Figure 5.3. Topographical head plots showing the associations between absolute sigma power uV^2/Hz (12 – 15 Hz) during NREM (N2 + N3) and allocentric spatial navigation OMC%. Black dots indicate uncorrected significant correlations ($p < .05$). No significant associations indicated between sigma power and OMC% in Controls (left panel). White dots on the MCI plot indicate corrected scores after TFCE for associations between sigma power (12 – 15 Hz) during NREM (N2 + N3) and OMC% ($p < .05$). These significant associations show that reduced sigma power in right central and parietal regions are associated with worse OMC% (right panel).

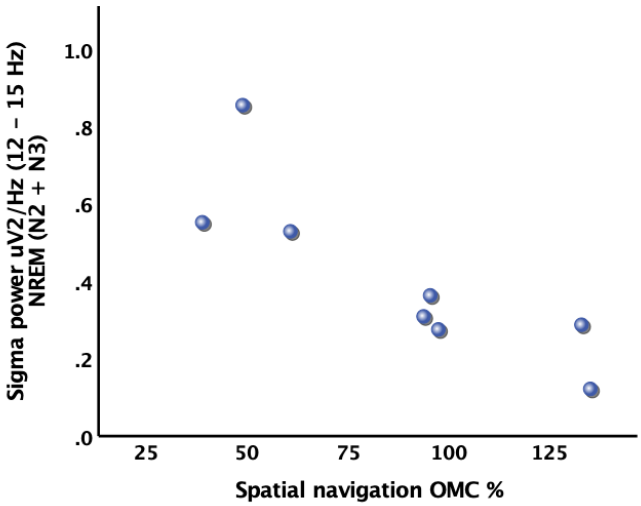

Figure 5.4. Scatterplot showing the correlation between OMC% and sigma power uV^2/Hz (12 – 15 Hz) from a representative channel within the cluster of significant electrodes in the right central region in the MCI group. The significant spearman's correlation (*rho* = -.929, p = .001) indicates that reduced sigma power in NREM sleep is associated with worse memory retention on the CASNAT. A greater OMC% score (error score) = worse overnight memory consolidation.

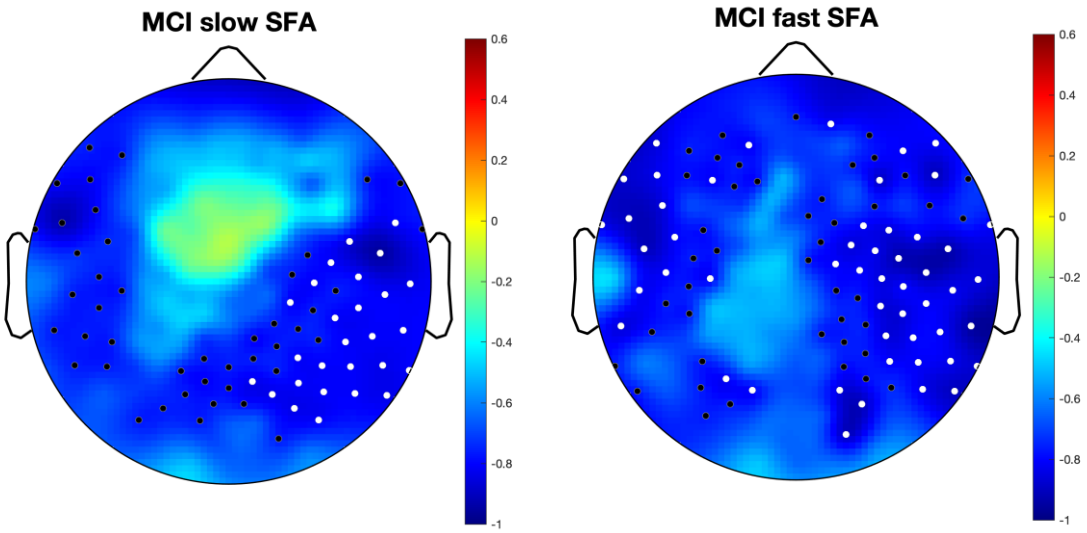

Figure 5.5. Topographical head plots showing the associations between slow SFA (11 – 13 Hz, left panel) and fast SFA (13 – 16 Hz, right panel) during NREM (N2 + N3) and OMC % in MCI. Black dots indicate correlations (uncorrected $p < 0.05$). White dots indicate significant correlations after multiple comparison corrections with TFCE ($p < .05$). Results indicate reduced slow SFA in the right central, partial and occipital region and fast SFA in lateral frontal, central, parietal and occipital regions are associated with worse OMC% in MCI participants.

Associations between regional EEG sigma power during NREM and structural neuroimaging

Given data loss (Controls n: CA1 = 9, DG = 13, ERC = 15; MCI n: CA1 = 6, DG = 8, ERC = 6), this study also calculated associations for the pooled sample of Controls and MCI.

a) *Medial prefrontal cortex thickness*: No post-hoc analysis was conducted between NREM slow waves and mPFC thickness as no significant associations were found between NREM slow waves and OMC%.
b) *CA1 volume*: No significant associations were found in Controls or MCI with right CA1 grey matter volume. In the pooled sample, greater CA1 volume was associated with greater sigma power in lateral frontal and centro-parietal regions (uncorrected $p < 0.05$) in 16 channels, however these associations did not remain after TFCE analysis (Figure 5.6).
c) *Dentate gyrus volume*: No significant associations between sigma power and right DG volume for Controls, MCI, or pooled sample were observed ($p > .05$).
d) *Entorhinal cortex volume*: No significant associations between sigma power and right ERC volume for Controls, MCI, or pooled sample were observed ($p > .05$).

A single channel EEG representative was used to illustrate significant associations with moderate to large effect sizes between sigma power and CA1 volume in the right parietal region (close to known reference P4 based on 10-20 placement: rho = .593, p = .020).

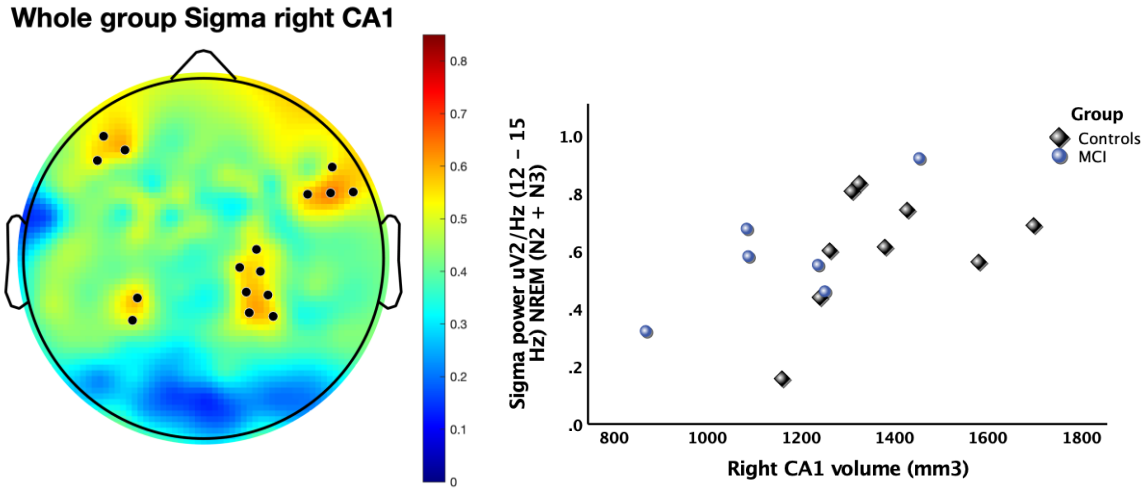

Figure 5.6. (left image) Topographical head plots showing the associations between sigma power uV^2/Hz (12 – 15 Hz) during NREM (N2 + N3) and right CA1 grey matter volume (mm^3). Black dots indicate uncorrected significant correlations (p < .05). (right image) Spearman's correlations were used to examine associations between sigma power and right CA1 grey matter volume in pooled sample from a single representative channel from the right parietal region (rho = .593, p = .020). Results indicate reduced sigma power is associated with lower CA1 volume but notably this did not withstand TFCE correction.

5.5. DISCUSSION

For the first time, this novel study utilised all-night hdEEG to examine how overnight consolidation of SN memory is associated with NREM slow waves and spindles in both older cognitively intact participants as well as those with MCI, whom are at high risk for dementia. Specifically, the study utilised a novel allocentric SN task custom-designed to be suitable for clinical samples with cognitive impairment, and in particular for older people with cognitive impairment (see Chapter 4). The findings show that reduced sigma power is associated with worse OMC in MCI only. Notably, for people with MCI, reduced sigma power in the right central, parietal and occipital regions of large magnitude was associated with worse SN OMC after correcting for multiple comparisons. Associations between slow and fast SFA and OMC in the MCI group showed slow SFA results similar to sigma power, however fast SFA revealed an additional cluster of associations in the left central, parietal and occipital regions, and in lateral frontal regions. Therefore, while reduced frontal and parietal sigma was associated with worse OMC as we expected, our results extend upon previous studies indicating that fast SFA has a more widespread association with memory consolidation in cognitively impaired older adults. Age did not appear to impact associations between OMC with sigma power, slow spindles, or fast spindles in the right central and parietal region. However, associations with fast spindles in the left central and parietal, and right frontal with OMC were no longer significant, although, moderate effect sizes remained, which may in part be due to the small MCI sample size. Slow waves (SO or SWA) were not associated with OMC in either group after correcting for multiple comparisons.

Given the link between sleep spindles and declarative OMC (Clemens et al., 2006; Lam et al., 2021; Seeck-Hirschner et al., 2012) and the association between medial temporal lobe atrophy and allocentric SN (Li & King, 2019), notably right hemisphere in MCI (Deipolyi et al., 2007; Delpoly et al., 2007; Laczo et al., 2017; Laczo et al., 2014; Lithfous et al., 2013; Nedelska et al., 2012), we further examined associations between sigma power and right CA1, dentate gyrus and entorhinal cortex volumes. However, no significant associations between these variables were found within controls nor those with MCI. When assessing the pooled sample, greater sigma power in lateral frontal and centro-parietal regions associated with greater right CA1 volume with moderate-large effect sizes, however, these relationships did not remain after corrections for multiple comparisons.

The findings of this study are aligned with prior work that has indicated a link between central spindles and memory consolidation in people with MCI but not in a control group (Lam et al., 2021). However, in the study by Lam and colleagues, it should be noted that although there were moderate effect sizes found between spindle duration and verbal episodic OMC in MCI, no other spindle measures (density or frequency, nor slow or fast spindles) were associated with OMC (Lam et al., 2021). By contrast, the findings of this study were not aligned with those reported in healthy older adults, whereby greater frontal SWA (Mander et al., 2013) and spindles (Mander et al., 2014) were linked to superior verbal episodic OMC, nor with those showing greater SWA being associated with better SN OMC in a pooled sample of younger and older adults (Varga et al., 2016). Notably, however, age appeared to reduce the strength of the relationship with SWA and SN OMC (Varga et al., 2016). Finally, there is partial alignment between the results of this study and Mullins and colleagues (2021) that showed SWA was not associated with SN memory in healthy older adults without obstructive sleep apnoea similar to this study. However, in their clinical sample with obstructive sleep apnoea, associations with reduced SWA and worse SN memory were observed (Mullins et al., 2021). In interpreting the limited literature in this field, and the lack of consistency in findings to date, it is important to note that there are key differences in the tasks utilised to probe SN. For example, two previous studies measuring SN OMC in older adults used a spatial maze task using reaction time as an outcome measure (Mullins et al., 2021; Varga et al., 2016). By contrast, our task was designed to measure hippocampal-dependent allocentric memory using the Morris Water Maze task (Morris et al., 1982), which is considered to be the gold standard measure for allocentric SN memory, as it does not allow the use of local cues or a fixed-escape formula (Klencklen et al., 2012). Thus, SN tasks that use other designs such as a maze may recruit more of the prefrontal cortex due to reliance on working memory (Piefke et al., 2012). Such tasks may be affected by diseases affecting frontal-subcortical networks such as vascular dementia or behavioural variant frontotemporal dementia (Feng et al., 2021; Jakabek et al., 2018). By contrast, the Morris Water Maze task has high sensitivity for hippocampal compromise (Laczo et al., 2017; Laczo et al., 2014).

In comparing this study to prior work, it is also worth noting that all prior studies examining SN OMC, have used limited EEG channels to examine the relationship between NREM EEG and OMC, that may not take into account non-examined brain regions. Whilst previous studies have indicated that greater frontal fast spindles (Mander et al., 2014) and central spindles are important for memory consolidation (Lam et al., 2021), this study reveals that the function of

spindles may not necessarily be limited to one region in MCI; information that is only possible to be captured with hdEEG. Whilst preliminary, this novel study using hdEEG for the first time has shown NREM sigma power associations with hippocampal CA1 volume. These findings could now be built upon in future work that focuses on other relevant subcortical structures such as the CA3 and thalamus (Broadhouse et al., 2019; Contreras et al., 1997; Fernandez & Luthi, 2020; Lam et al., 2021), or cerebrovascular integrity, as assessed by white matter tract integrity (Palmer et al., 2022), when attempting to delineate sleep-wake underpinnings in ageing samples.

Another factor to be considered in the findings of this study is sleep respiratory disruption. Given the effects of obstructive sleep apnoea on memory performance (Djonlagic et al., 2014; Kloepfer et al., 2009; Lam et al., 2021; Mullins et al., 2021; Varga et al., 2014), brain structure (Cross et al., 2018) and brain function (Chang et al., 2020; Naismith et al., 2020) in ageing, obstructive sleep apnoea may in fact moderate the relationship between sleep neurophysiology and OMC via its impact on brain integrity and/or sleep fragmentation to slow wave sleep. Whilst there were no group differences in obstructive sleep apnoea in our study, our control group did have moderate obstructive sleep apnoea severity (i.e. average apnoea hypopnea index of 20). As a secondary analysis for significant associations, sleep disordered breathing measured by AHI did not appear to influence associations between OMC and sigma power, slow spindles, or fast spindles in the lateral central or right parietal region, only for associations between OMC and fast spindles in right frontal and left parietal region. With a larger sample size, stronger evidence may have been provided whether sleep disordered breathing disrupted the relationship between NREM EEG and OMC.

Conclusions and limitations

Overall, this study, provides significant novel methodological advancements in understanding sleep neurophysiology and OMC in ageing and early neurodegenerative disease. Firstly, it utilised a custom-designed allocentric SN OMC task (CASNAT) tailored for a cognitively impaired sample, but built on gold standard Morris Water Maze probes. Secondly, it moved beyond using single sensor EEG to hdEEG in order to isolate regional deficits in NREM EEG and OMC. In order to explore the potential influence of brain volumes to the sleep EEG-memory relationship, the study also incorporated neuroimaging in subcortical MTL regions and key hippocampal subfields. For the first time, a multiple-domain MCI sample was examined, revealing the important relationship between regional deficits in NREM spindle

frequency activity and impaired OMC on the CASNAT. In addition, revealing that fast spindle frequency activity may have a more significant influence on OMC compared to other NREM measures such as slow spindles, SO or SWA, in an older clinical sample. Finally, preliminary evidence is provided for the association between NREM sigma and right CA1 volume.

Whilst it may be presumed surface level hdEEG recordings may not capture brain pathology in subcortical areas, a recent study found evidence for subcortical electrophysiological activity (measured in-vivo) being detectable with hdEEG source imaging (surface level EEG) in epilepsy patients (Seeber et al., 2019). This then provides support for the reliability of our findings between right CA1 volume and sigma power. However, more studies need to be conducted to confirm this association and interpret its clinical significance. These findings add to the theoretical and mechanistic model of the hippocampus to neocortex model of long-term declarative memory storage during sleep (Born & Wilhelm, 2012). Allocentric SN OMC could potentially be considered an early screening tool for cognitive decline and neurodegeneration given its sensitivity to both impaired spindles and CA1 volume respectively. We highlight the use of implementing similar hippocampal-dependent allocentric SN tasks above spatial cognition tasks in assessing OMC in ageing. Finally, as previous studies have examined structural atrophy associations with SWA and mPFC (Dube et al., 2015; Mander et al., 2013; Saletin et al., 2013; Varga et al., 2016), and Aβ pathology with SWA (Mander et al., 2015), this was the first study to capture the specific regional associations between NREM EEG and structural brain atrophy in a MCI sample.

However, whilst offering key field advances, some limitations warrant mention and indeed these results should be viewed as preliminary, albeit potentially informative for the subsequent design of further work. First, this study is limited by a small size sample in the MCI group. Therefore, examining MCI subtypes was not possible (i.e. amnestic and non-amnestic MCI). Given the heterogeneity in cognitive function (Petersen, 2005; Xie et al., 2002) and brain structure in MCI (Bell-McGinty et al., 2005; Broadhouse et al., 2019; Csukly et al., 2016; Delano-Wood et al., 2009), the examination of subtypes is crucial. With a large enough sample size, examination of MCI subtypes may have yielded differential NREM EEG associations with OMC. For instance, i) the amnestic subtype may have shown worse SN memory due to more widespread spindle deficits, particularly in areas indicative of neurodegeneration (temporal and parietal); ii) the non-amnestic subtype may have the greatest slow wave reduction due to more pronounced frontal lobe atrophy (Whitwell et al., 2007; Zhang et al.,

2012). Furthermore, as noted above, this study did not include AD biomarkers such as Aβ (CSF, PET or plasma), nor information about key genetic risk such as ApoE4. This information would have enabled better categorisation of the sample and would have enabled analyses of how AD pathology or genetic risk may mediate key sleep and cognitive findings, as eight of the eighteen controls subjects consisted of subjective cognitive decline (Reisberg et al., 2018), a group in which some begin to exhibit alterations in hippocampal atrophy (Cherbuin et al., 2015) and Aβ accumulation (Schwarz et al., 2021). Whilst being cognitively intact from a neuropsychological perspective, it is possible that such subjects are at heightened risk of MCI and dementia longitudinally when compared to general community samples (Jessen et al., 2020; Jessen et al., 2014). Thus, this could have contributed to the heterogeneity of slow wave power and OMC in this group. Whilst removing the eight participants with subjective cognitive decline did not yield differences in results, both were limited by a small sample size. Finally, previous studies have used spindle detection algorithms to identify discrete spindle events spindle count when assessing sigma power associations with OMC. This spindle measure has shown to indicate deficits in those with aMCI (Gorgoni et al., 2016; Kam et al., 2019) and has been associated with greater cerebrospinal fluid and tau (Kam et al., 2019), whereas in this study, we have used a surrogate measure of spindles. However, sigma power has been shown to correlate with spindle events (Purcell et al., 2017), and our preliminary results indicate that this may potentially be a suitable measure capture NREM EEG and OMC decrements in a clinical older sample.

Future directions

In addition to the inclusion of AD and vascular biomarkers to more accurately map the influence of these pathologies on EEG and OMC relationships, future studies could explore how such disruptions relate to functional decoupling in the brain. For example, studies could examine the link between EEG changes and alterations in the resting-state default mode network, as this network may precede structural brain atrophy (Broadhouse et al., 2021; Gili et al., 2011) and appears to relate to self-reported sleep disruption in MCI (McKinnon et al., 2016). Using combined functional MRI and hdEEG may help to identify early sleep EEG biomarkers and whether OMC tasks designed for older adults are able to capture these neurological changes. Utilising digital tasks like allocentric SN may then potentially be a cost-effective biomarker for cognitive decline, in particular AD. Lengthy neuropsychological testing may not always be feasible and this may be an alternative test to be utilised in memory clinics. In addition, whilst slow oscillation and spindle cross-frequency coupling during NREM

have provided preliminary evidence for associations with SN memory consolidation (Bastian et al., 2022), and evidence indicating impaired coupling to be predictive of greater tau within the medial temporal lobe (Winer et al., 2019), better regional specificity using hdEEG will identify where these coupling decrements are occurring. This will allow for a more targeted design of brain stimulation studies such as transcranial direct current stimulation with respect to placement of sensors. In addition, using hdEEG and simultaneous transcranial magnetic stimulation for precision regional specificity of stimulation and voltage (Napolitani et al., 2014). Studies using hdEEG-transcanial magnetic stimulation have been conducted in animals (Huber et al., 2007) and in people with schizophrenia (Marcu et al., 2020), however no known studies have been conducted in older adults. Further work employing hdEEG will help to close the gap in understanding the inconsistent results with OMC and sleep neurophysiology in both younger (Cordi & Rasch, 2021; Zhang et al., 2022) and older adults (Fillmore et al., 2021; Hot et al., 2011). Further examination of sleep neurophysiology and brain atrophy in MCI subtypes will provide greater insight to the sleep-memory relationship in ageing, and clinical interventions designed for boosting sleep spindles in a those at-risk of dementia.

Future studies building on this work have potential to improve our understanding of sleep neuroscience in humans. In turn, this information will help inform the development of targeted treatments to ultimately improve sleep and memory consolidation in older adults.

Chapter 6- Discussion and Conclusion

6.1. Summary of aims and findings

The primary aims of this study were to:

1. Identify if there are differences in verbal episodic, visuospatial and spatial navigation (SN) overnight memory consolidation (OMC) between cognitively intact Controls and older people with clinical Mild Cognitive Impairment (MCI) (and its subtypes; amnestic MCI [aMCI] and non-amnestic MCI [naMCI]);
2. Characterise the associations between OMC and NREM slow waves (slow oscillations [SO], slow wave activity [SWA]) and spindles (slow and fast) during non-rapid eye movement (NREM); and
3. Investigate the associations between OMC and medial prefrontal cortex (mPFC) thickness and medial temporal lobe volumes (hippocampal subfields CA1 and dentate gyrus, and entorhinal cortex).

To date, only two studies have examined OMC and their associations with sleep neurophysiology in MCI samples (Lam et al., 2021; Westerberg et al., 2012), and only one has examined OMC associations with neuroimaging measures (Lam et al., 2021), namely the mPFC and hippocampal subfields. No known studies have examined visuospatial or allocentric spatial navigation (SN) OMC comparing healthy and cognitively impaired older adults. Also, no known prior work has identified the regional specificity of associations between OMC and sleep neurophysiology in MCI. The empirical chapters of this thesis aimed to address these key gaps in the literature to advance our understanding of how OMC relates to sleep and brain degeneration in in 'at-risk' older adults, namely those with MCI. The specific aims and findings of each chapter are summarised as follows:

1) **Chapter 3** aimed to identify group differences using standardised neuropsychological tests measuring verbal episodic and visuospatial OMC in Controls, aMCI and naMCI subtypes, and to determine their associations with SWA, and slow and fast spindle density during NREM sleep. In a sample of 78 participants, the findings showed that while there was an overall impairment in verbal episodic memory in aMCI participants (pre- and post-sleep memory recall), OMC did not differ between groups. Conversely, visuospatial OMC was significantly reduced in aMCI compared to Controls. In Controls, superior verbal episodic OMC was linked to greater frontal slow wave activity. In MCI, reduced verbal episodic

OMC was associated with having more frontal fast spindle density, that was driven by the naMCI subtype. Similarly, in MCI, reduced visuospatial OMC was associated with increased frontal and parietal fast spindle density and these relationships were particularly pronounced in the naMCI subtype.

2) **Chapter 4** aimed to identify Control and MCI group differences in a task specifically developed for this thesis (clinical allocentric spatial navigation task [CASNAT]) measuring egocentric and allocentric SN OMC. In a sample of 57 participants, it examined associations between OMC and NREM SO, SWA and slow and fast spindle density, as well as with medial prefrontal cortex thickness and right CA1, dentate gyrus and entorhinal cortex volumes.

   As an exploratory aim, SN strategies were assessed to identify whether they interacted with OMC of SN memories. The findings showed that compared to the pooled MCI sample, Controls appeared to retain what they had learnt for SN information from a learnt start location, and improved slightly overnight when placed in a novel start location (allocentric SN). In contrast, MCI participants performed worse overnight in both conditions. Significant group differences were found between OMC from a familiar location between Controls and the pooled MCI sample, but no group differences were found when examining MCI subtypes. Allocentric SN OMC was significantly reduced in aMCI compared to Controls.

   No significant associations were found between OMC and slow waves in either group, however for the aMCI subtype, there was a large (significant) and moderate (trend, but non-significant) correlation between worse OMC and reduced frontal slow spindles and reduced slow oscillations respectively. A moderate-large effect size but non-significant correlation was also found between worse OMC and reduced parietal fast spindles.

   In Controls, worse OMC was significantly associated with greater mPFC thickness. In contrast, in the pooled MCI sample, worse OMC was associated with reduced right dentate gyrus volume, and with the with right CA1 volume, which approached significance (moderate effect size). No interaction was found between OMC and spatial strategies used.

3) **Chapter 5** examined a subgroup of 25 participants from **Chapter 4** that underwent a more comprehensive sleep neurophysiology examination using high-density EEG (hdEEG). The primary aim of this study was to examine the regional specificity of OMC associations with SO, SWA, sigma power, and slow and fast spindle frequency activity during NREM in Controls and multiple-domain MCI. As an exploratory analysis, associations between right CA1 volume and sigma power during NREM was examined. No significant associations were found between OMC and slow waves in either group, or spindles in Controls. However, worse OMC was associated with reduced sigma power and slow spindles in the right central and parietal region in MCI. More widespread associations were indicated between worse OMC and reduced fast spindles in lateral frontal, central, parietal and occipital regions in the MCI group. In the pooled Control and MCI sample, reduced sigma power was associated with reduced right CA1 volume, however this did not remain significant after conducting a multiple corrections analysis.

Key findings

The key findings of this thesis are that OMC is significantly impaired in the aMCI subtype on visuospatial and allocentric SN memory. Although one cannot ascertain causality from this work, the findings suggests that greater fast spindles could potentially have a negative influence on verbal episodic and visuospatial OMC in the naMCI subtype, whereas greater slow and fast spindles may be beneficial for SN OMC in those with aMCI. It further highlights the widespread regional associations between OMC and fast spindles in multiple-domain MCI using high-density EEG. Conversely, greater relative SWA appears to be integrally linked to better verbal episodic OMC in Controls.

Finally, in terms of underlying neural integrity, greater right hippocampal subfield volumes may play a role in underpinning allocentric SN OMC in MCI individuals. By contrast, greater mPFC thickness may be more pivotal for allocentric SN OMC in Controls (Figure 6.1).

KEY FINDINGS

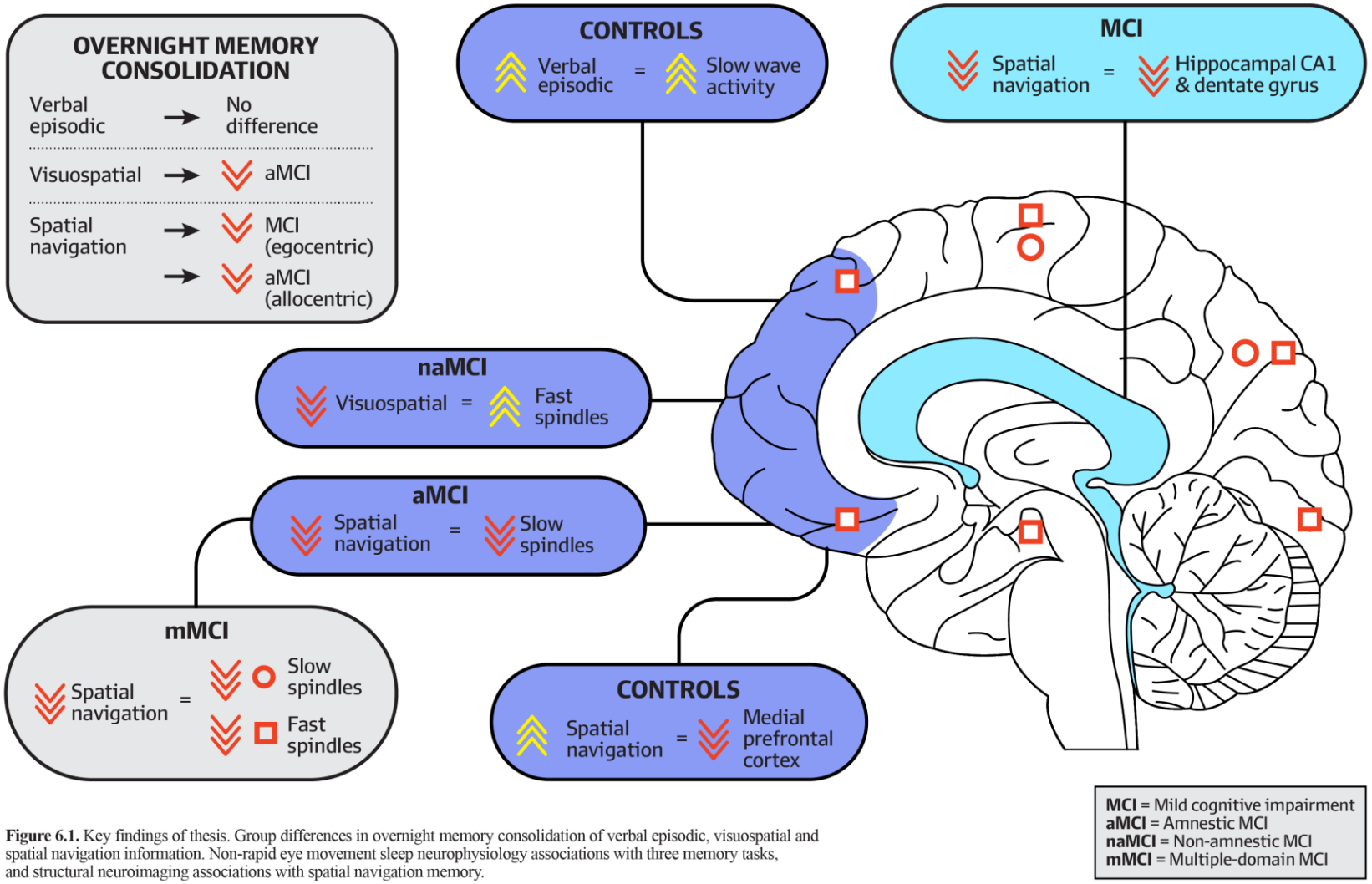

Figure 6.1. Key findings of thesis. Group differences in overnight memory consolidation of verbal episodic, visuospatial and spatial navigation information. Non-rapid eye movement sleep neurophysiology associations with three memory tasks, and structural neuroimaging associations with spatial navigation memory.

6.2. Unique contributions of the thesis

This thesis adds to a body of prior work that has examined verbal episodic OMC using a Word-Pair Associates Task (WPT) in healthy ageing (Baran et al., 2016; Lam et al., 2021; Mander et al., 2015; Mander et al., 2014; Mander et al., 2013; Westerberg et al., 2012). However, prior research has primarily compared younger and cognitively healthy older adults, and this thesis builds on one prior study by this group which compared *verbal* episodic OMC in MCI subtypes (Lam et al., 2021). The studies contained in this thesis provide both novelty and innovation to the literature in the following ways:

- An examination of both verbal and visuospatial OMC using standardised neuropsychological tasks that are typically used in clinical settings.
- The design, refinement and initial validation of the novel CASNAT test to examine SN in MCI before and after sleep. This work shows that the CASNAT is able to discriminate overnight consolidation of allocentric SN in cognitively intact older people and MCI subtypes, and is also sensitive to perturbations of sleep spindles and hippocampal volume changes in MCI. Therefore, this thesis offers a novel task that can be utilised by clinicians to screen for SN impairment in MCI or by sleep researchers to further investigate factors influencing OMC. It could also be used and further adapted for future studies of OMC and sleep or in relation to other clinical neuropsychiatric and neurodegenerative diseases.
- This thesis also for the first time deploys hdEEG; a highly specialised tool utilised to characterise neurophysiological correlates of SN in a clinical sample. The hdEEG patterns also show diffuse associations in the brain between worse SN OMC and reduced fast spindles in MCI, whereas slow spindles and sigma power are limited to the right central-parietal region.

A key finding of this thesis is that there are **unique and differential associations between OMC and sleep neurophysiology in healthy older and MCI groups**. Thus, future studies examining sleep-memory associations in older people should carefully phenotype the cognitive profile/status of participants. Considerations should also be given to AD biomarkers in phenotyping participants as well as structural brain integrity when interpreting findings.

6.3. General discussion

The findings of this thesis regarding OMC on standardised cognitive tests (Chapter 3) show a **lack of group differences in verbal episodic OMC and as such are discordant with previous studies** (Lam et al., 2021; Westerberg et al., 2012). However, it is important to consider that this discrepancy may well reflect differences in task design. That is, the verbal episodic tasks presented in prior work (Lam et al., 2021; Westerberg et al., 2012) included a greater number of items to remember, and an opportunity to remember via semantic relatedness (word-pairs *vs.* single word learning). Whilst no differences have been found between OMC of semantically related *vs.* unrelated word-pairs between Controls and MCI persons (Lam et al., 2021), research in younger adults has found unrelated word-pairs to be sensitive to deterioration in wake *vs.* sleep (Payne et al., 2012). Thus, the 15-tem word list used in this thesis (Chapter 3) may not have been sufficient to truly test memory degradation or enhancement overnight and/or may have lacked the sensitivity to detect subtle between-group overnight changes. Furthermore, although all three studies had cognitively phenotyped participants, given recent findings indicating daytime verbal episodic memory was correlated with verbal episodic OMC (Lam et al., 2021), it may indeed be that general impairment in episodic memory may underpin group differences and that additional nocturnal sleep memory decrements are minimal, once these are considered. Neither Westerberg and colleagues (Westerberg et al., 2012) nor Chapter 3 or 4 of this thesis considered whether overnight memory findings, were evident over and above those observed on daytime memory performance.

Comparing cognitively intact and impaired older adults' **overnight consolidation of visuospatial and SN information offers a significant methodological advancement in the sleep-memory literature**. Previous studies comparing healthy younger and older adults using an object location visuospatial task indicated that older adult's memory scores do not benefit from sleep compared to a wake condition (Cherdieu et al., 2014; Sonni & Spencer, 2015). Whilst each used differing study designs, the findings examining visuospatial OMC within this thesis are aligned with such prior work for both cognitively intact and MCI participants (Chapter 3). Other pertinent literature to consider in future studies is the examination of personal attributes such as cognitive reserve and the potential role of key critical windows throughout the night, as prior work has shown that 'high performing' older adults benefited from sleep by improving on memory recall. Greater rapid-eye movement (REM) sleep during

the first half of the night has been shown to preferentially benefit memory in 'high performing' older adults, whereas NREM in the first half of the night was beneficial for younger adults (Sonni & Spencer, 2015). It should be noted that the empirical studies in this thesis summed NREM stages of interest throughout the night. Furthermore, in 18 younger and 13 older adults, younger adult's memory benefited more from sleep when examined using a virtual maze task (Varga et al., 2016). Whilst that task differed to the SN task employed in this thesis, the findings in healthy older adults (Varga et al., 2016) were similar to those of cognitively intact older adults in this thesis with respect to SN overnight rate of forgetting. In a similar task design based on the MWMT, comparing performance in wake *vs*. sleep conditions in younger adults, in both conditions, participants generally performed better in the egocentric compared to allocentric SN condition (Samanta et al., 2021), findings that are discordant with results in this thesis. **Differences in performance in younger adults' egocentric and allocentric SN OMC and those reported in this thesis (Chapter 4), may partially be due to general cognitive function and strategies employed**. Therefore, the benefit of sleep for memory consolidation appears to decline with age, has preferential decrements based on cognitive domain, and memory associations with sleep in ageing may be dependent on critical timepoints during sleep.

Regarding key influences of OMC performance, **this thesis suggests there may be a key role of self-reported spatial strategies** (Chapter 4). Whilst no interaction was found between strategies and SN OMC, numerical observation indicated a benefit of using allocentric (compared to egocentric) strategies in both groups in a novel location, however, this was only beneficial for Controls when they were in a familiar location. Therefore, cognitive function, particularly those functions which may support performance on the OMC task, may be highly relevant when interpreting OMC. Indeed, previous reviews of the field have raised the question as to whether *sleep-dependent memory consolidation* can be solely attributed to sleep (Axmacher et al., 2009; Dastghejb et al., 2022; Muehlroth, Rasch, et al., 2020; Scullin & Bliwise, 2015) and the extent to which **consolidation may reflect cognitive or memory functions more broadly**. As expected, aMCI persons showed reduced pre-sleep verbal episodic and visuospatial memory recall, and performed worse from trial one to five on the CASNAT learning component. This highlights that learning 'to-criterion' may not always be feasible in sleep-dependent memory paradigm studies in cognitively impaired older adults, but rather, a set number of learning trials (as administered in some standardised neuropsychological tests) could be administered, whilst controlling for pre-sleep learning.

As previously noted, work in healthy ageing samples has suggested a key role for absolute slow wave activity in relation to verbal episodic OMC in healthy ageing (Mander et al., 2013; Westerberg et al., 2012). Findings of this thesis (Chapter 3) indicate **verbal memory consolidation in Controls were partially aligned with such work, but showed that 'relative' as opposed to 'absolute' slow wave activity was linked to overnight consolidation**, albeit using a different memory task. A most striking observation from this thesis, however, is that slow waves were not statistically linked to verbal, visuospatial nor SN OMC in people with MCI. It is noted that there was a moderate size correlation and trend significance for the positive relationship between SN OMC and slow oscillations in aMCI, but a fully powered study would be now be required to further examine this relationship. It may also be possible that slow waves in the first half of the night (Sonni & Spencer, 2015), or, their timing of occurrence with spindles (Helfrich et al., 2018), are more crucial for memory consolidation. Although no studies have examined SO and spindle coupling in MCI or Alzheimer's disease (AD) and how they differ to healthy ageing, older adults show misalignment in coupling compared to younger adults (Helfrich et al., 2018). Furthermore, higher EEG connectivity in delta during N2, quantified by 'spectral imaginary coherence', has shown associations with greater daytime processing speed in healthy younger and older adults, and lower connectivity in delta and sigma during REM with higher verbal memory (Bouchard et al., 2020). Preliminary results in 16 MCI persons showed that slow oscillatory (< 1 Hz) transcranial direct current stimulation during a nap improves visual memory, and memory in turn was significantly associated with coupling (Ladenbauer et al., 2017).

Further to the EEG observations described in NREM, findings of greater EEG slowing have been identified in resting-wake (D'Atri et al., 2021) and REM in MCI (Brayet et al., 2016; D'Atri et al., 2021) and early AD (Petit et al., 1993). Furthermore, altered brain perfusion appears to be more altered in REM compared to wake in aMCI persons, which correlated with verbal episodic measures (Brayet et al., 2017). Slowing during REM may be a potential early biomarker of progression to AD, and conversely, NREM oscillations and coupling may be possible modifiable factors for neurodegeneration disease progression. Longitudinal studies in MCI subtypes are now required to determine this. However, whilst there is a need to examine both sleep stages individually and their longitudinal outcomes, there is a need to consider the interaction between NREM and REM in ageing. One hypothesis for this is that **REM sleep may in fact function as a compensatory mechanism in response to reduced slow wave sleep (SWS)** (Scullin & Gao, 2018).

In contrast to the lack of clear associations with slow waves, the convergence of findings within this thesis suggest that spindles may be more pertinent for OMC in older people with MCI. However, their functions are not entirely clear and warrant some considerations. The negative association between spindles and OMC in MCI (Chapter 3), notably for the naMCI subtype, suggest that firstly, **the function of spindles may vary or be influenced by depressive symptoms**. In MCI, the prevalence of depression is 40% in clinic-based samples (Ismail et al., 2017). The naMCI subtype in this thesis (Chapter 3) had significantly greater depression scores (mean score of 13 on GDS-30). A recent finding showed that in patients with post-traumatic stress disorder, greater spindles were associated with increased intrusive memory symptoms (van der Heijden et al., 2022). Furthermore, insomnia in older adults has been shown to be associated with an increase in higher frequency brain waves (4 – 32 Hz) compared to those without insomnia (Hogan et al., 2020). This is of significance given the high prevalence of insomnia in older adults (Patel et al., 2018), sleep disruption in those with MCI (Torossian et al., 2021), and its co-morbidity with depression (Bao et al., 2017). In contrast, greater slow and fast spindles appeared to be positively associated with SN OMC in aMCI (but not naMCI) (Chapter 4) and multiple-domain MCI (Chapter 5); both groups of which had low depression scores (< 3 on GDS-15). The differences in these findings with spindles in MCI may be attributed to differences in clinical profiles, namely depression scores and psychotropic medication use, differences in memory functions, as well as factors unaccounted for such as AD pathology, or structural (i.e. disintegration of key white matter tracts) or functional 'decoupling' of key regions and networks within the brain. It is possible that increased spindles in an 'at-risk' group may be utilised as a compensatory mechanism or response due to grey or white matter decrements, or amyloid-beta (Aβ) or tau pathology.

Whilst it was not a primary focus of this thesis, no group differences in slow waves were identified. When comparing group differences in spindles, a non-significant trend showed aMCI persons had reduced frontal fast spindles compared to naMCI and Controls (Chapter 3). It is still unclear whether NREM sleep neurophysiology differs amongst various MCI subtypes. Such information is crucial when interpreting associations between sleep measures with memory and cognitive function. The findings from this thesis support the notion that fast spindles are critical to consider when examining associations between sleep, memory, and structural brain integrity. The use of a path and/or mediation analysis to delineate the relationship between frontal fast spindles, memory and brain integrity, has been conducted in

healthy, but not MCI older persons. White matter tracts have shown to mediate the relationship between fast spindles and motor memory consolidation (Mander, Zhu, et al., 2017), and fast spindles have also shown to mediate the relationship between ageing next day hippocampal activation, as measured by functional magnetic resonance imaging; a relationship to which then influences verbal episodic learning (Mander et al., 2014). Recently, increased tau has shown to be associated with impaired frontal fast spindles using hdEEG, and these regionally specific spindles were associated with worse verbal episodic OMC (Mander et al., 2022). Findings from this thesis (Chapter 4) and previous studies (Lam et al., 2021) indicate reduced hippocampal volumes are linked to worse OMC in MCI, and that perhaps reduced spindles are also linked to CA1 hippocampal volume (Chapter 5). Therefore, it is possible that brain degeneration due to neurodegenerative disease may underpin sleep changes or conversely that disturbances in sleep contribute to degeneration. Regardless of causality, they suggest that future studies examining memory should consider the role of spindles, hippocampal integrity and memory in MCI subtypes and ideally should examine these inter-relationships longitudinally.

Whilst preliminary and promising findings highlight a relationship between sleep, memory and underlying structural brain integrity in ageing, studies using multimodal neuroimaging techniques have the potential to provide greater insight into this relationship. One significant gap in the literature is the extent to which brain networks using resting state functional MRI (rsfMRI) or diffusion tensor imaging (DTI) can shed light on the neural networks required for OMC, and how they differ in healthy older and cognitively impaired older adults. As mentioned above and previously in this thesis, white matter tracts using DTI have shown associations with sleep spindles and OMC in healthy older adults (Mander, Zhu, et al., 2017) and sleep-wake cycle using actigraphy in ‘at-risk’ older adults (Palmer et al., 2022). In participants with moderate to severe traumatic brain injury, despite extensive white matter deterioration, no associations were found with sleep spindles (Sanchez et al., 2020). Whilst this has not been examined in older adults, one possibility may be that white matter may be more detrimental for slow waves and it’s coupling with spindles. Functional MRI studies have provided evidence for brain regions involved in memory processing pre- and/or post-sleep (Bastian et al., 2022; Mander et al., 2014). In addition, reduced connectivity between temporal and parietal regions using rsfMRI in ‘at-risk’ older adults has been associated with self-reported sleep disturbance, particularly for the aMCI subtype (McKinnon et al., 2016), and greater WASO using actigraphy (McKinnon et al., 2017). Resting-state fMRI has also indicated that the coactivation of parietal, occipital and temporal networks may be crucial for daytime memory consolidation

in healthy younger and older adults (Fassbender et al., 2022). However, only in younger adults was the changes in the medial temporal gyrus predictive of memory performance, suggesting that the effectiveness of the parietal-occipital-temporal network for memory consolidation may be reduced in older adults. However, the extent to which these network disruptions impact OMC in ageing is unknown. Therefore, a greater insight into the associations between sleep neurophysiology, neural networks using DTI and/or rsfMRI, and OMC in MCI, may help not only advance the scientific understanding of this complex relationship, but may also inform the design of targeted clinical interventions.

6.4. Clinical significance

The findings revealed in this thesis suggest that the early assessment of SN, in memory clinic samples may be worthy of further consideration. In such settings, where there is a multidisciplinary approach to cognitive decline (Mehrani et al., 2021), it would be worth further addressing accelerated forgetting of material over longer periods of time than is traditionally conducted in neuropsychological assessments (i.e. up to 30 minute delays). Spatial navigation is a key cognitive function in maintaining independent functioning in older adults. Deficits in navigational abilities have consequences such as getting lost even in familiar environments (McShane et al., 1998; Monacelli et al., 2003), as well as detrimental consequences for driving (Hunt et al., 2010). Spatial navigation tasks have the ability to capture complex cognitive processes specific to MCI and AD such as topographic disorientation and route learning that are not captured in standard neuropsychological assessments (da Costa et al., 2022).

The use of allocentric SN tasks in older adults may detect early difficulties with complex and flexible route learning strategies that are necessary for independent functioning. Furthermore, allocentric SN tasks like the CASNAT can provide information regarding the extent to which participants are relying on beacon-based strategies (egocentric) (Wiener et al., 2013). Whilst available allocentric SN tests have been validated in a clinical sample including the Four Mountains Task (Moodley et al., 2015b; Wood et al., 2016) and the Hidden Goal Task (based on the Morris Water Maze Task) (Bazadona et al., 2020; Gazova et al., 2012; Laczo et al., 2011; Laczo et al., 2012; Laczo et al., 2010; Laczo et al., 2009; Nedelska et al., 2012), they unfortunately do not assess recall following sleep, and this was a key consideration when designing the CASNAT and the empiric work of this thesis. Consequently, the CASNAT was

designed in such a way that performance can be re-examined after long delays such as up to 12 hours. Tasks suitable to capture changes in memory after such long delays are crucial to detect decays or enhancements to even minor changes in the memory trace over time. Using actigraphy, sleep variability over two weeks has been associated with worse memory in aMCI (Westerberg et al., 2010). In addition, decays in memory can even occur over periods as long as two weeks, that in turn have been related to actigraphy-recorded sleep efficiency disruption in 'at-risk' older adults (Lee et al., 2021). These studies highlight the need to use tasks suited to clinical populations to measure long-term memory decrements. Whilst as previously noted, polysomnography (PSG) is the gold-standard method to assess sleep, wearables such as actigraphy could be considered in future clinical studies of MCI in combination with the CASNAT.

For scalability and implementation beyond the sleep laboratory or clinical environment, further development of visuospatial and allocentric SN tasks could also be considered via mobile applications or weblinks. The development and use of digital tools are of clinical significance as they are easily accessible; in particularly for those living in regional, rural or remote settings, can be delivered at scale, translated for culturally and linguistically diverse groups and are cost-effective. In addition, digital memory and executive function tests have shown to be successful in diagnostic performance (Ding et al., 2022) and prognosis of 'at-risk' older adults (Buegler et al., 2020). Future sleep and memory studies could thus be conducted at larger scale and in more diverse groups by utilising the CASNAT or other SN tasks, deployed via mobile, tablet or other remote forms of administration. Capturing navigational specific data in clinical samples such as the environment cues and features utilised, could inform the development of home-care setting guidelines (O'Malley et al., 2017), as well as digital health tools. For example, applications to help with navigation and wayfinding. In addition, such data may inform the design of cognitive remediation interventions to include spatial strategies, which show promising signs for use in older adults (Lovden et al., 2012).

Whilst this thesis adds to converging evidence that sleep is linked to memory consolidation, it highlights inconsistencies in associations between OMC and sleep. Therefore, several gaps in the sleep, memory and ageing literature still remain. Other clinical factors could also be influencing the sleep and memory relationship in ageing, and are relevant considerations for future studies. These include education/cognitive reserve, depression (Naismith et al., 2011),

neuropsychiatric comorbidities (Keynejad et al., 2018), substance or medication use, medical comorbidities and sleep disordered breathing (Lam et al., 2021).

Several methods have been utilised to examine how altering sleep neurophysiology impacts memory using neuromodulation and targeted memory reactivation. **Auditory stimulation applied during slow wave sleep** has shown to increase slow waves and verbal episodic memory consolidation in 13 healthy older adults (Papalambros et al., 2017) and nine aMCI persons (Papalambros et al., 2019). A recent randomised cross-over trial for the first time using an at-home auditory stimulation device was conducted in 16 healthy older adults over a two-week period (Lustenberger et al., 2022). Results illustrated an improvement in the lower range of SWA, although subjective sleep quality, daytime sleepiness and vigilance were not affected, and memory consolidation was not measured. Overall, a suitable and validated methodological delivery of auditory stimulation in ageing samples is still unclear, with some work indicating that older adults appear to be less receptive to auditory stimulation than younger adults (Harrington & Cairney, 2021; Schneider et al., 2020).

Brain-computer interfaces modulating EEG such as **EEG-neurofeedback** applied during wake have also been shown to improve cognitive function in healthy and clinical older adults (Laborda-Sanchez & Cansino, 2021), however, only one known study has examined whether this technique is beneficial for sleep. Whilst not examining neurophysiology, four weeks of open-loop neurofeedback audio-visual stimulation has been shown to improve self-reported sleep and daily functioning in older adults (Tang et al., 2015). Another form of neuromodulation examined in the sleep literature is **transcranial direct current stimulation** (Cellini & Mednick, 2019). Of the five studies that have examined it's impact on sleep neurophysiology and memory in older adults (Eggert et al., 2013; Ladenbauer et al., 2017; Ladenbauer et al., 2016; Passmann et al., 2016; Westerberg et al., 2015), findings indicate a benefit for increasing slow oscillations and spindles (Ladenbauer et al., 2017; Ladenbauer et al., 2016; Passmann et al., 2016; Westerberg et al., 2015). Whilst positive (Ladenbauer et al., 2017; Ladenbauer et al., 2016) and negative (Passmann et al., 2016) changes were observed for declarative memory consolidation in those receiving the stimulation compared to the sham group (albeit mixed findings depending on task), correlations with neurophysiology vary, with studies indicating a positive association with spindles (Ladenbauer et al., 2017), and others indicating no associations (Westerberg et al., 2015).

Targeted memory reactivation during wake has been shown to be beneficial for episodic memory in a sample of 50 younger adults, 50 older adults and 50 aMCI persons (Fernandez et al., 2022). When applied during sleep via auditory cues, it has been shown to increase spindles and in turn, overnight consolidation of SN memory in younger adults (Shimizu et al., 2018). However, the function of targeted memory reactivation during sleep and its associations with memory in older adults have not yet been examined. Overall, studies with greater sample sizes are now required, as well as the utilisation of consistent tasks and methodologies (Salfi et al., 2020).

Other treatments for sleep and memory include, firstly, **pharmacological treatments**, notably z-drugs (Leong et al., 2022), that have been shown to increase spindles (Mednick et al., 2013) and slow oscillation-spindle coupling (Carbone et al., 2021; Zhang et al., 2020). The use of z-drugs on their own (Mednick et al., 2013), as well as when combined with targeted memory reactivation during sleep (Carbone et al., 2021), have been shown to improve memory consolidation in younger adults. However, significant caution should still be applied to the use of z-drugs according to the amended American Geriatrics Society Beer Society for Potentially Inappropriate Medication Use in Older Adults.

Sleep disordered breathing has also been identified as a possible modifiable risk factor for cognitive decline. Cross-sectional studies have identified elevated Aβ in those with obstructive sleep apnoea, with significantly higher rates in those with severe OSA (Jackson et al., 2020). Furthermore, greater prevalence has been identified in MCI (Mubashir et al., 2019), and it has adverse effects on driving (Cross et al., 2017; Doherty et al., 2022) and structural brain integrity (Cross et al., 2018) in ‘at-risk’ older adults. A recent finding indicated improved cognition and NREM neurophysiology (age 50 years ± 13) after six months of continuous positive airway pressure treatment (D'Rozario et al., 2022). These findings highlight the relevance of treating sleep disordered breathing in older adults. However, further robust clinical trials examining the benefits of treatment on sleep neurophysiology and OMC in ageing are still required, and while a number of trials are underway, it is currently unclear whether treatment of sleep apnoea will alter the longitudinal cognitive trajectory in ‘at-risk’ samples.

An important consideration in future study designs is the examination of clinical subtypes in ageing. Given the suggestion that the sleep and memory link is functionally dissociated or weakened in older adults (Scullin, 2013), a better understanding of which groups of older adults

would benefit from sleep interventions is key. Results of this thesis suggest that NREM oscillations are not homogenous in their relevance for memory across different clinical profiles. Therefore, **considerations for participants should include those who are cognitively intact controls without Aβ or tau pathology**, and aMCI and naMCI participants that are Aβ and tau positive. Further studies examining spindles and memory in AD biomarker confirmed samples are now required, and need to account for the various clinical factors mentioned. Such information would be crucial helpful in building the evidence-based required for personalised interventions as well as for informing the design of large scale clinical trials.

The examination of the glymphatic system and circadian system should also be considered in future studies assessing OMC in MCI. Animal studies have shown that sleep may play a role in "clearing out" neurotoxic waste via the glymphatic system (Xie et al., 2013). This process is supressed during wakefulness and activated during sleep, in particularly during SWS (Jessen et al., 2015), and is considered to 'clean' the brain of waste products that build up from neural activity (Mander, Winer, et al., 2017a). Furthermore, given the circadian decrements in MCI mentioned this in thesis, the extent to which this system impacts OMC in MCI warrant further examination. These include measures such as dim light melatonin onset, rest-wake activity and sleep fragmentation using actigraphy; a cost-effect and feasible measurement in ageing samples. One consideration for future studies may be the extent to which the circadian and glymphatic system impede on sleep microarchitecture, and in turn declarative OMC.

6.5. Strengths and limitations

The overall strengths of this thesis were firstly that all participants underwent detailed neuropsychological, medical, sleep and psychological phenotyping. All were classified as MCI based on cognitive profile and clinical consensus using an established and well published method.

Secondly, two tasks were identified to be suitable for a cognitively impaired population delivered after a long delay. In the largest known OMC study in MCI, visuospatial OMC utilising a standardised neuropsychological test, and the purpose designed CASNAT, are tests that can now be utilised in future sleep-memory studies in clinical populations.

Thirdly, multimodal techniques were utilised including standard EEG (10-channel based on 10-20 system), hdEEG, and T1 and T2 structural MRI. The use of high resolution T2 MRI acquisition of the hippocampus and analysis using the ASHS software is also a novel strength given the superior quality of data. This is especially important given the small size of hippocampal subfields, allowing a better distinction of dentate gyrus and CA subfields.

Fourth, memory consolidation and sleep associations were examined across distinct memory domains: verbal episodic, visuospatial and SN. This is important given the general predominance of work that has examined verbal episodic memory, utilising a WPT.

Several limitations have been addressed with respect to each chapter, however some general limitations should be discussed:

1) Controls included participants with subjective cognitive decline, a group that is twice as likely to convert to MCI and/or Dementia within five years, compared to those without subjective cognitive decline (Liew, 2020; Parfenov et al., 2020). While in many ways, they are similarly matched to the MCI sample in terms of their 'health seeking behaviour' it is possible that the Control group include people with preclinical disease;
2) Given the clinical heterogeneity in 'at-risk' older adults, the existence of underlying pathologies such as cerebrovascular disease, Aβ, alpha-synuclein and tau cannot be ascertained from the samples examined. That is, the participants with MCI did not have 'biomarker' evidence of AD (derived from PET or cerebrospinal fluid) (Albert et al., 2011) and thus their longitudinal trajectories may be diverse;
3) Conversely, the Healthy Brain Ageing Clinic excludes participants with stroke or transient ischemic attack, and thus, those with predominant large-vessel vascular aetiologies may be under-represented. However, age, education, cognitive function, depression, medication and sleep disordered breathing were accounted for where relevant;
4) Slow waves and spindles were solely examined in NREM therefore it is unclear whether a similar pattern was indicated in REM. In addition, given slow waves and spindles were calculated for the whole night, it could not be ascertained whether there was a benefit of either brain wave in the first or second half of the night;
5) An overall caution is required with automated spindle software in clinical samples (Warby et al., 2014), however the automated spindle algorithm used in this thesis has been validated internally and within a MCI sample (Lam et al., 2021);

6) Given the cross-sectional nature of all three studies, it is not possible to identify the onset of neurophysiological or structural brain changes. Therefore, longitudinal studies are crucial in order to delineate the bidirectional relationship between sleep neurophysiology and structural brain changes, and in turn, their impact on memory consolidation;
7) Whilst being larger than many existing studies, and often necessitated in detailed PSG studies such as this, the empirical studies of this thesis still contained fairly small sample sizes, in particular for aMCI. Indeed, many moderate to large effect sizes were observed in the empirical work of this thesis that did not reach statistical significance and was likely under-powered. In turn, the small sample size precluded methods such as path or mediation analyses which could have more eloquently identified whether structural brain changes mediate alterations in sleep neurophysiology and in turn OMC. In addition, the small sample sizes, notably for the aMCI group, may increase the risk for Type I errors.

6.6. Future directions

Considerations for future studies in sleep and ageing are described in four broad categories including:

Methodological considerations for OMC

1) In order to disentangle sleep's role in memory consolidation, future studies could consider a cross-over trial with a two-week wash-out period testing memory consolidation after a 12-hour period in the daytime, and again after a night's sleep;
2) Consideration of more effective ways to measure OMC would be ideal. For example, digital methods and home devices could more easily track changes in OMC over time and in response to treatments.

Sleep neurophysiology

3) A more comprehensive examination of sleep neurophysiology, examining EEG brain waves as a network such as slow wave and spindle cross-frequency coupling and EEG coherence. In addition, assessing critical sleep windows (e.g. first sleep stage), REM sleep neurophysiology and importantly, the interaction between NREM and REM warrants further investigation (Scullin & Gao, 2018);

4) Given the inconsistencies in OMC findings in ageing, harmonised neurophysiology metrics (i.e. frequency range, staging, spindle type) reported in OMC studies with clinical samples should be utilised. Considerations should also be given to reporting both absolute and relative SWA given mixed findings, and whether they are potentially more important for memory consolidation in the first or second half of the night.
5) Characterising sleep neurophysiology among MCI subtypes is crucial and examining brain waves beyond only slow waves and spindles, with evidence pointing to theta associations in NREM (Cordi et al., 2018; Westerberg et al., 2012; Zhang et al., 2020) and REM (Hot et al., 2011; Westerberg et al., 2012) with OMC in cognitively impaired and unimpaired older adults.

Neuroimaging and biomarkers

6) Use of personalised 'precision' medicine approaches based on clinical subtypes (i.e. aMCI and naMCI with and without AD pathology markers) could be considered. For example use of DTI and rsfMRI to improve understanding of decoupling or disintegration of key circuits involved in sleep and that may underpin effective OMC;
7) Alzheimer's genetic phenotyping (e.g. consideration of apolipoprotein E epsilon 4 allele [APOE-4]) is necessary, in particularly given its strong relationship with sleep disturbance (Wei et al., 2022) and AD progression (Burnham et al., 2020). Longitudinal studies using multi-modal techniques will help better understand the bi-directional relationship between sleep neurophysiology and brain integrity, and the role of sleep in disease trajectory. For example, the utilisation of hdEEG source localisation will highlight overlapping structural and spindle deficits. In addition, brain structure of key regions; mPFC, thalamus, and hippocampus, as well as white matter tracts that connect these regions, should be examined as potential mediating factors between sleep neurophysiology and OMC.

Spatial navigation memory and clinical interventions

8) The CASNAT presented in this thesis has been developed into a weblink format, that can be accessed by other research groups. A key alteration on the task includes a set time for capturing answers on the recall component (i.e. responses only after > five seconds included) and updates to visual settings using Unity software to enhance the virtual experience. A recognition component is also included in the task giving researchers an option to include this in the assessment (post-sleep only). The CASNAT

could potentially be utilised in other clinical groups known to have SN impairment such as in Parkinson's disease (Schneider et al., 2017), frontotemporal dementia and Alzheimer's disease (Tu et al., 2015; Tu et al., 2017), schizophrenia (Fajnerova et al., 2015), depression (Cornwell et al., 2010; Gould et al., 2007), temporal lobe epilepsy (Amlerova et al., 2013; Glikmann-Johnston et al., 2008) and post-traumatic stress disorder (Marlatte et al., 2022). The design of the CASNAT would be particularly useful for studies looking to test memory after a long-delay. Future studies using the CASNAT and other SN tasks should now consider other risk factors for SN impairment given its significant impact on everyday function, such as education, gender, alcohol use, neuropsychiatric disorders, sleep disordered breathing, disease onset and presence of comorbid brain pathology and medical comorbidities;

9) Finally, the development of clinical trials using methods such as auditory and brain stimulation, targeted memory reactivation, and neurofeedback to identify whether they impact sleep and memory. The development and outcomes of these studies are vital for translational outcomes in clinical settings.

6.7. Conclusion

Overall these findings advance our scientific understanding of OMC, otherwise termed 'sleep dependent memory consolidation' in older adults. They show that visuospatial and allocentric SN OMC is impaired in MCI, in particular aMCI. However, the empirical work in this thesis does not support changes in verbal episodic memory, albeit using a neuropsychological rather than purpose-designed task for measuring OMC. Fast sleep spindles appear to be integral for memory consolidation in MCI. However, whether this represents a beneficial or compensatory mechanism due to underlying brain degeneration requires elucidation. Hippocampal subfield volumes in MCI and mPFC thickness in Controls are relevant for SN OMC, with preliminary evidence pointing to hippocampal and spindle associations. High-density EEG adds value beyond that obtained via standard EEG by showing that slow spindles have localised associations with OMC in the right central and parietal regions, whereas fast spindle associations are widespread, and therefore potentially have a more crucial role in OMC in MCI. This overall body of work offers clinical insights in particular as such work could inform clinical practice such as screening for OMC and sleep disturbance in memory clinics, and highlights the need for a holistic approach when examining the function of sleep neurophysiology for memory in 'at-risk' populations.

Ultimately, the goal of such research is to determine how to improve both sleep and memory in older people with cognitive decline and potentially on the trajectory to dementia. Only by advancing our scientific understanding of the neural and sleep underpinnings of these memory systems can targeted interventions be developed and tested in clinical samples. The work represented in this thesis represents an early stage of this research pipeline but building on these foundations to now influence further work and research translation will now be required for longer-term research impact, and to improve the daily functioning and quality of living for older people and those living with MCI.

APPENDIX

Table 1A. Verbal episodic (RAVLT) and visuospatial task (ROCFT) descriptives (single and multiple-domain MCI).

	single-domain MCI	multiple-domain MCI			
	M, sd	*M, sd*	*F*	*p*	*omega*^{2}
Verbal episodic					
RAVLT PM (/15)	8.5 (3.5)	7.1 (3.1)	5.3	**.007*[1]**	.101
RAVLT AM (/15)	6.9 (3.6)	5.5 (2.7)	4.0	**.024*[1]**	.077
RAVLT OMC %	81.1% (25.6)	77.8% (25.7)	.23	.795	-.022
RAVLT OMC % (age)[a]	-	-	.17	.846	-
RAVLT OMC % (GDS)[b]	-	-	.42	.657	-
Visuospatial					
ROCFT PM (/36)	18.9 (6.5)	14.6 (5.6)	3.4	**.037*[2]**	.059
ROCFT AM (/36)	17.7 (7.2)	13.2 (6.0)	3.8	**.026*[3]**	.067
ROCFT OMC %	92.3% (13.4)	87.9% (25.1)	1.8	.171	.020
ROCFT OMC % (age)[a]	-	-	1.6	.214	-
ROCFT OMC % (GDS)[b]	-	-	5.3	**.007*[1]**	-

Note. * **p<.05.** One way ANOVA comparing Controls and MCI subtypes. Correct responses in evening and morning, and overnight change calculated by ([morning score – evening score]*100). GDS= geriatric depression severity. [a]Controlling for age using a univariate GLM. [b]Controlling for depression severity using a univariate GLM. [1]Significant group differences between Controls and multiple-domain MCI. [2]No significant differences between single-domain MCI and multiple-domain MCI (p = .070). [3]No significant differences between Controls and multiple-domain MCI (p = .066), or between single-domain MCI and multiple-domain MCI (p = .068).

Virtual Morris Water Maze (vMWM) Morning Questionnaire

1. **Are you left or right handed? (circle)**
   L/N

2. **Do you use a computer at home? (circle)**
   Y/N

3. **How often do you use a computer during the week?**

4. **Do you feel comfortable using a computer? (circle)**
   Not at all
   Somewhat
   Very much

5. **Do you have trouble orienting yourself in an unfamiliar environment? (circle)**
   Never
   Sometimes
   Always

6. **During the test, did you feel as though you were getting closer or further away from landmarks around you?**
   _____
   _____
   _____

7. **When you were learning the location of the target item over the 5 trials, were you trying to create a map in your head while looking for the target item? (circle)**
   Y/N

8. **When you were learning the location of the target item over the 5 trials, were you trying to learn the position of the treasure chest in relation to multiple landmarks or were you using one landmark only? If so, which landmark/s were you using?**
   _____
   _____
   _____
   _____

9. **Could you tell me more about how you were trying to find the hidden chest?**
   ***prompt*: was there something you tried at the very start of each trial?**
   ***prompt*: were you using any of the landmarks to help you find the chest? How were you using it?**
   ***prompt*: if you didn't find the chest, what would you do?**
   _____
   _____
   _____
   _____

10. **At the beginning of the trial, how did you determine which direction you would move towards?**
    _____
    _____
    _____
    _____

11. **Did you recognise in the second recall test that you started from a different location? (circle)**
    Y/N

12. **If you did recognise it was a different location, did you do anything differently to the first recall test starting from the same location you learnt?**
    _____
    _____
    _____
    _____

Figure A1. Spatial Navigation Questionnaire.

Questions were administered to identify other factors contributing to spatial navigation performance including computer use and spatial navigation strategies used.

Table A2. Group differences in left medial temporal lobe volumes between Controls and pMCI.

	Controls *M, sd*	pMCI *M, sd*	*t*	*p*	*hedges g*
Left hippocampal CA1, mm^{3a}	1377.3 (180.4)	1262.6 (219.3)	1.7	.107	.55
Left dentate gyrus left mm^{3a}	807.9 (109.2)	729.6 (112.0)	2.2	**.032***	.69
Left entorhinal cortex left mm^{3a}	468.4 (69.2)	428.6 (69.7)	1.8	.082	.56

Note. ***p<.05. ****p<.01.** Independent samples t-test. [a]Grey matter volume measured in mm^3.

Numbers in Controls: CA1 = 14, dentate gyrus = 17, entorhinal cortex = 16.

Numbers in MCI: CA1 = 24, dentate gyrus = 24, entorhinal cortex = 25.

Table A3. Group differences in left medial temporal lobe volumes between Controls and MCI subtypes.

	aMCI *M, sd*	naMCI *M, sd*	*F*	*p*	*omega*^{2}
Left Hippocampal CA1 (mm^3)[a]	1156.5 (283.9)	1315.7 (164.6)	3.2	.055	.10
Left Dentate gyrus left (mm^3)[a]	716.1 (134.2)	736.3 (103.4)	2.5	.094	.07
Left Entorhinal cortex left (mm^3)[a]	402.6 (90.3)	443.2 (52.9)	2.7	.084	.08

Note. ***p< .05.** One way ANOVA. [a]Grey matter volume measured in mm^3.

Numbers in aMCI: CA1 = 8, dentate gyrus = 8, entorhinal cortex = 9.

Numbers in naMCI: CA1 = 16, dentate gyrus = 16, entorhinal cortex = 16.

Table A4. Correlations between obstructive sleep apnoea allocentric spatial navigation OMC.

	Controls		aMCI		naMCI	
	rho n = 23	*p*	*rho* n = 10	*p*	*rho* n = 21	*p*
AHI total sleep time	.104	.638	.310	.383	-.120	.606
AHI REM	.052	.812	.115	.751	-.262	.252

Note ***p<.05.** Univariate spearman's correlation analysis.

AHI = apnoea hypopnea index.

REM = rapid eye movement sleep.

Table A5. Correlations between sleep microarchitecture and OMC of familiar location.

	Controls *rho* n = 23	*p*	aMCI *rho* n = 10	*p*	naMCI *rho* n = 20	*p*
Frontal						
Slow oscillations (0.25-1 Hz)	.120	.587	.188	.603	-.352	.128
Slow wave activity (0.5-4.5 Hz)	.113	.609	.333	.347	-.308	.186
Fast spindle density (13-16 Hz)	-.160	.466	.394	.260	.209	.376
Slow spindle density (11-13 Hz)	.120	.587	.515	.128	.250	.289
Parietal						
Fast spindle density (13-16 Hz)	.021	.925	.527	.117	.487	**.025***
Slow spindle density (11-13 Hz)	.126	.568	.006	.987	-.194	.401

Note ***p<.05.** Univariate spearman's correlation analysis.

Slow oscillations and slow wave activity absolute power calculated for slow wave sleep (N3).

Spindle density = events per hour, calculated for N2.

Table A6. Correlations between neuroimaging and OMC of familiar location.

	Controls *rho* n= 11-22	*p*	pMCI *rho* n= 20-26	*p*
Primary variables				
Medial prefrontal cortex[b]	-.307	.165	-.027	.896
Right Hippocampal CA1[a]	-.382	.247	-.162	.494
Right Dentate gyrus[a]	-.162	.535	-.112	.584
Right Entorhinal cortex[a]	-.161	.509	-.263	.226
Secondary variables				
Left Hippocampal CA1 (mm^3)[a]	-.429	.144	-.165	.440
Left Dentate gyrus (mm^3)[a]	-.156	.564	-.004	.984
Left Entorhinal cortex (mm^3)[a]	.029	.919	-.066	.753
Medial orbitofrontal cortex (mm)[b]	-.264	.236	-.075	.716
Rostral anterior cingulate cortex (mm)[b]	-.374	.086	-.038	.854
Caudal anterior cingulate cortex (mm)[b]	-.144	.523	-.018	.930

Note ***p<.05.** Univariate spearman's correlation analysis. [a]Grey matter volume measured in mm^3.

[b]Thickness measured in mm.

Numbers in Controls: Frontal regions = 22, CA1 (right) = 11, dentate gyrus (right) = 17, entorhinal cortex (right) = 19, CA1 (left) = 13, dentate gyrus (left) = 16, entorhinal cortex (left) = 15

Numbers in pMCI: Frontal regions = 26, CA1 (right) = 20, dentate gyrus (right) = 26, entorhinal cortex (right) = 23, CA1 (left) = 24, dentate gyrus (left) = 24, entorhinal cortex (left) = 25

Table A7. Correlations between right medial temporal lobe volumes and allocentric OMC in MCI subtypes

	aMCI		naMCI	
	r n= 7-9	*p*	*r* n= 12-16	*p*
Right Hippocampal CA1 (mm^3)	-.387	.391	-.370	.236
Right Dentate gyrus (mm^3)	-.519	.152	-.293	.271
Right Entorhinal cortex (mm^3)	-.407	.365	-.185	.508

Note ***p<.05.** Univariate pearson's correlations used.

Numbers in aMCI: CA1 = 7, dentate gyrus = 9, entorhinal cortex = 7

Numbers in naMCI: CA1 = 12, dentate gyrus = 16, entorhinal cortex = 15

Table A8. Correlations between left medial temporal lobe volumes and medial prefrontal cortex thickness subregions with allocentric OMC.

	Controls n= 14-21	*p*	pMCI n= 23-25	*p*
Left Hippocampal CA1 (mm^3)	.022	.943	-.387	.068
Left Dentate gyrus (mm^3)	-.258	.353	-.214	.326
Left Entorhinal cortex (mm^3)	.349	.222	-.385	.063
Medial orbitofrontal cortex (mm)	.493	**.023***	-.036	.865
Rostral anterior cingulate cortex (mm)	.696	**<.001***	-.062	.767
Caudal anterior cingulate cortex (mm)	.077	.741	.432	**.031***

Note ***p<.05.** Univariate spearman's correlation used for medial prefrontal cortex subregions. Univariate pearson's correlations used for CA1, dentate gyrus and entorhinal cortex.

Numbers in Controls: Frontal regions = 21, CA1 = 13, dentate gyrus = 15, entorhinal cortex = 14

Numbers in pMCI: Frontal regions = 25, CA1 = 23, dentate gyrus = 23, entorhinal cortex = 24

Table A9. Correlations between left medial temporal lobe volumes and medial prefrontal cortex thickness subregions with OMC (controlling for age and coil type).

	AGE				**COIL**			
	Controls	*p*	pMCI	*p*	Controls	*p*	pMCI	*p*
Left Hippocampal CA1[a]	.430	.163	-.460	**.031***	.005	.987	-.400	.065
Left Dentate gyrus[a]	.147	.617	-.250	.263	-.265	.360	-.254	.255
Left Entorhinal cortex[a]	.409	.165	-.437	**.037***	.350	.241	-.382	.072
Medial orbitofrontal cortex[b]	.373	.106	-.042	.844	.447	.048	-.038	.861
Rostral anterior cingulate cortex[b]	.620	**.004***	-.060	.780	.682	**<.001***	-.063	.770
Caudal anterior cingulate cortex[b]	-.110	.644	.422	**.040***	.017	.943	.416	**.043***

Note ***p<.05.** Univariate spearman's correlation used for medial prefrontal cortex subregions.

Univariate pearson's correlations used for CA1, dentate gyrus and entorhinal cortex. [a]Grey matter volume mm^3. [b]Measured in mm.

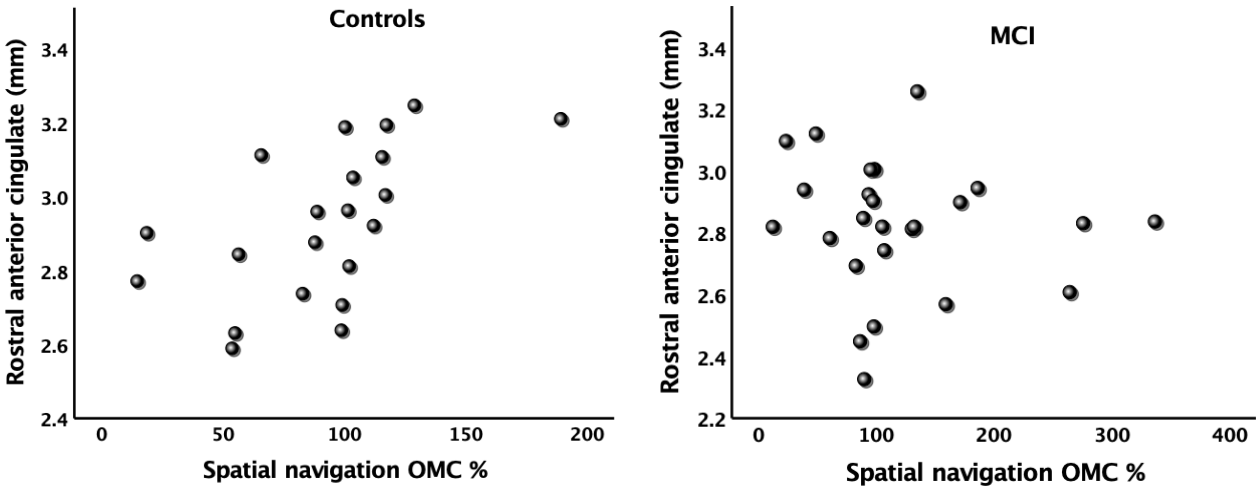

Figure A2. Scatterplots show associations between spatial navigation OMC% and rostral anterior cingulate cortex thickness (mm). Greater OMC% is significantly associated with reduced rostral anterior cingulate thickness in Controls (rho = .696, p = <.001), but in MCI group. Spearman's correlation analysis used. Results were unchanged after controlling for age.

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