MECHANISMS OF MEMORY CONSOLIDATION

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ABSTRACT

Extensive research has shown that sleep supports memory. Newer work suggests that wakefulness can also benefit retention of new information. However, the exact mechanisms which govern memory consolidation in sleep and wake are largely unknown. The implementation of new technologies, which draw on these natural memory processes, allows some insight into their characteristics. This work aims at elucidating some aspects of memory consolidation processes in the realm of sleep and wake. Firstly, we train novel non-words, a material previously indicated to benefit from sleep-associated consolidation, with explicit and implicit methods to determine whether the implicit learning (via the Hebb repetition task) would facilitate lexical integration independently of sleep. The results reveal that lexical integration of novel words is contingent on a good level of explicit training, followed by a consolidation delay with sleep. We speculate that sleep-associated consolidation may be mediated by the degree of overlap between new and already known material. To further capitalise on these findings, we test whether applying non-verbal cues during sleep can improve learning of novel words and their integration within the lexicon using Targeted Memory Reactivation (TMR) paradigm. Our results indicate that reactivating novel lexical representations in sleep improves their consolidation and facilitates their recall. However, the lack of lexical integration observed suggests the need for future research. Finally, based on recent evidence that quiet wakeful rest can result in comparable memory increases to sleep, we explore the consolidation during awake state using transcranial direct current stimulation (tDCS). We found that applying tDCS to the right occipital-parietal site enhances memory for a list of words as compared to no stimulation. The findings imply that memory consolidation during quiet wakefulness can be manipulated externally, which may direct future research. Nevertheless, the exact neuro-correlates of memory consolidation in quiet wake are yet to be fully investigated.

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DECLARATION

This thesis comprises the author's own original work and has not been submitted to this or any other University for a degree. All experiments were designed and conducted by the author under the supervision of Professor Gareth Gaskell. Some parts of the work presented in this thesis have been presented elsewhere as posters, conference talks and informal lab group presentations. All sources are acknowledged as References.

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CHAPTER 1
GENERAL INTRODUCTION AND LITERATURE REVIEW

How humans remember events, facts and words is one of the most researched parts of human cognition. The things we memorise in childhood influence us and the way we function. In later life we continue to encounter new facts, new words and new experiences that shape how we see the world. This thesis is an attempt to explore some of the processes that govern our memory in a state of sleep and wake.

According to neurocognitive models of memory formation it has been argued that the newly formed memory trace must undergo a specific sequence of events in order to become a part of our long-term experience. This assimilation process may occur over hours or even days following the learning event itself. It assures that the new memory trace becomes consolidated and subsequently integrated within the pre-existing knowledge.

Before introducing the experimental part, I will review the literature that was instrumental in motivating this work. The experimental context of this thesis draws from a diverse body of previous research; thus, a broad range of topics will be covered. In the review, I will firstly evaluate the general view on the role of sleep in memory formation by discussing relevant models of memory consolidation. I will further demonstrate evidence that sleep-related memory processes are critical for neural plasticity and memory re-organisation. I will argue that sleep is vital when learning new information, using novel words as a specific example. In the next step, I will outline the methodological advances which facilitated the development of novel experimental methods, such as Targeted Memory Reactivation (TMR) and Closed Loop Stimulation (CLoS), both of which draw directly on the physiological processes taking place in sleep, for example a neural replay of memories acquired during the day. These methods allowed for a new approach to sleep research, namely sleep engineering which is gradually paving the way towards possible clinical applications. In particular, the use of the TMR method motivated one of the aims of this thesis — to apply this new approach to the standard word learning paradigm in order to further explore the sleep-dependent integration of new linguistic entries into the lexicon. An additional goal here was to broaden our understanding about the neuro-correlates of successful targeted reactivation of memories in sleep.

After considering the literature related to memory consolidation processes in sleep, I will discuss the importance of sleep-like states, such as quiet wakefulness, for memory consolidation. I will evaluate evidence of transformation of memory traces taking place in

quiet wakefulness and discuss how it resembles the consolidation processes normally observed in sleep. Here, I will evaluate current research on this topic and outline more general concepts of spontaneous memory reactivations in wake. As the reactivation and consolidation of memories in wake may be related to a specific ongoing brain activity, the EEG markers will also be discussed. Some of the concepts debated in this section will provide a basis for the experiment reported in Chapter 4 which employed the transcranial Direct Current Stimulation (tDCS) method to facilitate consolidation of memories in quiet wake.

1.1 Models of Memory Consolidation

Memory function encompasses three sub-processes, i.e., encoding, consolidation and retrieval (Rasch & Born, 2013). However, it is worth pointing out that the notion of memory consolidation has been controversial and some researchers argued against its concept (Weingartner & Parker, 1984). Following encoding, the newly formed memory trace is highly susceptible to distribution and decay. It is only due to the consolidation process that this highly labile memory trace stabilises into a strong and lasting representation (McGaugh, 2000). Ultimately, through the consolidation processes, this once new memory trace becomes reinforced and integrated within the pre-existing knowledge networks. During retrieval, this memory is accessed and recalled. Neural models of declarative memory formation highlight the importance of the medial temporal lobe (MTL) and hippocampal region (Squire, 1992) where novel experiences are first encoded as 'episodic' memories of their first occurrences before being transformed into a long-lasting memory representation assimilated within the neocortical networks. These consolidation processes which lead to the transfer of memory into neocortical network allow the memory to become less dependent on the hippocampus (Frankland & Bontempi, 2005). Research into the time-course and mechanisms underlying memory consolidation are divided according to the type of distinct neurophysiological properties they take their theoretical foundation from. For example, the first being represented by synaptic and the second by system consolidation, both of which being integral components of *the standard consolidation model* (Dudai, 1996, 2004). Synaptic consolidation, which is accomplished within minutes or hours following encoding, involves the stabilisation of synaptic changes in the neural circuits that encoded the memory representation (Born, Rasch, & Gais, 2006). Therefore, within a very short time after training, memories that underwent synaptic consolidation may become resistant to interference or decay— the processes that would normally inhibit the formation of long-term memory (Freeman, Rose, & Scholey, 1995). Systems consolidation on the other hand,

can take days, months or even years to be completed. In comparison to synaptic consolidation, it entails a neural re-organisation whereby the brain regions supporting memory formation and retrieval are modified over time (Dudai, 2004). The systems-level consolidation may take place simultaneously or as a consequence of synaptic consolidation (Frankland & Bontempi, 2005). The most influential model of memory formation which posits a complementary learning between systems of the hippocampus and neocortex, the Complementary Learning Systems (CLS) model (McClelland, McNaughton, & O'Reilly, 1995) is directly derived from the principles of the standard consolidation account. In this thesis, from this point forward, I will mainly focus on the systems consolidation of declarative memories.

1.1.1 Complementary Learning Systems (CLS) Account

According to the standard theory of systems-level consolidation (Frankland & Bontempi, 2005; Marr, 1970; McClelland et al., 1995; Squire & Alvarez, 1995), memory processes are dependent on two distinct memory stores in order to avoid the overwriting of pre-existing knowledge by a flow of new information. Following encoding of new information, the memory traces are initially represented in hippocampal patterns of activity which are covertly reactivated in the hippocampal-neocortical networks (see Figure 1.1). These covert reactivation results in a robust establishment of cortico-cortical connections whilst, at the same time, the hippocampal-cortical connections are steadily fading away. In consequence, newly formed memory representations become gradually integrated within the long-term neocortical memory networks and are no longer dependent on the hippocampus (Frankland & Bontempi, 2005; Marr, 1970; Squire & Alvarez, 1995). This progressive hippocampal independence enables restoration of the hippocampal capacity to encode new information.

The CLS framework capitalises on the dissociation between different aspects of learning and memory formation and presents memory as a dual system with hippocampal and neocortical components that dynamically interact together in the process of memory consolidation. In its core, as in the standard consolidation model, the CLS account proposes two distinct memory systems; the first system, mediated by the hippocampus and the MTL, rapidly encodes sparse representations and experiences and then transfers them into a second, long-term system where memory traces are integrated with pre-existing knowledge.

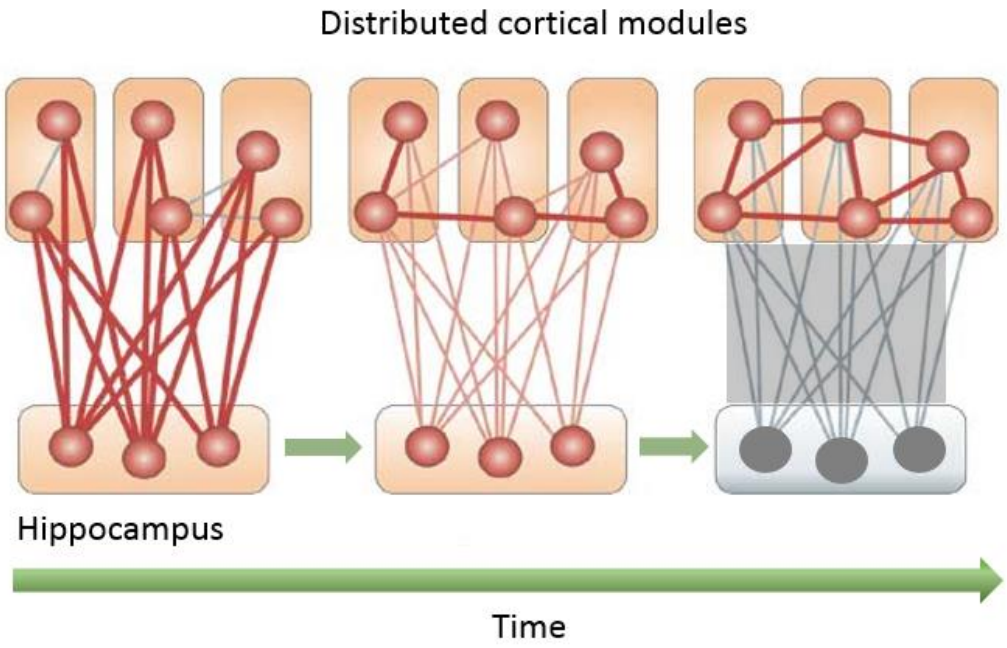

Figure 1.1. The standard model of systems-level consolidation between the hippocampus and neocortex. Incoming information is first stored in the hippocampus and over time gradually integrated with existing representations in the neocortex. Successive reactivations of the hippocampal-cortical connections allow an independent memory trace to form in the neocortex and the hippocampal connection decay until the new memory trace is independent of the hippocampus (adapted from Frankland & Bontempi, 2005).

Importantly, the interactions between the two memory systems are believed to be bi-directional; new memories are not simply moved into the long-term store via a hippocampal-neocortical transfer. Instead, an on-going cross-talk between these systems enables a continuing refinement and adjustment of what is already known in the face of new information (McClelland et al., 1995; Stickgold & Walker, 2013). A central connectionist principle of the CLS account outlines the optimal way the subsystems operate to overcome the potential problem of introduction of new information into the neocortical system, particularly if it is incompatible with what is already known which can disrupt the pre-existing patterns. Disruption of these training patterns can lead to a *catastrophic interference* (French, 1999; McCloskey & Cohen, 1989) in which learning of new information abolishes previously learnt material. The dual character of memory systems allows retention of stable memory representations for longer, despite the on-going changes in the form of the input (generalisation) and structure of the network.

The presence of the hippocampal system offers plasticity and acquisition of new episodes without interference from previously or subsequently learnt knowledge. The

temporary representations stored here are sparser and independent therefore they can be learnt swiftly and can be used to support the slower and interleaved learning within the cortical system. On the other hand, the neocortical route seems to operate on different principles. The memories that are formed gradually through multiple repetitive exposures, for example the procedural skills, can be acquired in the absence of the hippocampal storage. The CLS model does not superimpose a bottleneck or any 'gating' mechanism that regulates which memories may or may not need the hippocampal mediation. The procedural and the declarative memories should be processed by neocortical as well as hippocampal routes providing the learning complies with the nature of learning adequate to the route (for example, a slow gradual learning for neocortex; Squire, 1992). Some evidence for this comes from the studies on amnesic patients. Due to hippocampal lesions, those patients show learning deficits in forming and retaining new memories, however they also showed, for example an unimpaired Hebb repetition effect (Baddeley & Warrington, 1970), a memory of new information acquired through many repetitive exposures (Hebb, 1966) and some knowledge acquired post-lesions when tested using familiarity measures (Bayley, Reilly, Curran, & Squire, 2008). Indeed, the investigations into memory representations in amnesiacs shed some light on the memory systems involved in memory formations in general. This will be returned to in a later part of this thesis when discussing hippocampal involvement in mechanisms underlying word learning.

From the perspective of this thesis however, the most crucial part of the model is the aforementioned dialogue between the hippocampus and the neocortex. In fact, it is this dialogue that enables our newly formed memories to be consolidated and subsequently remembered via the processes involving the reinstatement of memory traces and straightening of their neocortical representations. Initially, this hippocampal-neocortical cross-talk was believed to be facilitated by an active rehearsal, reminiscence and other inactive states such as sleep (McClelland et al., 1995). The idea that sleep may play an imperative role in consolidation of new memories originated from the studies on place cell firing in rats (Wilson & McNaughton, 1994) and was later elaborated on in the CLS revision proposed by Norman, Newman, Detre, and Polyn (2006). Further evidence which showed how different from its initial 'inactive state' sleep turned out to be in terms of memory consolidation will be presented in later parts.

1.1.2 Multiple Trace Theory (MTT)

MTT is a memory consolidation model that offers an alternative account to the CLS model. It proposes potentially independent processing of semantic and episodic information (Moscovitch & Nadel, 1998; Nadel & Moscovitch, 1997). Support for this model

is often taken from studies on amnesic patients where it is argued that retrograde memory deficits extend over decades and are often dependent on the extent of hippocampal damage and the type of declarative memory being tested. MTT posits that when episodic information is presented, it is encoded in the brain as a unique memory trace consisting of a combination of its attributes. Richness of episodic and contextual details rely on multiple memory traces generated in the hippocampus that remain linked to corresponding neocortical networks. However, as neocortical representations are believed to be context-free or semantic in nature, the retrieval of remote semantic memories is thought to be possible even in the absence of a functioning hippocampus. Consequently, the prediction of this account is that an incomplete hippocampal damage should selectively disrupt the retrieval of recent (rather than remote episodic or semantic) memories. Comprehensive hippocampal damage however, should abolish all episodic memories, irrespective of age, but spare those memories which are predominantly dependent on the neocortex such as remote semantic memories (Frankland & Bontempi, 2005). In support of this view, several cases were reported where patients who suffered from retrograde amnesia after hippocampal damage (Cipolotti et al., 2001; Rosenbaum, Winocur, & Moscovitch, 2001) showed retrieval of memories that span up to 35 years back (Maguire, Henson, Mummery, & Frith, 2001). Furthermore, some research provided evidence for distinct post-encoding time courses for the consolidation of semantic and episodic memories. One such study examined the vocabulary acquired by a patient with retrograde amnesia. Although the patient displayed profound impairment of episodic information, he also showed a prominent retention of words that he learnt during his amnesic period (Warrington & McCarthy, 1988). This study provided argument for dissociated consolidation processes for episodic and semantic memories.

Neuroimaging research offered additional support for the MTT. A study by Bosshardt et al. (2005) used functional imaging technique to explore the involvement of the hippocampus in retrieval of episodic information. The authors reported that, relative to an interval of one day, episodic memory information was associated with more robust activity in the hippocampus and neocortex one month after learning. In a comparable study, the retrieval of episodic memories was associated with increased responses in the left hippocampus following a delay of 24 hours, compared to delay of 10 minutes (Bosshardt et al., 2005). However, this model was shown to have some discrepancies. For example, Squire and Teng (1999) described a patient who showed an exceptional episodic memory from his youth despite elaborated bilateral lesions of the MTL. This indicated that episodic representations have the potential to become entirely independent of the hippocampus. More generally, a number of studies have reported the reduction in hippocampal activity

when testing newly acquired memories at remote time points, including the neuroimaging investigations. For example, Takashima et al. (2006) found that activity in the MTL, observed during retrieval of previously studied pictures, gradually decreased over the course of three months whereas the medial prefrontal cortex activity progressively increased.

To conclude, despite some differences related to the time course required for consolidation, the CLS and MTT models agree on the presence of systems-level consolidation for semantic memory (Meeter & Murre, 2004) that unfolds over time. Whilst systems consolidation theory assumes a consolidation process taking place over months or even years (Dudai, 2004), newer reports show a more graded picture. For example, human neuroimaging research suggests that a substantial amount of memory re-organisation can occur over just one day (Janzen, Jansen, & van Turennout, 2008; Takashima et al., 2009). This was inconsistent with previous work on amnesiacs which indicated that repetitive learning can lead to long-term memories despite the hippocampal damage, but over a much longer time frame. In an attempt to reconcile these inconsistent findings, it was suggested that different neural pathways take part in learning that allows amnesic patients to acquire new information (Foerde, Race, Verfaellie, & Shohamy, 2013). These would utilise interleaved and extensive exposure to new information in order to allow for some neocortical learning to take place.

Out of the two memory consolidation models presented in this section, the systems consolidation model forms a primary focus of this thesis and is an integral part of the theory that this work will explore: the sleep-dependent memory consolidation. The sleep-dependent memory consolidation will be discussed in more detail in the next paragraph.

1.2 Sleep and Memory Consolidation

Decades of research has demonstrated that memory consolidation can be modulated by post-learning sleep. Use of modern research techniques (Gais et al., 2007; Takashima et al., 2009) has helped to create the concept of sleep-dependent consolidation and fuelled the theories regarding the mechanisms underpinning this effect (Born & Wilhelm, 2012; Diekelmann & Born, 2010; Tononi & Cirelli, 2003, 2006).

With regards to the CLS account, Norman et al. (2006), in their update of the model, argued that sleep provides a perfect opportunity for hippocampal-neocortical dialog. The offline consolidation processes occurring during sleep originate from the spontaneous hippocampal replay of memories and re-organisation of the neocortical memory networks

via the slow oscillatory activity in the neocortex. The importance and sophistication of processes taking place during sleep received substantial attention in the past decade. The pioneering work by Buzsáki (2005) laid the foundation for modern understanding of how two distinct brain regions, the hippocampus and the neocortex, communicate during sleep (Buzsáki & Peyrache, 2013; Peelle et al., 2013; Schellenberger Costa et al., 2016; Sirota & Buzsáki, 2005; Sullivan et al., 2011). This cross-brain communication will be outlined in the following sections and will begin with a short introduction to sleep physiology.

1.2.1 Sleep and its cycle

It was once believed that sleep represents a state when the mind shuts down and plays mostly restorative functions (Oswald, 1980). However, across many years this view has changed and evolved indicating how essential sleep is; not only for restoration but mainly for its functions in formation and reorganisation of declarative and procedural memory (Born et al., 2006; Diekelmann & Born, 2010).

Sleep in mammals consists of sleep stages with the most defined being *slow wave sleep* (SWS) and *rapid eye movement* (REM) sleep which alternate in a cyclic manner (Figure 1.2, A). In human nocturnal sleep, SWS is predominant during the early part and decreases in intensity and duration across the sleep period. REM sleep on the other hand, becomes more intense and pronounced towards the end of the night.

With regards to the brain oscillatory activity that occurs during sleep, SWS is marked by low frequency and high-amplitude EEG oscillations. These slow oscillations (SOs) greater than 75 μV are the hallmark of SWS and are generated within cortical and thalamic networks. They appear to be particularly important for declarative memory consolidation (Timofeev & Chauvette, 2011). REM sleep (also termed paradoxical sleep), on the other hand, is characterized by a wake-like fast and low-amplitude oscillatory brain activity (Rasch & Born, 2013). Almost 50% of sleep in adult humans consists of a lighter form of non-REM sleep (stage "N2") that is characterized by the occurrence of distinct (waxing and waning) sleep spindles (Figure 1.2, B), K-complexes in the EEG and minimal Slow Wave Activity (SWA).

Interestingly, the SOs in SWS can be externally amplified by applying, for example transcranial direct current stimulation (tDCS; Binder, Berg, Gasca, Born, & Marshall, 2013; Marshall, Helgadóttir, Mölle, & Born, 2006; Marshall, Kirov, Brade, Mölle, & Born, 2011; Westerberg et al., 2015), transcranial magnetic stimulation (TMS; Massimini et al., 2007) and acoustic stimulation (Cox, van Driel, de Boer, & Talamini, 2014; Ngo, Martinetz, Born, & Mölle, 2013). Findings from these studies elucidated the role of both SOs and also delta

waves in general (~0.5-4 Hz, together termed *slow wave activity;* SWA) in offline processing and consolidation of declarative memory. Moreover, some studies pointed at the fine-tuned synchronisation and grouping that occurs between hippocampal ripples, sleep spindle activity and SOs (see Figure 1.2, C; Feld & Born, 2017; Feld & Diekelmann, 2015; Mölle, Bergmann, Marshall, & Born, 2011; Mölle, Marshall, Gais, & Born, 2004). More specifically, the hippocampal ripples are grouped by spindle troughs whilst sleep spindles themselves were shown to co-occur with up and down-states of SO (Clemens et al., 2007; Cox, Hofman, & Talamini, 2012; Mölle et al., 2009) taking place in SWS during which the classic replay of waking neural patterns are believed to happen (Buzsáki, 1996).

In sum, the specific oscillatory phenomena associated with sleep was shown to underlie the consolidation processes and recent research have exposed a precise coordination of different oscillatory activity during non-REM sleep. The next paragraph will outline in more detail how hippocampal replay, and sleep in general, supports memory consolidation. It will also present evidence that the brain maintains its responsiveness to external stimuli during sleep despite its loss of consciousness. This will provide a basis for the later parts of this chapter where I will discuss how this brain responsiveness can be used to intensify sleep-dependent memory benefits by including external augmentation of naturally occurring consolidation processes in sleep.

1.2.2 Sleep-dependent memory consolidation

A substantial body of evidence has accumulated to support the hypothesis that sleep plays an active role in declarative memory processing, an effect known as sleep-dependent memory consolidation (Gais, Lucas, & Born, 2006; Lovatt & Warr, 1968; Newman, 1939; Takashima et al., 2006; Van Ormer, 1933; Wilhelm et al., 2011)

In order to optimally guide our behaviour, new memories and experiences must be assimilated into existing knowledge. A previously outlined, well-established view is that sleep promotes learning by consolidating these new and unstable memory traces and integrating them with the already existing knowledge stored in the neocortex (Rasch & Born, 2013). According to this, sleep assists the quantitative strengthening of newly encoded information which, in result, is moved into more stable long-term storage. It has been proposed that, apart from these quantitative changes, sleep also stimulates the qualitative re-organisation of memories. More precisely, sleep promotes the emergence of new memories that had not been directly learned, for instance via such processes as generalisation and abstraction (Landmann et al., 2014). Stickgold and Walker, (2013) proposed a comprehensive model of sleep and memory where they indicated different

memory processes that are often interlinked and inter-dependent. These processes include: selecting information for initial encoding, subsequent strengthening of memories and later generalisation, and the integration of new memories with existing ones. On the neural level, the classic consolidation theory suggests that these processes are facilitated by the immediate encoding of new information in the MTL followed by its gradual transition into the neocortex (McClelland et al., 1995). The transition of new memories into the neocortex is believed to happen during a deep stage of sleep (SWS) via the replay of new memories by the hippocampus. Indeed, research points to SWS, particularly SOs, and spindle activity (12-15 Hz) as the most crucial in sleep-dependent memory processing (Mölle et al., 2011). In fact, SOs are thought to drive the redistribution of initially hippocampal-dependent memories to long-term neocortical memory networks as consolidation processes unfold.

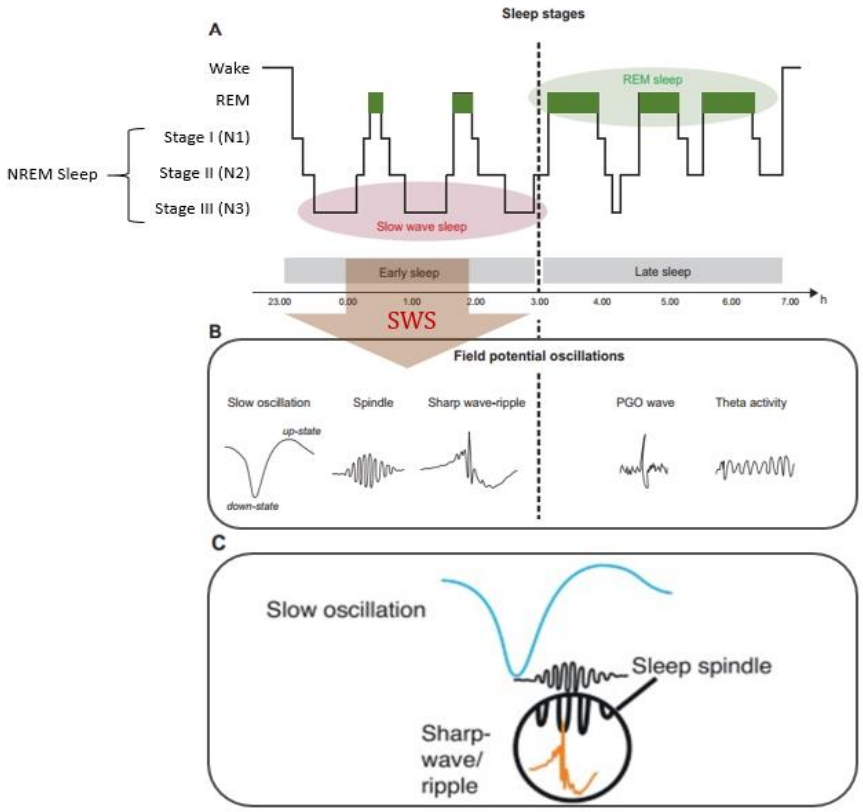

Figure 1.2. Typical sleep profile and sleep-related EEG signal. **A**: A depiction of cyclic occurrence of rapid-eye-movement (REM) sleep and non-REM sleep. Non-REM sleep includes slow-wave sleep (SWS) corresponding to Stage III sleep (N3), and lighter sleep stages: Stage I (N1) and Stage II (N2). **B**: The most pronounced oscillations during SWS are the neocortical slow oscillations (~0.75 Hz), thalamo-cortical spindles (waxing and waning activity between 10 –15 Hz), and the hippocampal sharp wave-ripples (SW-R; adapted from Rasch & Born, 2013). **C**: Memory replay in NREM sleep is characterised by synchronised hippocampal sharp-wave/ripples and the troughs of the thalamo-cortical sleep spindle. The spindle is phase-locked to the up-state of the neocortical slow oscillation. This synchronised activity of different brain oscillations allows the information reactivated during sleep to reach the neocortex precisely during the excitable up-state of the slow oscillation (adapted from Feld & Born, 2017).

SOs are believed to support information processing in two ways: firstly, by reinstating the synaptic homeostasis whereby the brain's encoding capacity for new information becomes renewed, and secondly, by supporting the mediation and consolidation of hippocampus-dependent memories (Huber & Born, 2014). Ample evidence has confirmed that long-term neural plasticity contributes to memory formation and that sleep plays a particularly critical role in this process through replaying the newly acquired memories during the SWS (Chauvette, Seigneur, & Timofeev, 2012).

As noted before, this memory reactivation can be externally triggered, for example by replaying cues that were previously associated with learnt material during subsequent SWS. The overt replay of the cues, termed Targeted Memory Reactivation (TMR), selectively promotes reactivation and enhancement of the sleep-dependent memory benefits for information associated with the cues. The studies using TMR paradigm shed more light on the replay processes underlying sleep-dependent memory consolidation. For example, one such study by Fuentemilla et al. (2013) compared learning and subsequent consolidation of new material between patients with temporal lobe epilepsy and healthy controls. Firstly, researchers asked participants to learn associations between certain words and sounds and then re-presented half of the sounds from the learning phase during following SWS. The results showed that strengthening of selectively reactivated memories was present but only in healthy participants or in those with selective unilateral hippocampal sclerosis, but not in participants with bilateral hippocampal damage. Moreover, the amount of memory strengthening was predicted by the volume of spared hippocampus. Hence, the study provided evidence that the hippocampus plays a vital role in consolidation of new memories via their covert reactivation during sleep (Fuentemilla et al., 2013).

Although research on sleep related consolidation processes elucidated some aspects of sleep that are important for declarative memory formation, the process of memory consolidation *per se* appears to remain elusive. Sleep stages such as REM, Stage 2 and the slow-wave activity of SWS have all been implicated as playing an important role in sleep-dependent memory processing. When compared to wakefulness, sleep has been shown to not only reduce the forgetting of newly attained information but also to provide enhancement in terms of post-sleep improvement in performance. Often, such effects of sleep correlated with the amount of specific sleep stages or sleep events, such as sleep spindles (Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002) but detailed characteristics of these processes remain unclear. What seems to be widely accepted however, is the view that memory consolidation

depends on cellular and molecular processes as well as system-level reorganisation that take place during the offline period of sleep.

Overall, evidence outlined in this section supports the view that sleep plays a fundamental role in the process of memory consolidation. The vital role of sleep is described in more detail by two alternative models of sleep-dependent memory processing, the active systems consolidation model (Born et al., 2006; Born & Wilhelm, 2012; Diekelmann & Born, 2010) and the synaptic homeostasis theory (Tononi & Cirelli, 2003, 2006). The fundamental components of both models, central to declarative memory processing, will be discussed next.

1.2.2.1 Active systems consolidation

By providing neural and computational background for the consolidation process, sleep assists the "active systems consolidation" of memory (Gais, Mölle, Helms, & Born, 2002; Prehn-Kristensen et al., 2014; Walker & Stickgold, 2006). The active systems consolidation model provides a modern adaptation of the standard consolidation account mentioned earlier in this chapter (Marr, 1970; McClelland et al., 1995). The active systems model proposes that consolidation takes place during SWS when memories are reactivated in order to be consolidated. The SOs play a crucial role in the reactivation and subsequent reorganisation of hippocampal-dependent memory representations (Figure 1.3). More specifically, SOs reflect widespread and synchronised down-states of neural hyperpolarisation and neural silence which are followed by depolarising up-states of excitation. The neural firing taking place during the excitation phase resembles the waking level (Steriade & Timofeev, 2003). By using efferent pathways, SOs are able to synchronise the activity with other brain regions, for example the thalamus, where sleep spindles are generated, and also with the burst of sharp-wave ripples that correspond with memory reactivations in the hippocampus (Kudrimoti, Barnes, & McNaughton, 1999).

Indeed, within the active systems consolidation model, Mölle et al. (2009; 2002) demonstrated that the hippocampal sharp-wave ripple events together with thalamo-cortical spindles can be temporally driven by slow oscillations. This synchronised activity of sharp-wave ripples, occurring during memory replay in the hippocampus, stimulate the transfer of this information into the neocortex (Diekelmann & Born, 2010) which is vital to permanent redistribution of these declarative memories and their integration within neocortical networks.

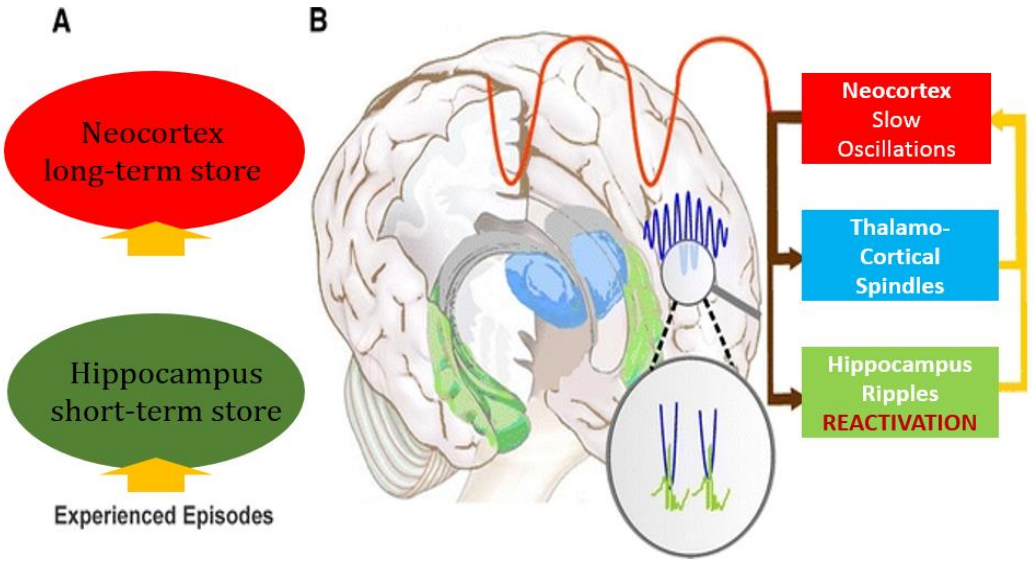

Figure 1.3. The active systems consolidation during sleep. **A** During SWS newly acquired memories, stored in the temporary store (i.e. the hippocampus), are reactivated and transferred to the long-term store (i.e. the neocortex). **B** System consolidation during SWS depends on a dialogue between the neocortex and the hippocampus which is mediated by the neocortical slow oscillations (marked in red). The depolarising up-phases of the slow oscillations drive the reactivation of hippocampal memory traces together with sharp-wave ripples (marked in green). Their synchronised activity allows the formation of spindle-ripple events where sharp-wave ripples and associated reactivated memory information become nested into single troughs of a spindle (adapted from Born & Wilhelm, 2012).

In sum, ample evidence exists for the role of SOs in synchronising the brain activity during sleep and the following transfer of memory from short-term to long-term storage. Some studies that capitalised on these findings employed various sleep modification techniques such as tDCS of slow oscillations (Marshall et al., 2006) or external targeting of memory reactivation in sleep (Rasch, Büchel, Gais, & Born, 2007). Additionally, the active system consolidation clarifies how important sleep is for preparing the brain for learning new information the following day (Yoo, Gujar, Hu, Jolesz, & Walker, 2007; Yoo, Hu, Gujar, Jolesz, & Walker, 2007).

1.2.2.2 The Synaptic Homeostasis Hypothesis

An alternative model of memory consolidation, the synaptic homeostasis theory (Tononi & Cirelli, 2003, 2006), proposes that sleep (and SWS in particular) plays a restorative role at a cellular level. For example, slow wave activity (SWA), where neocortical neurons fire in waves of activity at a frequency of <1Hz, increases as a function of previous wakefulness and decreases in the course of sleep (Borbely & Achermann, 1999). The synaptic homeostasis hypothesis outlines vital points of its mechanical sequence (see

Figure 1.4). These points will be discussed in order, according to the account given by Tononi and Cirelli (2003).

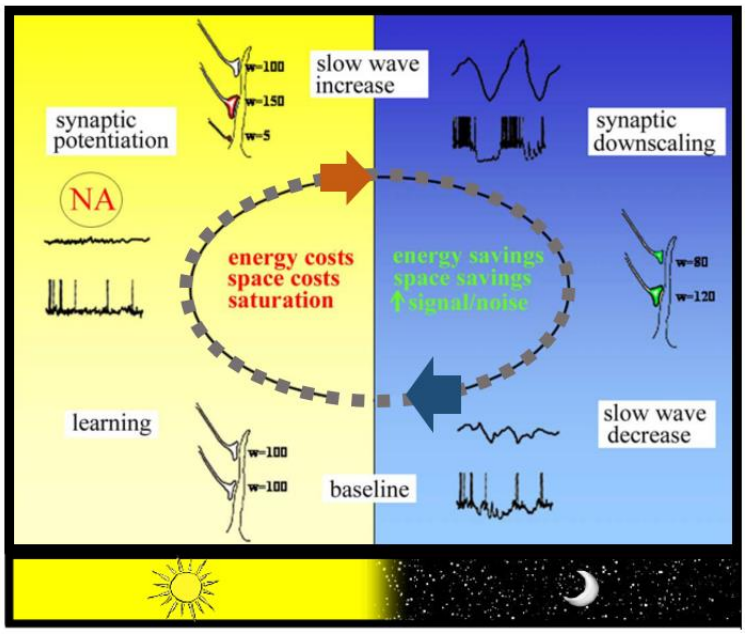

Figure 1.4. The Synaptic Homeostasis Hypothesis. During wake (yellow field) the long term potentiation (LTP) of synaptic strength enables the encoding of information. Sleep (blue field) and the SWA with slow oscillations facilitate global downscaling of synaptic strength (adapted from Tononi & Cirelli, 2006).

Firstly, everyday activities and learning that take place during the day are believed to result in long-term potentiation (LTP) changes occurring in neural circuits and an overall increase in synaptic weights. This reflects the plastic changes happening at the synaptic level during wakefulness which favour the storage of information. The plastic changes however, result in a systematic imbalance between synaptic potentiation and synaptic depression. In the next step, depending on the amount of synaptic potentiation occurring during the preceding period of wakefulness, sleep, and the SWA in particular, offers the homeostatic regulation. For example, the more synaptic potentiation occurred during day, the more SWA is observed during subsequent sleep. Consequently, this homeostasis offered by SWA is associated with synaptic downscaling. For example, SWA promotes a generalised depression or downscaling of synapses where the weights of neurons return to the baseline level. In fact, the amplitude of slow waves seems to be dependent on synaptic weights. Thus, the process of synaptic downscaling is in fact self-limiting—during sleep, the strength of each synapse would decrease by a proportional amount, until the total amount of synaptic weight imposed on each neuron, returns to a baseline. Lastly, the synaptic downscaling reflects directly the beneficial effects of sleep on performance. For example, the synaptic

downscaling is believed to occur proportionally to synaptic potentiation, thus the relative strengths of cortical synapses, and in consequence memory traces, can be maintained. Here, the synapses contributing to the noise, on average weaker than those contributing to the signal, would stop interfering and the signal-to-noise ratio would improve. Therefore, weak and inefficient synapses, representing for example labile and irrelevant memories, will be downscaled beyond a preservation threshold and eradicated. In consequence, only the strongest memory traces will be maintained after sleep and in a more efficient form, which manifests itself in increased performance.

This synaptic homeostasis hypothesis offers an explanation of a potential mechanism of consolidation taking place in sleep. Moreover, it also provides a clarification of how sleep prevents synaptic over-potentiation during wakefulness, allowing new learning to continue throughout life. Evidence supporting this hypothesis is mostly derived from animal studies. For example, Cirelli, Bushey, Hill, and Huber (2005) showed that despite the length of sleep being normal, the noradrenergic lesions in animals' brains led to a substantial reduction in the SWA normally observed following enriched waking experience and a decrease in the normal SWA response to sleep deprivation. With regards to human studies, Huber, Ghilardi, Massimini, and Tononi (2004) used high definition EEG to examine a sleep structure after participants implicitly learned some object rotation skills. The researchers predicted that the rotation learning should be reflected in activity in the right parietal cortex, specific to its skill, meaning that an increase in synaptic potentiation would occur in that area. Their results were consistent with the authors' prediction: SWA increased over the cluster of electrodes in the right parietal cortex area. Furthermore, the post-sleep performance enhancements were exclusively correlated with SWA increases in this area. These results provided strong evidence of the mnemonic impact of localised changes in synaptic weights.

1.2.3 Summary

The active systems consolidation model and the synaptic homeostasis hypothesis indicate that the brain slow oscillations occurring during SWS are an essential component of consolidation processes. However, both models present different views of sleep-dependent memory processing. For example, the active systems model proposes that memories are actively strengthened and re-organised during sleep, whereas the synaptic homeostasis hypothesis suggests that sleep improves learning and memory through a proportional downscaling of synapses and bringing them down to the baseline level. In comparison to the active systems model, what the synaptic homeostasis theory does not account for is the mnemonic influences of several subcortical structures, including the

hippocampus. Additionally, the synaptic homeostasis theory predicts that any manipulation that affects the natural rhythm of SWS would have the potential to abolish the mnemonic advantage of downscaling during sleep (Tononi & Cirelli, 2003). This is in disagreement with recent studies which showed that external stimulation of SOs results in memory improvement and not its impairment (Ngo, Martinetz, Born, & Mölle, 2013). Nevertheless, the active systems consolidation model also has some challenging issues to face. For example, the active systems consolidation model does not explain how post-learning sleep strengthens the synaptic connections which represent the new memory traces (Diekelmann & Born, 2010). Furthermore, recent investigations have indicated that other sleep stages, as well as SWS, may play a complimentary role in memory consolidation. For example, REM sleep specifically has been shown to be important in mnemonic processing (Walker & Stickgold, 2010). These findings call for a new updated approach to facilitate a broader spectrum of processes taking place during memory consolidation.

To conclude, so far, memory consolidation has been understood as a process whereby new information is selectively retained and assimilated into the long-term networks (Paller, 2009). According to a newer view, the consolidation process depends on interactions between the hippocampus and the neocortex and through these interactions, the consolidation process impacts how information is represented within cortical networks (Moscovitch, Cabeza, Winocur, & Nadel, 2016). The most recent findings on the function of sleep in memory brought in an advanced technology to elucidate further how sleep can alter our learning outcomes. At the same time this cutting edge research has brought more evidence and insight into mechanisms underlying memory consolidation in sleep. Below I will outline the most important findings. I will first focus on word learning research and show how they allow us to gain more understanding of sleep-dependent memory consolidation. Following this, I will review the most innovative methods that use external manipulation of brain activity in sleep to strengthen memory of newly learnt material.

1.3 Role of Memory Consolidation in Novel Word Learning

As pointed out in the previous paragraph, sleep plays a vital role in reinforcing memories. The strengthening of new memories after sleep has also been repeatedly demonstrated for word learning. A decade of research has unravelled how sleep supports different aspects of language learning with a potential to enlarge our mental lexicon. Evidence from both children's (Brown, Weighall, Henderson, & Gaskell, 2012; Gómez & Edgin, 2015; Henderson, Weighall, Brown, & Gaskell, 2012; Henderson, Weighall, Brown, & Gaskell, 2013) and adults' (Davis & Gaskell, 2009; Gaskell et al., 2014; Tamminen et al.,

2010) literature indicates that sleep benefits not only the native language acquisition in infants but also a second language learning and learning new words of a native language in adults (Kurdziel, Mantua, & Spencer, 2017; Kurdziel & Spencer, 2015). Thus, a growing body of research implicates the importance of sleep for language ability across a lifespan.

1.3.1 Sleep and word learning

Scientific investigations have revealed that apart from the reinforcing role in learning new words, sleep also actively supports their integration into pre-existing lexicon (Dumay & Gaskell, 2007; Gaskell & Dumay, 2003b; Lindsay & Gaskell, 2010). Additionally, research pointed out the vital role of sleep in other aspects of word learning such as generalisation of a new linguistic rule (Mirković & Gaskell, 2016; but see Werchan & Gómez, 2014), abstraction (Stickgold & Walker, 2013), learning artificial grammar rules (Nieuwenhuis, Folia, Forkstam, Jensen, & Petersson, 2013) and language production (Gaskell et al., 2014).

Due to the specificity of linguistic material, the word learning studies have the potential to inform us about the consolidation processes taking place during sleep. The time-course of word learning has been shown to be particularly insightful. For example, some research suggests a longer time-course needed to learn new linguistic tokens and unequivocally indicate that sleep and overnight consolidation play a crucial part in this process. Other research, however, has shown more rapid word learning over a time-course spanning from a few minutes to a few hours, with no need for overnight consolidation.

1.3.1.1 Lexical integration after sleep

Studies into vocabulary acquisition have shed some light on the involvement of sleep in the process of word learning. For example, Gaskell and Dumay (2003b)and Dumay and Gaskell (2007) examined whether the acquisition of novel spoken word forms (e.g. *cathedruke*) would interfere with the recognition of known English words (e.g. *cathedral*) when learning was followed by either sleep or wake. In that way, the authors not only tested the strengthening effect of sleep on learning, but also the integration of newly learned words into pre-existing lexicon. For example, if novel items were successfully integrated within the existing knowledge networks, they will gain a lexical status similar to already known words and become capable of inducing a lexical competition during spoken word recognition. The authors demonstrated that the recognition of the already existing English words, which overlapped with the new items, was inhibited. Importantly however, they showed that time was a critical factor in the generation of a new lexical representation; the lexical competition effect was present after sleep but not after equal time spent awake (see Figure 1.5). This

work delivered strong evidence that sleep-associated memory consolidation processes are important for the engagement of novel items into lexical competition and therefore word learning.

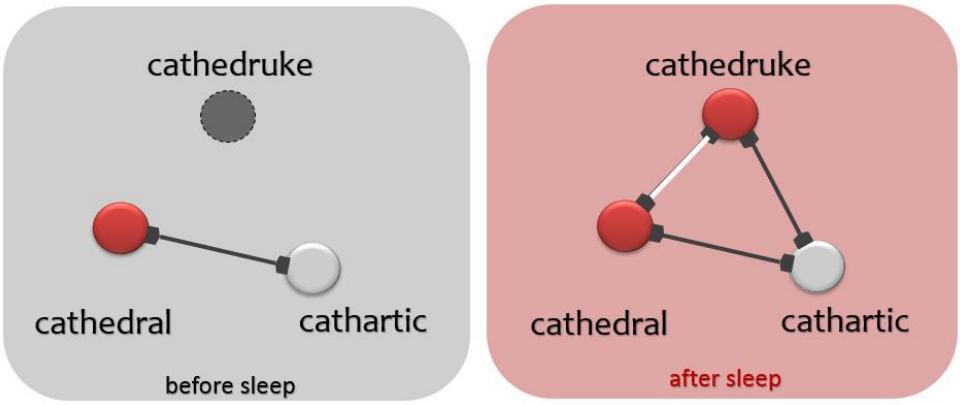

Figure 1.5. The process of lexical competition. Following learning, the novel word *cathedruke* is stored separately from the rest of the lexicon and therefore it cannot enter the lexical competition process with its English counterpart *cathedral* (left diagram). Following sleep-related consolidation, the novel word becomes fully integrated within the lexicon and its form-overlapping neighbours. Thus it can compete with them for selection in the spoken word recognition process which is manifested in slower responses to *cathedral* (the inhibitory link between their representations is shown in white, right diagram). Based on Davis & Gaskell (2009).

Similar sleep-related benefits were also revealed for grammar learning. In a study by Nieuwenhuis et al. (2013) participants were exposed to letter sequences based on unknown artificial grammar. After a delay of 15 minutes, 12 hours and 24 hours, participants were asked to indicate whether new items were grammatical or not, based on the artificial grammar they learned. The classification performance showed that the most prominent improvement occurred after a delay period containing sleep. This overnight improvement showed that sleep enhances the rule abstraction and extraction of complex structure. The performance was not, on the other hand, affected by the frequency of information presented to participants during the training. These results showed that the supportive role of sleep is not limited to the acquisition of novel word forms but extends to other aspects of language learning.

1.3.1.2 Neural underpinnings of lexical integration in sleep

This direct relationship between word learning and sleep was attributed to reduced susceptibility to interference for declarative memory caused by rapid learning of new information (French, 1999) as well as the neural plasticity that underlies the effective learning of new vocabulary. Several studies confirmed the role of sleep-dependant

consolidation in novel word learning (Brown & Gaskell, 2014; Dumay & Gaskell, 2007, 2012; Henderson, Devine, Weighall, & Gaskell, 2015; Henderson et al., 2012; Tham, Lindsay, & Gaskell, 2015). Interestingly, the successful integration of novel words was associated with sleep spindle activity observed during post-learning sleep (Tamminen et al., 2010). Similarly, research showed that some properties of newly learned words, such as semantic neighbourhood density, can in fact influence sleep architecture (Tamminen, Lambon Ralph, & Lewis, 2013). For example, Tamminen et al. (2013) showed that participants exhibited more sleep spindles and slow-wave activity during post-learning sleep after learning words from sparse compared to dense neighbourhoods. This result provided some evidence that sleep spindles and slow-wave activity may mediate integration of new linguistic information into existing knowledge networks. Importantly however, the study also pointed out that the neighbourhood density may impact both the lexical integration of new words and the requirement for sleep-related consolidation that accompanies this process.

1.3.1.3 Complementary Learning Systems for novel words

Within the context of the CLS framework (McClelland et al., 1995) outlined earlier, Davis and Gaskell (2009) proposed a CLS model specifically for word learning where they specified the functional and anatomical organisation of the neocortical networks involved in recognising spoken words (see Figure 1.6). Their account closely relates to the active systems consolidation model outlined in the previous sections. According to the model's main principles, the word learning starts with an initial familiarisation phase with novel word forms that results in weak memory representations of lexical entries and their later slow lexical consolidation. The crucial role in strengthening and lexical integration of novel words belong to the hippocampus which stores their first weak representations and then reactivates them during subsequent NREM sleep. By providing first temporal storage for newly learnt words, the hippocampus system prevents the interference of newly encoded information with the existing lexicon. As *per* the CLS theory, the mnemonic reactivation taking place in NREM sleep enable gradual consolidation and integration of fresh information into mental lexicon. After the lexical representations have been successfully integrated within pre-existing vocabulary, the precision of speech perception is improved sufficiently to facilitate automatic word recognition (Davis & Gaskell, 2009).

Stickgold and Walker (2013) provide a specific illustration of how reactivation processes, taking place during sleep, lead to improved generalisation and abstraction, which is utilised in most aspects of language acquisition (e.g. grammar learning). These two processes are thought to originate from the repeated reactivation of overlapping memory representation together with a selective strengthening of shared elements. Nevertheless,

the precise mechanism of how covert reactivation in sleep can support consolidation and integration of new lexical entries is still unclear. Recent evidence, using the novel TMR method, has shed some light on the role of hippocampal replay in sleep in strengthening memory of new vocabulary (Schreiner & Rasch, 2014) and also the grammatical rules abstraction (Hennies, Lambon Ralph, Durrant, Cousins, & Lewis, 2017). These findings will be discussed in more detail in Chapter 3 of this thesis where I directly address the role of the TMR method for the learning and integration of novel words.

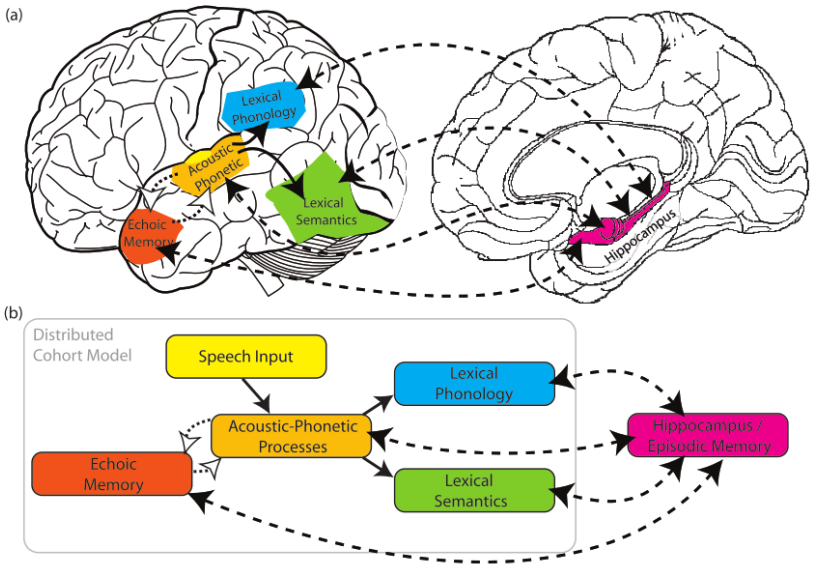

Figure 1.6. Neural and functional organisation of the systems involved in learning novel words. (a) Brain regions involved in spoken word perception and recognition and their communication with the hippocampus for word learning. (b) The Distributed Cohort Model (Gaskell & Marslen-Wilson, 2002) illustrating connections to the hippocampal/episodic memory system for learning new words (reprinted from Davis and Gaskell, 2009).

1.3.2 Fast and slow consolidation of novel words

It is commonly assumed that a new word can be learned quite swiftly. This assumption is based on the speed with which a child acquires new vocabulary. For example, by the age of six a child can learn an average of nine words a day (Carey, 1978). This observation prompted investigations into the time-course of word learning in children and formed the basis for the fast mapping theory (Carey & Bartlett, 1978). The fast mapping approach proposes that children are capable of inferring a meaning of a new word after minimal exposure and, more importantly, that they can create a new lexical entry and maintain it in their memory for several days after very a few encounters (Swingley, 2010). Additionally, in older children, hearing a word used in a semantically neutral context

facilitates later learning of that word, probably by promoting construction of an accurate phonological representation (Graf Estes, Evans, Alibali, & Saffran, 2013). Fast mapping is thus more of a process instead of an event, as it represents gradual learning. It supports the creation of an initial representation of a word in a child's lexicon, allowing the word to be maintained until a more stable and complete representation can be developed through further experience (Carey, 1978). However, many words will require "extended mapping", as opposed to the fast mapping, and therefore the process of establishing more robust representations is referred to as slow mapping.

The idea that learning a word is a process and that different aspects of this process emerge at different time points was reflected in the approach of Leach and Samuel (2007). Leach and Samuel considered two aspects of word learning; namely, lexical engagement and lexical configuration. Lexical configuration involves learning a word form, its meaning and its syntactic category. Lexical engagement, on the other hand, indicates the word's ability to interact with and affect the processing of existing lexical items. It also appears that some aspects of lexical configuration and engagement emerge immediately after training but some only after a delay, suggesting that they change over time (Leach & Samuel, 2007).

Correspondingly, Ullman (2004) proposed a distinction between two learning systems involved in language learning: a declarative memory system consisting of the medial temporal lobe (MTL) structures and so-called procedural memory system involving frontal, subcortical parietal and cerebellar areas. The declarative system, responsible for fast learning, would be necessary for the formation of a mental lexicon. The procedural system, located at the other end of the spectrum, underlies domain-general cognitive abilities that cannot be accessed consciously or described explicitly. This procedural system is responsible for the processing of rules, especially with regards to sequentially presented stimuli that unfolds over time, such as language. Thus, this system would match the implicit processing that drives statistical learning. Karuza et al. (2013) provided evidence that this indeed could be the case. The authors demonstrated that a word segmentation task induced the pattern of activity within the proposed procedural network, i.e. frontal and subcortical structures, but not the MTL.

1.3.2.1 Factors influencing time-course of lexical integration

Indeed, studies on word learning have shown that the item's involvement into lexical dynamics is far from being straightforward. Lack of consensus regarding the time-course of word learning appears to be a consequence of various factors accompanying the learning process and different training procedures used (i.e. implicit *versus* explicit training tasks). For example, studies which indicated the role of sleep in the process of integrating

new items into one's mental lexicon have mostly focused on explicit word learning (Dumay & Gaskell, 2007; Tham et al., 2015).

In the previously outlined study exploring the relationship between neighbourhood density and sleep, Tamminen et al. (2013) demonstrated that learning new words from dense neighbourhoods may require less sleep-mediated support than learning new words from the sparse neighbourhoods. Other research on neighbourhood density suggest that words based on the shared segmental content (i.e. having dense neighbourhood) also share lexical links. The number of highly similar items activated via these links has differential effects on lexical processing depending on the size of the neighbourhood and the frequency of the neighbours (Leach & Samuel, 2007). This means that novel words which sound similar to other familiar items can be learnt more swiftly than new words based on a completely new phonology.

Similarly, the phonotactic probability indicates that speakers are sensitive to the probability of a given word as a function of the frequencies of its constituent parts, independently of the number of highly similar words. The word-likeness of novel items includes recognition of the probability of the morphological composition of a possible word but also the phonotactic constraints. For example, speakers are able to use their knowledge of frequency patterns across the entire lexicon to boost their memory for non-words (Gathercole, 1995). This ability to implicitly extract statistical properties of a language is a powerful tool that helps listeners discover a language's structure: the sound patterns presented in a language (i.e. phonotactics), the words, and grammar rules. Research suggests that the abstraction of an implicit probabilistic structure in sequential auditory stimuli is promoted by sleep-dependent, but also a sleep-independent, consolidation (Hennies, Lewis, Durrant, Cousins, & Lambon Ralph, 2014). Moreover, other findings suggest that consolidation for certain types of learning, for example, category learning or generalisation of language rules, might only benefit from consolidation during wakefulness (Hennies et al., 2014; Werchan & Gómez, 2014). Contradictory to that, Gaskell et al. (2014) showed that implicit learning of phonotactic rules benefits from sleep-related consolidation when comparing performance after a delay with sleep and a similar time awake. Moreover, these newly learned rules were successfully applied to new material only in the group of participants that slept, suggesting that sleep effectively facilitates not only the integration but also the generalisation of new linguistic knowledge (Gaskell et al., 2014).

1.3.2.2 Lexical integration without sleep

Evidence of swift lexicalisation effects has recently started to accumulate with different factors present during training supporting fast neocortical integration. For example,

previous work suggests that massive exposure to novel words might result in immediate and long-lasting lexicalisation effects (Gaskell & Dumay, 2003a). Also, spacing out learning over the course of a day resulted in lexicalisation of novel items within a time period that did not include sleep (Lindsay & Gaskell, 2009). This within-a-day lexical competition effect was further investigated by Lindsay and Gaskell (2012) who showed that the effect is obtainable only when the training of novel words is interleaved with a spaced exposure to their phonological neighbours. These findings are in line with the CLS account, where repeated exposure to the novel words and their existing phonological competitors would provide an on-line alternative to the off-line consolidation occurring during sleep (Lindsay & Gaskell, 2009; McClelland et al., 1995). Additionally, results from a study using the Hebb repetition paradigm suggest that long-term lexical integration can occur during a period of wakefulness without sleep-associated consolidation (Szmalec, Page, & Duyck, 2012).

In sum, these data indicate that the consolidation processes supporting word learning are still under ongoing debate. Although sleep plays a crucial role in learning new words, this process is far from being uniform. Novel word learning and their lexical integration are not exclusively sleep-dependent but represent processes that begin at the encoding and gradually bring a quantitative shift in behaviour (cf. McMurray, Kapnoula, & Gaskell, 2016). Furthermore, many factors mediate the time-course of lexical integration. The experiments reported in Chapter 2 attempt to address some of the incongruities reported in the literature of word learning in order to gain a better understanding of how sleep-dependent word learning processes are.

1.3.3 Neural correlates of word learning

Language learning involves a widely distributed, dynamically interacting network of different cortical areas. Recent findings enabled to gain more insight as to which brain regions are primary involved and what processes accompanying word learning. The investigations into what regions participate in the language acquisition sheds some light as to what processes are involved in memory formation for words and other linguistic structures.

The CLS account proposes how different brain regions interact together in order to facilitate vocabulary acquisition and memory formation. Some evidence for CSL framework was provided by fMRI study that demonstrated different neural responses to novel non-words learnt one day prior to the study, novel non-words learnt on the day of the study, and untrained items (Davis, Di Betta, Macdonald, & Gaskell, 2009). The brain's responses to untrained new words resulted in elevated hippocampal activity in comparison to

consolidated words, whereas the cortical activity was comparable between untrained and unconsolidated items. At the same time, the level of cortical activity in the superior temporal gyrus was lower for consolidated words and it was similar to the activation shown for existing words. These results were in line with the CLS account and confirmed that novel phonological representations are integrated with pre-existing knowledge on the neural level, but only after a period of offline consolidation.

Although the fMRI technique allows for invaluable insight as to what regions are involved in word learning, it does not allow a tracking of the emergence of lexical representations on a faster time scale. In order to establish the time-course of word learning, researchers employed neurophysiological measures, such as electroencephalography (EEG) and magnetoencephalography (MEG), which produce a more fine-grained picture of brain responses on the temporal scale. For example, event-related potentials of brain activity were taken to investigate the neural markers of lexical consolidation (Bakker, Takashima, van Hell, Janzen, & McQueen, 2015b). The study showed that the difference in the amplitude of well-establish lexical component N400 between newly learned and known words was reduced following a 24-hr consolidation period. The authors concluded that it was the consolidation processes taking place during sleep that aided the lexicalisation of novel words. A similar resemblance between newly learned items and known words after a 24- hr consolidation delay was also observed in the oscillatory activity (Bakker, Takashima, van Hell, Janzen, & McQueen, 2015a). Here, the authors observed a similar increased theta oscillatory response to known words and to newly learned novel words but only if they underwent the offline consolidation. This suggested that the offline consolidation period enables novel tokens to acquire word-like neural representations. However, it is worth nothing that Borovsky, Elman, and Kutas (2012) showed an immediate priming effects with novel words also with N400 component.

To conclude, the EEG measure has the potential to inform about the graded changes in lexical representations of newly learned linguistic information (Brandmeyer, Farquhar, McQueen, & Desain, 2013). Moreover, the neural correlates of lexical integration, such as ERPs, may be more sensitive than behavioural measures in determining the lexical status of newly learned novel words. Nevertheless, further research are required to provide a more established account on the relationship between ERPs and lexical integration.

1.3.4 Summary

The standard two-stage account of memory formation posits that novel words are transitorily encoded in a temporary store, represented by the hippocampus, before they can

be transferred into the long-term store in the neocortex. Also, this standard view postulates that the lexicalisation requires an offline consolidation that happens during sleep and helps to mediate between fast hippocampal learning and slow neocortical learning. However, claims have been made that lexical representations formed in certain circumstances such as a massive exposure to novel words, co-presentation with existing neighbours and more implicit novel word training, enter mental lexicon more swiftly than representations formed as a result of more explicit training. The possible explanation points to different mechanisms utilised in word learning depending on encoding conditions which, in some situations offer a more rapid learning due to by-passing the hippocampal route and therefore with no need for sleep-mediated consolidation. Additionally, the psychophysiological measures provided some evidence that the explicit measures may not be sensitive enough to capture an initial rapid acquisition of novel phonological items. Consequently, the goal of the experiments in Chapter 2 was to gain a better understanding of factors affecting the time-course of word learning. By exploring different training procedures such as an explicit training traditionally used in word learning studies and a relatively more implicit Hebb repetition task, the present research attempted to provide a better understanding of how human cognition facilitates language learning, with or without sleep.

1.4 Memory Manipulations during Sleep

The compelling evidence that sleep contributes to formation of the long-term memory and memory consolidation sparked attempts to employ techniques which would alter or enhance the sleep benefits on memory. These external techniques were believed to work in a manner similar to the brain stimulation in wake (Speth, Speth, & Harley, 2015) and targeted mainly the slow oscillations. Although in this paragraph I will mainly focus on the manipulation of slow brain activity and its benefits to sleep consolidation, it is important to emphasise that functions of sleep are dependent on a more fine-grained synchronised activity arising from different neural networks and oscillatory rhythms.

1.4.1 Spontaneous mnemonic reactivations

Sleep has been shown to be particularly suited to facilitating memory consolidation, a process whereby initially fragile memory traces become stabilised. As mentioned in the earlier parts of this chapter, the sleep-dependent consolidation relies on replay of the neural patterns acquired at encoding and taking place during SWS. These spontaneous reactivations of mnemonic patterns formed during wake support the transfer of weak and labile memory traces from hippocampal system into long-term neocortical storage aiding

consolidation. This neural replay of encoding activity during sleep was first demonstrated in rodents (Wilson & McNaughton, 1994), but similar effects have since been shown in humans (Peigneux et al., 2004). It was reported that the extent of this activity during post-learning SWS was positively correlated with memory performance after sleep (Peigneux et al., 2004). Although compelling, this research was criticised as demonstrating only a correlational, but not causal, relationship between replay in sleep and memory consolidation (Gais & Born, 2004). The causal role of mnemonic reactivations in memory processing during sleep was supported by recent investigations which indicated that the neural replay can in fact be externally manipulated in humans. This manipulation involved re-presenting associative mnemonic cues from the encoding phase during SWS. Many studies had built on these findings and provided further evidence that cuing of specific memories (i.e. targeted memory reactivation-TMR) improves memory consolidation selectively during sleep (Cairney, Durrant, Hulleman, & Lewis, 2014; Cairney, Lindsay, Sobczak, Paller, & Gaskell, 2017; Groch et al., 2016; Rasch, Büchel, Gais, & Born, 2007; Schreiner & Rasch, 2014). The TMR paradigm will be discussed in more detail later in this chapter.

The underlying mechanisms for spontaneously occurring memory replay in sleep have been associated with the specific pattern of neural oscillations, in particular, slow oscillations, sleep spindles and ripples that support consolidation process (Staresina et al., 2015). Replay has been indirectly linked to sleep spindles whereas its relationship with sharp-wave ripples is more elusive. For example, studies indicated that sleep spindles are related to consolidation of different memory systems (Fogel & Smith, 2011; Gais et al., 2002). These findings were supported by pharmacological manipulations that strengthened the view that sleep spindles are functionally related to consolidation processes during sleep. With regards to hippocampal ripples and sharp-waves, research showed that although physiologically relevant the basic mechanisms underlying the phenomenon remains largely enigmatic (Butler & Paulsen, 2015; Buzsáki, 2015; Buzsáki, 2013).

Although sleep has been indicated as particularly important in memory consolidation processes, stimulus-specific activity replay occurs also during awake state following learning (Sara, 2000). However, the principles that rule memory reactivations in sleep and wake are different, with neural replay having distinct functions depending on the brain state. For example, the beneficial effect of TMR in sleep on memory was not present when cueing was applied during wakefulness (Diekelmann, Büchel, Born, & Rasch, 2011). In fact, re-presenting associated memory cues during wakefulness destabilises memories, making them more susceptible to interference, an effect directly opposite to the one

observed after cueing in sleep. However, differences in awareness levels and encoding ability may be crucial factors in determining the state-dependent role of memory reactivation. For example, the post-learning memory replay can have different functions depending whether participants are engaged in concurring activity or entering the quiet wakefulness state (Diekelmann et al., 2011).

In sum, memory reactivation is not a unitary phenomenon and involves distinct processes depending on the mode of the brain, for example waking or sleep. Research suggest that spontaneous replay of neural pattern observed post-learning is a crucial part of memory consolidation. Moreover, the beneficial effect of memory replay in sleep can be further extended by external manipulations. Although fascinating, investigation into the phenomenon of memory replay in the human brain is still evolving with many questions remaining open.

1.4.2 Reactivating memories in sleep -Targeted Memory Reactivation paradigm

As indicated in the previous section, recent investigations have demonstrated that SWS-dependent neural replay can be manipulated in humans with associative mnemonic cues in order to boost memory consolidation. This method, deemed Targeted Memory Reactivation or TMR, has been widely used across different cues and memory types. This non-invasive strategy involves re-presenting cues learnt prior to sleep during subsequent SWS in order to enhance the memory for material associated with these cues. Its non-invasive nature and ease of application make it a particularly attractive technique that offers more options for out-of-laboratory studies in comparison with other methods such as tDCS or Transcranial Magnetic Stimulation (TMS).

Physiologically, consolidation during sleep involves a cascade of neurophysiological events that include slow waves, thalamo-cortical sleep spindles and hippocampal sharp-wave ripples (Staresina et al., 2015). TMR is believed to capitalise on the natural consolidation mechanisms to further promote plasticity. The method has also provided the most direct evidence of the active rehearsal of memories in sleep (Schouten, Pereira, Tops, & Louzada, 2017). In the first experiment in the field, Rasch and colleagues (2007) presented their participants with odour cues during learning of object-location associations and then re-exposed half of them to the same odour cues during subsequent sleep. Strikingly, the authors found that participants who were re-exposed to odour cues during sleep showed superior memory accuracy of learnt locations at the post-sleep test in comparison to participants who were not re-presented with odour cues during sleep. Similarly, Rudoy et al. (2009) also used TMR paradigm to improve object-location learning.

This time however, instead of the odour context, the authors presented their sleeping subjects with sound cues. In keeping with TMR protocol, half of the sound cues, paired with specific objects and played during learning phase, were replayed during SWS. Again, memory for objects associated with those replayed in sleep sounds was shown to be significantly improved in comparison with the objects that were not cued in sleep. Comparable effects have since been showed for variety of cue types, for example sounds and verbal stimuli. These studies demonstrated that TMR has potential to aid the memory strength and also modify specific memories.

Nevertheless, the causal link between cueing of selective memories in sleep and observed enhancement in post-sleep behavioural performance is still a matter of debate. For example, sleep not only strengthens new memories but also inhibits neurons required for forgetting (Gais & Born, 2004; Hardt, Nader, & Nadel, 2013). Thus, it is still unclear whether these manipulations in sleep enhance processes actively supporting memory gains (i.e. their consolidation) or processes that play a role in maintaining memory traces formed at encoding phase (i.e. their forgetting). Some studies utilising TMR in sleep report their findings in a domain of memory forgetting (Rudoy et al., 2009) whereas other show the improvement of memory in comparison to the pre-sleep level (Schreiner & Rasch, 2014).

1.4.3 Manipulating brain activity in sleep

Apart from the TMR method outlined above, the on-going brain activity can also be directly altered by other more or less invasive techniques. Below I will describe some of the methodological advances that opened up a new chapter in sleep engineering research. I will first outline studies that developed tools to selectively manipulate slow oscillatory activity in sleep in order to dissect their role in sleep-dependent memory processes. I will then discuss how similar technological progress has begun to broaden our understanding of the role of spindles in memory formation.

1.4.3.1 Manipulating slow oscillations

In one of the first experiments that forever changed the views on the role of sleep in memory formation researchers used a weak electrical current of oscillating potentials to induce slow oscillations in the sleeping brain. In her pioneering studies, Marshall and colleagues (2006; 2004) used the tDCS method applied to the scalp in order to modify the membrane potential of neurons in the brain. The electrical current corresponded to the dominant frequency of slow oscillations, 0.75 Hz. Strikingly, the results showed that the tDCS in sleep not only enhanced the naturally occurring slow oscillatory activity but also increased the retention of declarative memories learned prior to sleep in comparison with

no stimulation (i.e sham; Marshall et al., 2006). By doing so, the authors provided direct evidence for a causal role of slow oscillations in strengthening declarative memory. It was also the first study to show that endogenous slow oscillations had a causal role in sleep-associated memory consolidation and, importantly, that it is possible to induce them externally (Marshall et al., 2006). In contrast, the stimulation with faster frequency of 5 Hz brought no effect upon declarative memory performance. The stimulation was also ineffective when applied during the post-learning period of quiet wakefulness (Kirov, Weiss, Siebner, Born, & Marshall, 2009), indicating that the consolidation processes guided by SOs are specific to sleep.

Building on these findings, the newest methodological advances enabled intensification of slow oscillatory rhythms in a less invasive way. For example, Ngo, Martinetz, Born, and Mölle (2013) showed that slow oscillations can be boosted by a simple rhythmic acoustic stimulation (short burst of pink noise or a click) providing the stimulation is presented in phase with SO up-state. Importantly however, Ngo, Martinetz, Born, and Mölle (2013) showed that this closed-loop acoustic stimulation (CLoS) significantly increased not only the slow oscillation activity in the sleeping brain but also, correspondingly, improved subsequent memory performance for declarative items learned prior to sleep. It is worth noting that the beneficial influence of this method is largely dependent on the fine-tuned timing of auditory stimulation in relation to SO phase during nocturnal sleep (Ngo, Claussen, Born, & Mölle, 2013) or afternoon nap (Lynn et al., 2016). The investigation into the neural activity that accompanies the benefits of acoustic stimulation showed an enhanced power in the fast spindle band (12-15Hz) occurring during SO up-states that also correlated with this improved memory retention (Ngo, Martinetz, et al., 2013). This pointed out that it is not only the SOs but also spindle activity, occurring in synchrony with SO phases, that plays an important part in memory consolidation.

Following their work, Ngo and colleagues (2015) suggested that the CLoS method may have some natural limitations. The researchers tested the extent to which the method could be used to enhance the slow wave sleep and the resulting consolidation benefits. In comparison to their previous work which used only one or two clicks synchronised with SO up-states, the researchers applied a train of several auditory clicks, presented as long as ongoing SO train could be identified. The findings showed no additional benefits of multiple clicks stimulation over the two clicks trials due to the network refractoriness against additional stimulation. The network refractoriness was attributed to an induced spindle activity, resulted from stimulating the SOs, which appeared to reduce sensory transmission during sleep (Bellesi, Riedner, Garcia-Molina, Cirelli, & Tononi, 2014; Schabus et al., 2012).

Indeed, Ngo and colleagues (2015) pointed out that thalamic spindle generating networks can develop an immediate resistance to stimulation in order to prevent any brain response that would induce the neuronal hyperpolarisation and possible paroxysmal spike-wave seizure. Cairney, Ashton, Roshchupkina, and Sobczak (2015) proposed that this inhibitory mechanism may carry a critical importance for memory.

In line with synaptic homeostasis hypothesis, the role of SOs is to promote a global proportional downscaling of synapses potentiated as a result of learning (Tononi & Cirelli, 2014). In consequence, some neural circuits are highly potentiated in comparison to others, improving signal-to-noise ratio and facilitating efficient memory storage. The excessive stimulation would lead to unnecessary downscaling and have a potentially damaging influence on memory. Similarly, the active systems model of sleep dependent memory consolidation (Born & Wilhelm, 2012) assumes a close relationship between SOs and spindles with the latter having a multifaceted role in memory processing. Sleep spindles can therefore display a dual duty. Firstly, by inhibiting an overriding of SOs, and hence the hyper-synchronicity, and secondly by, at the same time, providing support for memory reactivation in sleep and strengthening of individual memories (Cairney, Ashton, et al., 2015). In fact, research showed that spindles may be associated with reduced sensory responsiveness in sleep (Astori, Wimmer, & Lüthi, 2013). It would represent a healthy and self-induced brain mechanism that prevents induction of SOs in order to prevent hyper-synchronicity and possible seizures.

1.4.3.2 Manipulating sleep spindles

Based on the notion that external stimulation can enhance specific brain oscillations (Buzsáki & Draguhn, 2004) it was shown that acoustic stimulation represents an ideal medium to augment SOs without using invasive techniques such as tDCS or TMS. Additionally, the CLoS method pointed out the close interplay of SOs and spindle activity in memory formation with spindle serving protective functions against hyper-synchronicity of neural networks (Ngo et al., 2015). Other research looked specifically at the sleep spindles and their role in memory consolidation and indicated that these are crucial in development of stable long-term representations. For example, an increase spindle activity was observed following intense training and correlated with subsequent memory performance (Gais et al., 2002; Schabus et al., 2004). However, it has been suggested that spindles may play a more general role in terms of memory consolidation. For example, as well as playing an important role in declarative memory formation, the sleep spindles have been indicated to participate in procedural motor learning (Nishida, Pearsall, Buckner, & Walker, 2009).

Different functions attributed to sleep spindles may be related to their diverse character; they can be separated into slow frequency (12-13.5Hz) and fast frequency (13.5-15Hz) subtypes (Knoblauch, Martens, Wirz-Justice, & Cajochen, 2003). These two types of sleep spindles are believed to have different effects on memory consolidation. The fast spindles are associated with activity in the hippocampal circuitry, lateral and medial prefrontal cortices and posterior parietal regions (Schabus et al., 2007), areas participating in consolidation of declarative memory. Indeed, the fast spindles have been shown to predict both memory performance and learning ability in the declarative domain (Mander, Santhanam, Saletin, & Walker, 2011; Saletin, Goldstein, & Walker, 2011; Van Der Helm et al., 2011). Slow spindles, on the other hand, were associated with increased activity in the superior frontal gyrus and predominantly related to a coupling among cortical networks. Mölle and colleagues (Mölle et al., 2011; Mölle & Born, 2011) proposed that both fast and slow spindles are in fact equally important for memory formation. Whereas the fast spindles, coinciding with hippocampal sharp wave ripples, may represent a mechanism that facilitates the transfer of memory-related information from the hippocampus to the neocortex, the subsequent slow spindles may be related to a cortico-cortical cross-linking of transferred information with prefrontal circuitry. The authors considered the latter to be particularly important in the formation of neocortical long-term memory representations.

The importance of sleep spindles in memory formation prompted attempts to selectively manipulate spindles to elucidate their role in sleep-dependent memory processing (Antony & Paller, 2017; Astori et al., 2013). Research indicated that some function of sleep spindles may include sensory transmission, for example, maintaining sleep quality and controlling the arousal threshold (Bonjean et al., 2012) which can be enhanced pharmacologically in rodents (Wimmer et al., 2012). Antony and Paller (2017) used oscillating sounds to selectively and noninvasively manipulate spindle activity. By using the acoustic resonance, they induced slow and fast spindles which resembled naturally occurring spindles in their duration and scalp distribution. The results provided further evidence for functional distinction between two types of spindles and their role in cellular plasticity and memory consolidation.

1.4.4 Summary

In sum, recent studies have generated a broader view on function of brain activity in sleep such as slow oscillation and sleep spindles. This in turn motivated novel approaches based on selective manipulation of the brain rhythms in sleep to extend our understanding of the sleep's function to memory consolidation. Emerging technologies showed that slow

oscillatory and spindle activity are accessible for selective interventions and actively participate in mnemonic processes.

1.5 Memory Consolidation during Quiet Wakefulness

A growing body of research confirms that sleep after learning supports memory retention in comparison to staying awake. The improvement of memory after sleep has been largely attributed to memory consolidation processes taking place during sleep (Diekelmann, Biggel, Rasch, & Born, 2012; Diekelmann & Born, 2010; Stickgold, 2005; Stickgold & Walker, 2013; Walker, 2005). In contrast, wakefulness has been typically indicated as important for memory enhancement as far as active rehearsal is concerned. Indeed, active rehearsal is undoubtedly helpful for improving memory during waking (Oudiette & Paller, 2013). However, some research reported that the time lapse itself, with no need for sleep, may be sufficient for the consolidation effect to emerge providing that certain conditions have been fulfilled. For example, this was observed in word learning (Kapnoula, Gupta, Packard, & McMurray, 2015; Szmalec et al., 2012) and grammar learning (Mirković & Gaskell, 2016; Werchan & Gómez, 2014) studies. These investigations indicated an alternative route that leads to neocortical integration of new memories that by-passes hippocampal mediation and therefore with no need for sleep-related consolidation. This alternative route could support swifter learning, particularly learning of new memories of a less episodic nature (and therefore more independent of hippocampal involvement). On the other hand, however, an alternative view has been proposed according to which the brain consolidates previously encoded memories whenever the hippocampus is not occupied by encoding new information (Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011) be it either in sleep or wake. According to this approach, the boundaries between sleep and wake are considered more elusive than proposed by the standard model of memory consolidation (McClelland et al., 1995). For instance, some simple learning has been demonstrated to take place during sleep. Arzi and colleagues (2012) using conditioning technique, showed that new associations between tones and smells can be formed in sleep. This finding demonstrated that, although very simple and limited, some learning is possible despite the “offline” mode that the brain goes into during sleep. Thus far, only a wake state, as opposed to sleep, has been associated with encoding of new memories whereas sleep played a major role in memory replay and consolidation. A growing body of evidence also suggests that the latter is not exclusively restricted to sleep and that hippocampal-dependent memories can still undergo consolidation process during wakeful state. Here, a wakeful rest has been shown to be particularly effective in supporting

memory consolidation. For example, merely 10 minutes of quiet rest after an encoding has been shown to result in better recollection of learnt material in comparison to 10 minutes of game playing (Dewar, Alber, Butler, Cowan, & Della Sala, 2012). This memory improvement was observed even after a period of 7 days from initial training suggesting long-term consolidation effects.

This, and similar findings, suggest that some consolidation processes may take place if an intake of new information straight after learning is prevented. However, it is still a matter of debate whether consolidation processes taking place during quiet wake follow the same principles as consolidation processes in sleep. Below, I will review some evidence that quiet wake supports memory improvement. I will then discuss physiological underpinnings that make quiet rest a suitable state for memory consolidation to happen. Lastly, I will evaluate possible mechanisms that stand behind memory formation in wake with a particular role of alpha and theta oscillatory activity of the brain.

1.5.1 Quiet wakefulness and memory improvement

Research suggest that activities people engage in following the first few minutes after learning affect how well they remember the newly learnt material in the long-term (Dewar, Alber, Butler, Cowan, & Della Sala, 2012; 2014). Dewar et al. (2012) asked their participants to listen to two short stories and try to remember as many details as possible. Immediately afterwards, the participants were asked to describe what happened in the story. Then they were given a 10-minute delay that consisted either of wakeful resting or playing a spot-the-difference game on the computer. During the wakeful resting portion, participants were asked to just rest quietly with their eyes closed in a darkened room. No instructions were provided regarding the resting interval and participants could daydream or think about the story as long as they remained undistracted by anything else. The results showed that a long-term enhancement of memory performance was observed following wakeful rest, when compared to game playing. This suggested that wakeful rest after learning allows memory traces to undergo a form of consolidation, leading to a long-term increase in retention of new information. However, the study was criticised for lack of control over the quiet rest interval when participants could simply engage in active rehearsal to boost their memory. In response to this criticism, Dewar et al., (2014) tested whether the wakeful rest offers optimal condition for the consolidation processes to take place or rather facilitate intentional rehearsal of recently acquired memories. To prevent active rehearsal, the researchers used novel, non-recallable words which they later tested using recognition paradigm. Results indicated that the memory for non-recallable words benefited from a post-learning interval of wakeful rest in comparison to a comparable time

spent in a highly stimulating condition. The authors concluded that this rest-induced memory boost emerged due to consolidation processes taking place during quiet wake and not the deliberate rehearsal.

Additional evidence for the role of quiet wakefulness in memory consolidation has come from studies on integration of new spatial memories, a function that has, hitherto, been strongly associated with sleep. Craig, Dewar, Harris, Della Sala, and Wolbers (2016), using virtual reality navigation task, demonstrated that wakeful rest supports formation of cognitive maps by boosting knowledge of spatial relations that were never experienced directly during navigation task. By doing so, the authors showed that quiet wakefulness strengthens memories which are heavily hippocampal-dependent and, importantly, that quiet wakefulness has potential to support a wider integration of memories within relevant networks. In a similar study, Craig, Dewar, Della Sala, and Wolbers (2015) showed that benefits of quiet rest extend to spatial associative and temporal order memory in humans, and hypothesised that the improvement is due to superior consolidation/hippocampal replay of novel information taking place during rest. Moreover, a superior retention was still observed one week after training suggesting that the memory benefits endured over the long-term.

The benefit of memory stabilisation during sleep and wake has been attributed to covert replay of stored information in order to support systems consolidation. Previous studies indicated a pivotal role of memory reactivations in sleep-dependent memory consolidation (Diekelmann & Born, 2010; Stickgold, 2005). Moreover, recent experiments demonstrated that it is possible to bias these endogenous reactivations by external replay of memory associated cues (Rasch et al., 2007; Rudoy et al., 2009) to induce preferential consolidation. Interestingly, the selective consolidation can also be induced by a much simpler memory tagging taking place at encoding by, for example, presenting emotionally salient stimuli (Hu, Stylos-Allan, & Walker, 2006; Sterpenich et al., 2009), inducing intention to remember (van Dongen, Thielen, Takashima, Barth, & Fernández, 2012; Wilhelm et al., 2011) or anticipation of a future reward for correct remembering (Fischer & Born, 2009). Similar selective consolidation, especially for experiences associated with reward, has also been indicated to take place during wakefulness (Marr, 1970; Paller, 2009). Yet, the selectivity of memory consolidation may not be due to reactivations of memories but a consequence of global downscaling of synaptic connectivity as pointed out by the synaptic homeostasis theory (Tononi & Cirelli, 2006). The targeted memory reactivations studies using cues replayed in wake suggested that covert reactivations taking place during wakefulness may differ in their function to those taking place during sleep. For example,

Oudiette, Antony, Creery, and Paller (2013) showed that wake reactivations help to strengthen individual, salient memories whereas sleep reactivation can potentially affect all items belonging to the same category. Indeed, Diekelmann et al. (2011) revealed that reactivation during wakefulness serves a different function to reactivation during sleep and they also involve different brain regions as assessed with fMRI method; the prefrontal cortex in case of wake reactivations and the hippocampal and posterior areas in sleep. Moreover, the study showed that TMR applied during waking destabilised memories and made them vulnerable to forgetting, whereas similar procedure in sleep brought an opposite effect-an immediate memory stabilisation.

Taken together, the studies investigating memory consolidation in wake indicate that some strengthening of memory traces is possible during waking. However, whether processes governing memory consolidation are qualitatively similar in wake and sleep is still unclear. Quiet wakefulness may potentially offer some preferential conditions for memory consolidation yet sleep may still be the most optimal mode for it to take place. Alternatively, quiet wakefulness may provide qualitatively different memory strengthening. It is important to emphasise that the memory benefits observed after quiet wake have also been obtained following similar states of reduced information intake such as meditation (van Vugt & Jha, 2011; Wagstaff et al., 2004), exercise (Hogan, Mata, & Carstensen, 2013; Quelhas Martins, Kavussanu, Willoughby, & Ring, 2013) or even listening to music (Kuschpel et al., 2015). Nevertheless, research indicates the potential benefits of quiet wake for memory retention, also in the long-term. Providing the fast track of our daily lives this may offer additional memory and health benefits in a situation when sleep is a limited option.

1.5.2 Physiological underpinnings of memory consolidation in quiet wakefulness

Contemporary studies have provided growing evidence that quiet wakefulness, as opposed to active wakefulness, can aid memory consolidation in a similar manner, but perhaps not to the same extend as sleep does. The physiological evidence supports the findings that sleep and quiet wake may make similar contributions to memory consolidation.

According to the active systems model of memory the oscillatory activity of the brain can operate in either a “slow” or “fast” mode (Headley & Paré, 2017). The slow mode, which is believed to support memory consolidation, is characterised by large irregular activity in the hippocampus and delta oscillations in cortical and striatal circuits. The brain enters the slow mode naturally in SWS but interestingly, also during quiet wake. In contrast, the fast

mode occurs during active waking and REM sleep. The irregular activity observed in the hippocampus during SWS includes oscillatory patterns of large amplitude activity called sharp wave ripples (SWRs), which results from the synchronous activity of two hippocampal regions: CA1 and CA3 cells. It is the SWRs that have been indicated to play the most important role in memory consolidation by reactivating, endogenously, hippocampal and cortical activity patterns that occurred before sleep (Sirota & Buzsáki, 2005). Interestingly, the SWRs, associated with replay events in CA1, also occur during quiet wakefulness and therefore have potential to facilitate memory consolidation (Headley & Paré, 2017). Additionally, the formation of associative links for memory in CA3, CA1, entorhinal cortex and even neocortex is facilitated by a lower level of acetylcholine. The acetylcholine supports the formation of memory traces by allowing a stronger spread of activity within the hippocampus itself and from the hippocampus to the entorhinal cortex, otherwise supressed during active wake. This promotes reactivations and further strengthening of associations encoded within the CA3 region of the hippocampus. Interestingly, a lower level of acetylcholine had been observed during both the quiet wake and deep part of sleep (SWS), in contrast to active wake (Hasselmo, 1995), pointing out that comparable mechanisms may be taking place at a neural level during quiet wake and sleep.

1.5.3 Reduced interference and inhibition hypothesis

One of the prominent characteristics of quiet wakefulness is its similarity to sleep in the reduced interference that is offered by this state. The reduced interference has been showed to benefit consolidation of recently encoded memories by creating favourable conditions for both cellular and systems consolidation (Alger, Lau, & Fishbein, 2012; Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006; Korman et al., 2007) by blocking LTP-like potentiation and new learning or “stabilisation” of synapses tagged during wake (Mednick et al., 2011; Tononi & Cirelli, 2003, 2014). According to opportunistic consolidation hypothesis (Mednick et al., 2011) periods of quiet rest, just as during sleep, offer reduced interference and reduced encoding of new memories which might facilitate the evolution of memory-consolidating processes in the brain. For instance, neuronal replay has been observed during both sleep and restful waking with reduced interference (Foster & Wilson, 2006). It is worth noting that the alpha band (8-12 Hz) activity changes have been specifically indicated to reflect the low level of attentional state that accompany reduced interference in quiet wake. Interestingly, alpha EEG power (8-12 Hz) during SWS was also indicated as an important marker of qualitative memory changes, for example, the transition from implicit knowledge to explicit insight (Yordanova, Kolev, Wagner, Born, & Verleger, 2012). Furthermore, Marshall et al. (2006) have demonstrated that using slow

oscillating direct current stimulation (0.75 Hz) to increase slow oscillation in SWS has specifically enhanced the spectral power in alpha frequency band (8–12 Hz), characteristic of slow sleep spindles activity. This modulated brain activity was also accompanied by an improvement in declarative memory performance after sleep (Marshall et al., 2006). The interference hypothesis is supported by studies demonstrating enhanced memory retrieval due to protection of new memory traces from disrupting input during a critical period after acquisition offered by sleep and quiet wake (e.g. Gottselig & Re, 2004; Mednick, Makovski, Cai, & Jiang, 2009).

Another potential explanation that also indicates how alpha activity can facilitate memory enhancement during quiet wake is the idea of inhibition or disengagement (Cooper, Croft, Dominey, Burgess, & Gruzelier, 2003; Jensen, 2002; Klimesch, Doppelmayr, Schwaiger, Winkler, & Gruber, 2000; Klimesch, Sauseng, & Hanslmayr, 2007; Tuladhar et al., 2007; Vanni, Revonsuo, & Hari, 1997). For example, strong alpha power has been shown to serve an inhibitory role in preventing task-irrelevant perceptual stream into the brain areas that are involved in target processing (Klimesch et al., 2007). Alpha power has also been shown to facilitate a state of inhibition or suppression by those brain regions that are relevant to the current task (Jokisch & Jensen, 2007; Van Dijk et al., 2010). In that way the alpha activity would help to suppress the flow of new information into brain areas relevant to cognitive processing. Moreover, studies exploring the role of neural oscillations in cognition have revealed sustained increases in alpha-band (~8–14 Hz) power when performing short-term memory tasks. These increases have been proposed to reflect the inhibition, for example, of cortical areas representing task-irrelevant information, or of potentially interfering with representations from previous trials.

More recently and alternatively, it has been proposed that alpha band power can in fact reflect more the selection and maintenance of information during the memory task, rather than, or in addition to, the inhibition of task-irrelevant information (Johnson et al., 2011). For example, Johnson et al. (2011) demonstrated elevated alpha-band oscillations during the retention interval in a short term memory task involving memorising different shape locations. Their study was designed to contrast two views on the role of alpha in memory processes. According to the first view the increase in alpha activity was to reflect the functional inhibition of cortical areas representing potentially disruptive task-irrelevant information (see, e.g. Jensen & Mazaheri, 2010; Klimesch et al., 2007). The second view held that the increased alpha band power may represent an integral part of the distributed network activity related to the active processing of information in perceptual and cognitive tasks (see Palva & Palva, 2007). Since the memory task employed by Johnson et al. (2011)

did not require any inhibition of irrelevant information, upon examination of their results the authors proposed that elevated alpha is indeed related to selection and maintenance of shape information rather than inhibition of irrelevance of material.

Studies indicate a direct involvement of alpha oscillations in the mechanisms of attention, consciousness and memory. In the next paragraph I will discuss why alpha oscillations may hold a key to our understanding of large-scale integration in the brain networks (i.e. fronto-parietal synchrony) that governs acquisition and maintenance of new information.

1.5.4 Oscillatory basis for memory consolidation in quiet wake

In the domain of memory, alpha power has been shown to index a cognitive load associated with item retention and an increased performance of working memory (Haegens, Osipova, Oostenveld, & Jensen, 2010; Jensen, Gelfand, Kounios, & Lisman, 2002). In particular, within the framework of the "functional inhibition" hypothesis, it has been argued that higher alpha power during item retention in working memory reflects the inhibition of task-irrelevant information (Klimesch, 2012) and/or brain regions (Jensen & Mazaheri, 2010). Compatible with the "functional inhibition" framework, a decrease of alpha power can be related to active stimulus processing (e.g., Hanslmayr, Staudigl, & Fellner, 2012) and to increased excitability in sensory cortices (e.g., Jensen, Bonnefond, & VanRullen, 2012). Moreover, controlled inhibition (as reflected by alpha power increases) and active processing (as reflected by alpha power decreases) are likely to play a role in improving the signal-to-noise ratio (SNR) of the relevant information stored in memory (Klimesch, 2012). Wilsch et al. (2014) found that elevated alpha power was equally effective in predicting performance benefits as other cues supporting performance. Similarly, Hsu, Tseng, Liang, Cheng, and Juan (2014) showed that the positively-charged electric current through the skull can rapidly and effortlessly change people's pre-stimulus alpha power and improve subsequent performance on a visual short-term memory (VSTM) task. Furthermore, Zaehle, Rach, and Herrmann (2010) showed that participants whose alpha activity was induced by anodal tDCS performed better at working memory tasks than participants in the sham condition. Interestingly, using polarity-specific alterations as a function of tDCS, the authors indicated that relevant increases and decreases in event-related alpha power were accompanied by modulation in another frequency band that was previously shown to participate in memory formation, the theta activity (Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011).

An accumulating body of evidence emphasizes the role of alpha and theta in memory performance. Event-related changes indicate that the extent of upper alpha desynchronization is positively correlated with (semantic) long-term memory performance, whereas theta synchronization is positively correlated with the ability to encode new information (Klimesch, 1999). The formation of episodic memory traces is one of the most important tasks of working memory. It has been proposed that alpha may be an oscillation that synchronises very large populations of neurons. For example, Klimesch, Schack, and Sauseng (2005) suggest that theta activity reflects working memory functions whereas upper alpha may be important for the reactivation of long-term memory codes in short-term memory. Similarly, Kawasaki, Kitajo, and Yamaguchi (2010) demonstrated that working memory task-relevant brain regions are coordinated by distant theta synchronization for central executive functions, and by local alpha synchronization for the memory storage buffer, and, importantly, also by theta–alpha coupling for inter-functional integration. Scheeringa et al. (2008) used fMRI technique in conjunction with EEG recording to gain more insight into brain regions related to alpha and theta oscillatory activity. The researchers found that increases in alpha power were associated with activity in brain regions related to inhibition of neuronal activity whereas increases in the theta power were associated with activity in regions related to default network. Interestingly, the default mode network is naturally activated in a state of quiet wakefulness due to the absence of task demands (Graner, Oakes, French, & Riedy, 2013).

1.5.5 Summary

The question of whether quiet wakefulness simply provides favourable conditions (i.e. reduced interference) or actively participates in memory consolidation, remains open. Activity patterns involved in memory consolidation do not occur specifically in sleep. For example, sharp waves ripples are observed both in SWS and quiet waking. Studies indicate that the pattern of brain activity, rather than SWS per se, would be a sufficient condition for memory processing (Kudrimoti et al., 1999).

1.6 Conclusions

To conclude, the role of sleep and wake in memory and learning processes has been extensively investigated. The findings showed that sleep has an important involvement in consolidating new memories and promotes learning. In particular, learning new words heavily depends on overnight consolidation. Nonetheless, learning also seems to be supported by other mechanisms. Firstly, not all memories are chosen for consolidation and, secondly, learning of certain information, such as frequency information, may not require

sleep after all. Hence, the disentanglement of different mechanisms participating in consolidation of new information has proven difficult. What mechanisms take place independently of sleep, how independent of sleep they are and whether they result in qualitatively similar learning is still unclear.

1.7 Aims and Outline of the Thesis

The aim of this thesis is to investigate mechanisms of memory consolidation during both sleep and wake. In the first two parts of the thesis (**Chapter 2 and 3**) I will focus on memory consolidation in the realm of word learning, using the integration of novel words within mental lexicon as a marker of their successful consolidation. In **Chapter 2** I will present implicit and explicit training procedures used in novel word learning and show how they help not only to form memories but also to tell us more about the undergoing integration processes. Here, I will shed some light on the role of sleep in the integration of new linguistic knowledge and memory consolidation in general. After discussing the implicit and explicit training tasks, I will further investigate the relationship between learning novel words and sleep in **Chapter 3**, using a novel TMR paradigm. At this point, I will also explore the potential for detecting neural markers of successful external memory reactivation in sleep and word integration using electrophysiological measures such as polysomnography (PSG)/electroencephalography (EEG). Finally, in the third part of this work (**Chapter 4**), I will look at mechanisms participating in memory consolidation in a quiet wakeful state, as opposed to sleep. Here, I will investigate the relationship between the ongoing brain activity during the quiet wakefulness and its influence on long-term memory formation. Specifically, I will use the tDCS method in order to alter the on-going oscillatory brain activity and examine how this affects the formation of long-term memory traces. In sum, the experiments reported in this thesis were designed to test how the offline consolidation period, following the learning phase, changes the representation of a newly acquired memory trace (i.e. a newly learned word). These investigations were also designed to explore how sleep and sleep-like processes participate in the consolidation and integration of new memories into the pre-existing knowledge.

CHAPTER 2
IMPLICIT VERSUS EXPLICIT MECHANISMS OF VOCABULARY LEARNING AND CONSOLIDATION

Previous research has suggested that integration of novel words into lexical competition benefits from a consolidation delay containing a period of sleep (Dumay & Gaskell, 2007). However, a recent study argued that learning novel words via a relatively implicit Hebb repetition task leads to later lexical integration independently of sleep (Szmalec et al., 2012). It is not clear whether this different time course of lexical integration is a consequence of the learning method chosen, as opposed to other between study differences. Three experiments directly compared the learning of novel words using explicit and implicit methods, namely phoneme monitoring on isolated tokens vs. Hebb repetition of syllable sequences. The impact of the learning was tested at a range of later time-points using two tests of explicit knowledge (recognition and recall) and a test of lexical integration (pause detection on related existing words). Between experiments, we also manipulated exposure frequency and the impact of syllable grouping cues in Hebb repetition. The results suggested that learning novel words via Hebb sequence repetition does not confer a benefit on lexical integration prior to or after sleep. We observed an engagement in lexical competition only in the case where a good level of explicit training was followed by a consolidation delay. Recognition and recall performance was generally poorer for Hebb learning. We conclude that Hebb-style implicit learning of words does not allow consolidation processes to be bypassed in lexical integration.

2.1 Introduction

Language learning is undoubtedly one of the most crucial processes in human development, yet the time-course and mechanisms underlying the establishment of lexical entries are not fully understood. On the one hand there is a well-documented argument in the adult (e.g., Fernandes, Kolinsky, & Ventura, 2009; Kapnoula & McMurray, 2015; Kapnoula, Gupta, Packard, & McMurray, 2015) and developmental literature (e.g., Carey & Bartlett, 1978; Carey, 1978; Spiegel & Halberda, 2011) that phonological forms may be acquired swiftly. On the other hand, there is evidence to suggest that the development of a fully-fledged representation of a novel word may be a more extended process over the course of days or weeks (Bakker, Takashima, van Hell, Janzen, & McQueen, 2014; Bakker et al., 2015a; Dumay & Gaskell, 2007; Gaskell & Dumay, 2003b). To what extent the time-

course of novel word learning is modulated by the encoding circumstances is currently under debate.

Successful word learning includes an integration process that allows novel items to gain properties and status similar to established lexical items. Once a novel word has been fully integrated into mental lexicon it should engage in the automatic lexical recognition process whereby it becomes identified in competition with other similarly sounding words (Gaskell & Marslen-Wilson, 2002; Norris, 1994). Research on word learning has indicated that this integration of novel spoken words is typically supported by a consolidation process often associated with sleep (Davis & Gaskell, 2009; Dumay & Gaskell, 2007; Gaskell & Dumay, 2003b; Henderson et al., 2012; Tamminen et al., 2010). For example, Gaskell and Dumay (2003b) and Dumay and Gaskell (2007) investigated the possible role of sleep in lexical integration by teaching their participants fictitious novel spoken words such as *cathedruke* (designed to partially overlap with existing words) and then testing how learning these novel words affected processing of their existing neighbours (e.g., *cathedral*) across different time delays. In an auditory lexical decision or pause detection (Mattys & Clark, 2002) task an increase in response time to the existing word is taken to indicate engagement of the novel word in lexical competition with existing neighbours and therefore some level of lexical integration. Dumay and Gaskell (2007) found no evidence of changes in lexical competition immediately after learning. However, they observed a clear enhanced competition effect after a 12 hr period that included nocturnal sleep but, notably, not after a similar period of wakefulness. This time-course and association between sleep and the lexical integration of novel words can be interpreted within a two-stage account of novel word learning and a neurocognitive models of declarative memory formation such as the Complementary Learning Systems framework (CLS; McClelland et al., 1995). The CLS model proposes that new declarative information is initially and temporarily stored using hippocampal mediation (Davis et al., 2009) and later becomes hippocampally independent as it is incorporated into existing long-term neocortical memories. Here, sleep provides optimal conditions for such transfer as the cognitive system is offline and not engaged in processing of new information (McClelland et al., 1995). This hippocampal mediation of new memory traces has been supported by the active systems model of sleep-dependent consolidation (Born & Wilhelm, 2012; Diekelmann & Born, 2010; Rasch & Born, 2013). The relationship between lexical integration of novel words and sleep has also been more directly tested, revealing one particular aspect of sleep architecture (sleep spindle activity) that was associated with the emergence of lexical competition (Tamminen et al., 2010).

Based on the above, sleep appears to play a prominent role in consolidation of new lexical knowledge. However, the learning of new vocabulary is not necessarily a

homogeneous process. Although, sleep was shown to play an important role in a variety of learning contexts, including relatively implicit word learning from stories (Henderson et al., 2015), one may argue that the studies that uncovered a possible role of sleep in novel word integration predominantly relied on explicit learning mechanisms. For example, Gaskell & Dumay (2003b) asked participants to listen for particular phonemes within the novel words, which were presented in isolated form with instructions to memorise the novel words for later test. This is quite an explicit form of tuition, and it is possible that more implicit learning tasks and/or less explicitly segmented speech might recruit different learning mechanisms, which might change the nature of the lexical integration process and reduce the importance of sleep. This possibility has been investigated in a series of studies by Szmalec and colleagues (2009, 2012) using the Hebb repetition effect. The Hebb paradigm involves gradual learning of serially ordered information via repetition. In an immediate serial recall task, Hebb (1961) presented a specific sequence of digits repeatedly every third trial interspersed with nonrepeating sequences and demonstrated that sequence repetition led to superior recall over time. The Hebb effect is thought to be implicit as it occurs irrespective of awareness (Stadler, 1993). Although this learning effect was originally shown for sequences of digits it has since been successfully used across different modalities and with a range of stimuli such as visuo-spatial (Couture & Tremblay, 2006; Guérard, Saint-Aubin, Boucher, & Tremblay, 2011), pictorial (Page, Cumming, Norris, Hitch, & McNeil, 2006), facial (Horton, Hay, & Smyth, 2008), and tactile sequences (Johnson, Cauchi, & Miles, 2013; Johnson, Shaw, & Miles, 2016).

Szmalec et al. (2009; 2012) explored the Hebb effect in novel word learning and argued that processes underlying sequence learning in the Hebb repetition paradigm are vital in language acquisition (see also Cumming, Page, & Norris, 2003; Page & Norris, 2008) and that the task offers a more naturalistic model of learning. Consistent with this argument, impaired Hebb sequence learning has been found in people with dyslexia (Szmalec, Loncke, Page, & Duyck, 2011, but see Staels & Van den Broeck, 2015; Henderson & Warmington, 2017). More directly, Szmalec, Duyck, Vandierendonck, Mata, and Page (2009) used a variant of the Hebb procedure to examine the learning of wordlike "chunks" from sequences of nonsense syllables (e.g., *zi-lo-ka-ho-fi-se-be-ru-mo*). The sequences used three trisyllable groupings that were presented in different orders across repetitions. The consistent grouping allowed the trisyllables to become familiar units (e.g., *ziloka, hofise, berumo).* In order to assess this familiarity, they used them in a lexical decision task soon after training. The results showed that the three-syllable groupings extracted from the Hebb sequences were somewhat harder to reject as nonwords than filler trisyllables suggesting a more wordlike representation. The authors argued that the Hebb repetition procedure reflects

the implicit way children learn to segment and sequence words from phonological regularities in their environment (but see also Mosse & Jarrold, 2008). Indeed, this form of implicit learning of linguistic regularities from environment has been previously successfully established by statistical language learning studies (Saffran, 2002, 2003) and suggests that the Hebb effect variant, as a form of a statistical learning, may utilise the same mechanism.

Building on these findings, Szmalec, Page, and Duyck (2012) applied similar experimental procedures to investigate the time course of novel word integration. The researchers presented their participants with visual sequences of 9 consonant-vowel (CV) syllables for immediate serial recall (i.e. *sa-fa-ra-sa-la-mo-fi-na-lo).* The Hebb sequences were repeated every third trial and again the grouping of the sequences facilitated the extraction of trisyllabic nonwords (i.e. *safara, salamo, finalo*). Based on the logic of Dumay and Gaskell (2007), the authors then used pause detection to test whether the novel sequences would show engagement in lexical competition with their existing Dutch counterparts (*i.e. safari, salami, finale*). As in Dumay and Gaskell, groups were trained either in the morning or the evening, and were tested immediately after training and 12 and 24 hours later. Diverging from Dumay and Gaskell, both groups showed a similar profile of lexical competition induced by the newly learnt trisyllables. Specifically, lexical competition was not found immediately, but emerged after a 12-hour delay in both groups regardless of whether they slept in the intervening period. This pattern of results suggested that although some time delay is necessary to integrate the new items into lexicon, the time lapse itself is sufficient and there is no need for overnight consolidation. The researchers concluded that the exposure to reoccurring Hebb sequences leads to a formation of lexical representations independently of sleep, in contrast with more explicit learning.

The Szmalec et al. (2012) result in comparison with Dumay & Gaskell (2007) strongly suggests that Hebb repetition and more explicit learning utilize distinct memory systems (cf. Foerde, Knowlton, & Poldrack, 2006). Interestingly, the Hebb repetition effect was shown to be unimpaired in hippocampally amnesic patients (Baddeley & Warrington, 1970; Gagnon, Foster, Turcotte, & Jongenelis, 2004), strengthening the case that Hebb repetition does not rely on the hippocampal complex for learning and so allows swifter (although not immediate) consolidation. At the same time, this sparing of Hebb repetition learning in hippocampal amnesia somewhat weakens the case for it representing the main mechanism for word learning, given that amnesic patients tend to manifest major deficits in novel word learning (Bayley et al., 2008).

A second learning paradigm that may recruit separate neuroanatomical substrates in comparison with explicit encoding is fast mapping (Sharon, Moscovitch, & Gilboa, 2011).

Fast mapping was coined as a term to describe how children use mutual exclusivity to identify new word meanings (Carey & Bartlett, 1978), often maintaining this knowledge in memory for several days after very few exposures (Swingley, 2010, but see also Horst & Samuelson, 2008). In a typical fast mapping trial, a novel object is presented alongside an object for which the name is known. If a new word is then heard, the correct association between word and object can then be made simply by ruling out the already known item. Coutanche and Thompson-Schill (2014) examined how fast mapping affects the time-course of novel word integration in comparison with explicit encoding using a semantic decision task (Bowers, Davis, & Hanley, 2005). In the fast mapping condition participants were presented with images of unfamiliar animals together with the well-known ones and asked a question that referred to the new animal by name (e.g., "are the antennae of the torato pointing up?"). In the explicit condition, participants were presented with unfamiliar animals and their names and were asked to memorise the novel names (e.g., "remember the torato"). The semantic decision task showed that fast mapping but not explicit encoding led to slower responses to related existing words (e.g., tomato) 10 minutes later, suggesting that fast mapping supported swift lexical integration (Bowers et al., 2005). Moreover, a second experiment suggested that it was the presentation of the already known item during learning that allowed for the rapid integration effect. This indicates that the presence, or accessibility, of previous knowledge may facilitate and speed up learning of novel information. Additionally, these findings provide further evidence for different mechanisms underlying fast mapping and explicit learning and are in agreement with studies on amnesic patients who, despite hippocampal damage, showed rapid learning of information through fast mapping but not the standard memory tasks (Sharon et al., 2011 although cf. Greve, Cooper, & Henson, 2014).

Although the Hebb repetition task resulted in a substantially different time-course of lexical integration in comparison to explicit tasks, it is worth noting that the picture drawn from standard word learning studies themselves is not entirely straightforward. The progress of engagement in lexical competition for novel words is partly dependent on training properties. Although a large body of evidence supports the argument that newly learnt items engage in lexical competition after sleep, in some cases this effect has been found sooner. For instance, Gaskell and Dumay (2003a) found immediate lexical competition when manipulating the frequency of the items to be learnt. Low frequency items, presented 12 times during the encoding phase, showed no evidence of lexical competition effect when tested on the same day of training or even when re-tested a week later. Conversely, the high frequency items, presented 60 times in training, appeared to engage in lexical competition immediately. Correspondingly, immediate lexical competition

was also shown in an artificial language learning paradigm for which training involved extensive exposure to novel items in a continuous stream (Fernandes et al., 2009). These results suggest that substantial exposure to novel items can effectively alter the time course of lexical integration, perhaps due to increased automaticity in the novel word recognition (Geukes, Gaskell, & Zwitserlood, 2015; Tham et al., 2015) .

Another factor that appears to influence the time course of novel words integration is their co-presentation with existing words. For example, Lindsay and Gaskell (2009) tested whether exposure to novel words spaced throughout a day would accelerate their integration into the lexicon. The authors found that the competition effects indeed emerged before sleep, but only when the exposure to novel items was interleaved with test phases where phonologically similar existing words were presented. This suggests that the time-course of novel word integration can be changed by spaced interleaving with their existing phonological neighbours during learning (Lindsay & Gaskell, 2009). Similarly, Kapnoula et al. (2015) found an immediate lexical competition effect in the co-activation of novel and familiar words using a visual word paradigm (cf. Weighall, Henderson, Barr, Cairney, & Gaskell, 2016). Therefore, whilst offline consolidation plays a crucial, and perhaps optimising, role in improving automaticity with which novel words are accessed, the process of lexical integration itself seems to follow a more graded curve, often dependent on different factors such as a learning condition (cf. McMurray, Kapnoula, & Gaskell, 2016).

In sum, whilst offline consolidation clearly plays an important role, the process and time-course of lexical integration appear to depend on a range of different factors such as learning and testing conditions. The extent to which different profiles of learning and consolidation are available is a crucial issue to address, so that we understand the mechanisms that support vocabulary acquisition in a natural linguistic environment. However, clear evaluation of the different learning mechanisms is only possible if other potentially confounding factors can be eliminated. Some of the apparent differences between different types of word learning may instead be a consequence of different training properties such as the level of overlap between new and known items, be it semantic or phonological. In the current study, we examined the consequences of novel word learning via Hebb repetition and a more explicit phoneme monitoring task whilst at the same time controlling, as far as possible, for potential confounding factors. We used the time-course of engagement in lexical competition as a measure of lexical integration, alongside other declarative memory tests. If differences in the time course of lexical engagement remain when other factors are controlled, then we can be more confident that tasks exploit different learning mechanisms.

Previous Hebb repetition studies of word learning have differed from more explicit novel word training in potentially important ways such as the number of novel words and the number of presentations. In Szmalec et al. (2012) participants were exposed to 6 novel words twelve exposures each during training. The studies based on the phoneme monitoring task used more words and a higher exposure rate (typically thirty exposures or more; Bakker et al., 2014; Dumay & Gaskell, 2007; Gaskell & Dumay, 2003b; Henderson et al., 2012; Tamminen et al., 2010), with fewer exposures sometimes proving to be insufficient for generating lexical competition effects (Gaskell & Dumay, 2003b). On the basis that a low level of exposure sufficed for Hebb repetition to show interesting effects on lexical competition, we decided to retain this low exposure level for both tasks in Experiments 1 and 2. Given previous studies, this should offer a sufficient level of encoding to induce lexical competition after a delay in the Hebb repetition condition even if this is not necessarily the case in the more explicit condition.

A second important way in which previous studies have differed is the relationship between the fictitious novel words and existing words. In Szmalec et al. (2012) novel words overlapped very closely with their Dutch base words, diverging only in the final vowel (e.g., *bikina* versus *bikini*). In contrast, the studies using more explicit learning methods have tended to use either more substantial final deviations (e.g., the final vowel and consonant, as in *cathedruke–cathedral*) or using embeddings (e.g., *lirmucktoze* embedding *muck*). In principle, this should not matter; after all, real word competitors can differ by as little as a single final vowel (e.g., *window–windy*). That said, having such a small deviation could alter the trajectory of learning or the nature of any lexical competition. It has been shown across several languages, including Dutch and English, that vowel changes in words are more easily relatable to the base words than changes in consonants (Cutler, Sebastián-Gallés, Soler-Vilageliu, & van Ooijen, 2000). This fits with the idea that there may be more leniency in the word recognition system for deviations in vowels than consonants (van Ooijen, 1996). It has also been argued that vowels and consonants have different contributions in early word learning (Nazzi, Gopnik, & Karmiloff-Smith, 2005) and that both play different roles in speech processing and language acquisition, with consonants being more important than vowels at the lexical level (Nespor, Peña, & Mehler, 2003). A single vowel deviation between novel and known items may therefore lead to the novel word being treated as a variant of the existing word (Bürki & Gaskell, 2012) which could change the nature of the learning experience. Therefore, the novel items and English base words used in the present study differed on their final CV syllable (e.g., *bikiso–bikini*), in a similar way to the explicit learning studies. By changing the full final syllable, we put to test whether the Hebb repetition learning extends to these more varied competitors.

A final modification of the Hebb repetition task used in the current study concerned stimulus presentation. In contrast to Szmalec et al. (2012), who presented their stimuli visually, we used auditory stimuli. The reasons for this were twofold: firstly, this helped to avoid any potential cross-modal conflict in the interpretation of consolidation effects (cf. Bakker et al., 2014). Secondly, as the current study used the English language, which has a more complex relationship between spelling and the sound compared with the Dutch language used by Szmalec et al. (2012), abandoning visual presentation allowed us to avoid spelling-pronunciation ambiguity.

We hypothesised that participants who learned novel nonwords via the Hebb repetition task would show lexical integration of novel items after a delay but without needing sleep, similar to the results in Szmalec et al. (2012). It was less clear whether the exposure level would be sufficient for participants who learned novel items via the phoneme monitoring task to show lexical integration of new items (Gaskell & Dumay, 2003a, 2003b), but if there was an effect we expected that this would be strongest after sleep (Dumay & Gaskell, 2007). With regards to the explicit declarative memory tests, our prediction was that learning via a more explicit phoneme monitoring task would result in a more robust declarative memory for novel words (recognition and cued recall tests), in comparison to a more implicit Hebb repetition task, due to the recruitment of attention and conscious control, as a function of training condition (Batterink, Reber, & Paller, 2015).

2.2 Experiment 1

2.2.1 Method

Experiment 1 hypotheses, design, procedures and planned analyses were subject to pre-registration at the Open Science Framework (https://osf.io/6p9my/), with some minor alterations noted below. Furthermore, a planned vigilance task was initially included, but was later removed from the experiment due to repeated software failure.

The overall procedure for Experiment 1 is illustrated in Figure 2.1. Participants attended Session 1 in the morning when they completed either the phoneme monitoring or the Hebb repetition task as a way of familiarising themselves with the novel sequences (e.g. a novel word *bikiso* pronounced as *bih-kee-soo*). The effect of exposure on the lexical competition process for neighbouring existing words (e.g., *bikini*) was then tested using a pause detection task immediately after training. Participants completed another pause detection tasks in the evening, after a 12-hour delay. The third lexical integration test was completed next morning, 24 hours after encoding, following a night of sleep. This experimental design was motivated by the fact that the main interest here was to assess the

emergence of lexical competition in the Hebb repetition condition after a delay without sleep. Apart from the lexical integration task there were also explicit tests of novel sequence knowledge: cued recall and recognition tasks, which took place only after the 24-hour delay. In the cued recall task participants heard the first CVC of the novel words and were asked to recall the novel sequences they learnt on the previous day. In the recognition task participants were required to pick up the familiar novel words from spoken pairs differing only in their final syllables (e.g., *bikiso* vs. *bikita*).

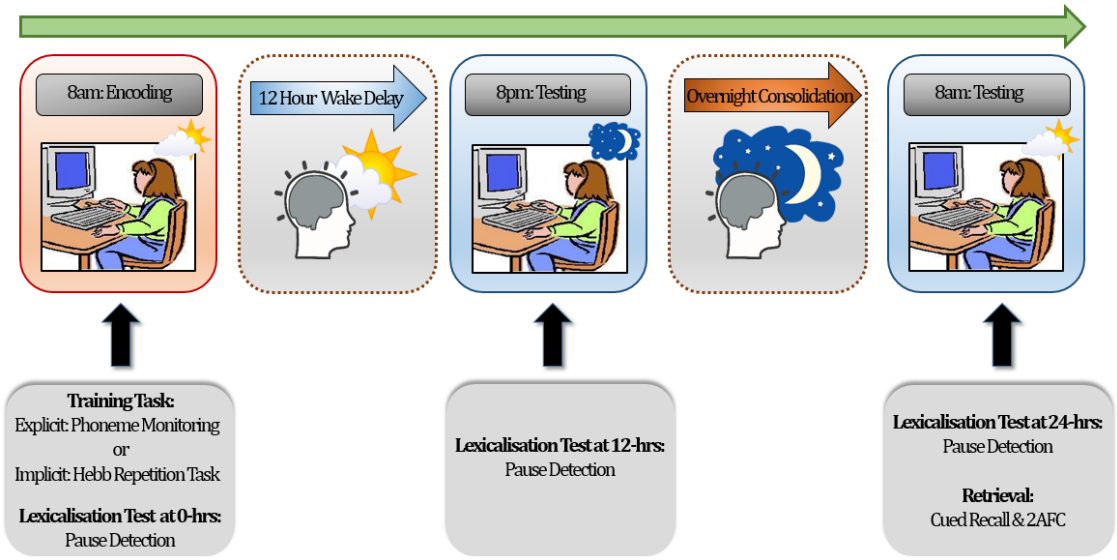

Figure 2.1. Experimental procedure in Experiment 1 and 2. The encoding phase took place in the morning when participants completed either the Hebb repetition or phoneme monitoring task. The lexical integration test was administered at three time points: immediately after learning (0-hr delay), 12 hours from the learning phase (12-hr delay; during this time, participants were instructed to refrain from taking naps) and 24 hours after training (24-hr delay, following nocturnal sleep). The final session also consisted of explicit tests: Cued Recall and 2AFC.

2.2.1.1 Participants

Forty-eight students (forty-one females), between 18 and 26 years old, (mean age: 19.6 years), participated in this experiment. The preregistration stated 44 participants, but four participants were excluded from analyses at the encoding stage, due to either equipment failure or more than 50% incorrect trials in the training task, and so were replaced. Participants in all experiments reported in this paper were University of York students and participated for course credit or financial reward (£6/hour). All reported English as their first language and had no self-reported diagnoses of hearing problems or developmental language disorder (e.g. dyslexia). All participants were informed about the

nature of the tasks and their right to withdraw from the study at any time without penalty. All participants provided written consent before the experiment and were debriefed at the end of it. All experiments received ethical approval from the University of York Psychology Department Ethics Committee.

2.2.1.2 Materials and design

The novel sequences were designed so as to parallel the materials used in Szmalec et al. (2012) unless there was a clear reason to deviate. In contrast to Szmalec et al., (2012) where participants learnt 6 novel words, in our experiment we doubled this number. This was intended to improve statistical power and generalizability. We therefore created 24 trisyllabic CVCVCV novel nonwords that overlapped phonologically with existing English base words, with the intention that these could become new cohort competitors to the English words (Gaskell & Marslen-Wilson, 2002). In contrast to Szmalec et al. (2012), the English base words and novel nonwords differed in their final consonant and vowel to increase the phonological contrast between the two. For example, for the English base word *bikini* we created a novel nonword *bikiso* (see Appendix A for a complete list of English base words and novel nonwords). The 24 base words were all nouns ranging in frequency (SUBTLEX, Brysbaert & New, 2009) between 0.35 and 20.37 occurrences per million (mean: 4.44) and their uniqueness point was always located between the third and fifth phonemic position (Celex; Baayen, Piepenbrock, & van Rijn, 1993). The novel nonwords retained the stress pattern of their English base words, with primary stress falling on either the first or the second syllable. All materials were recorded in a soundproof booth by a native speaker of British English (MGG). The novel nonwords were recorded both as continuous trisyllabic forms and as three separate syllables for use in the Hebb repetition task. Care was taken to ensure that the vowels of the separate syllables matched those of the trisyllabic sequence. The sound files were normalised for maximum amplitude and all editing was performed in the Adobe Audition software (Adobe version 3.0).

The test items were then divided into two equal lists which were matched pairwise on the frequency of their base words. During training, participants heard 12 novel items (from one list, counterbalanced across participants). During the lexical integration test participants heard all 24 English base words; half of these had potentially acquired a new competitor (competitor condition) and the other half had not (control condition). This allowed estimation of the speed of recognition for each English base word, with and without influence of the novel competitor.

Participants were allocated randomly to one of two training procedures. In the phoneme monitoring task the novel words were heard as single trisyllabic forms. In the Hebb repetition task the novel words were presented as sequences of syllables and were

arranged specifically so that no syllable was repeated within one Hebb sequence of three trisyllable groupings (see Appendix A).

2.2.1.3 Procedure

The experiment spanned three sessions (see Figure 2.1). The first and third sessions were administered between 8 and 9 am and the second session between 8 and 9 pm. In the first session participants were exposed to novel sequences in either the phoneme monitoring or the Hebb repetition task. The first session took approximately 1 hour to complete for participants in the Hebb repetition group or 20 minutes for participants in the phoneme monitoring group. Participants returned to the laboratory after a 12-hour break for Session 2 and were instructed to refrain from taking a nap during that time. In the second session participants completed the pause detection task (in a 10-minute session). After another 12-hour break, this time including a normal night's sleep, the third session took place. Participants completed the pause detection task for a third time, followed by two tasks that measured the explicit knowledge of novel nonwords: cued recall and 2-alternative forced-choice (2AFC). Stimulus presentation over high-quality headphones, timing and data collection were controlled using DMDX (Forster & Forster, 2003), excluding the Hebb repetition task which was presented using E-Prime software.

In the *phoneme monitoring* task participants listened to each novel nonword and indicated whether a pre-specified phoneme (one of /p/, /n/, /d/, /r/, /m/ and /l/) was present. The target phoneme was the same throughout a block and specified on each trial by displaying the corresponding letter on the screen. The task was preceded by four nonword practice trials. Each item occurred 12 times, once per block and twice per target phoneme. The order of the novel nonwords was randomised within a block. Participants were instructed to respond as quickly as possible by pressing one button if the target was present at any location in the words or press another if it was absent. 250 ms after their response, or after 5,000 ms time-out, the next trial began. As is typical with these experiments, participants were explicitly instructed to try and memorise the novel nonwords as well as possible in preparation for future tests and to treat them as they were real words of English.

In the *Hebb repetition task* participants listened to ordered sequences of nine syllables. Importantly, care was taken to promote the implicit nature of the task, thus participants were not given any instruction relating to segmentation or chunking of the sequence, or to treat the items as real words. Each participant completed four blocks of 36 sequences each. In each block there was one Hebb sequence (containing three novel nonword sequences) presented repeatedly every third trial (12 times in total), and 24 filler sequences. Following the Hebb learning protocol (Couture & Tremblay, 2006; Guérard et

al., 2011; Horton et al., 2008; Johnson et al., 2013; Page et al., 2006) all nine syllables were presented consecutively one after another with 500 ms breaks in between. As in Szmalec et al. (2012), but in contrast to the majority of Hebb learning studies, the presentation of the three trisyllable groupings was permuted pseudorandomly. For example, the sequence "mih-mow-lee-row-zuh-no-lih-bee-may" could also be presented as: "row-zuh-no-lih-bee-may-mih-mow-lee"). The order of the syllables in sequences constituting the novel trisyllabic nonwords was always preserved (e.g., "mih" was always followed by "mow" and then "lee"). There were three practice trials at the beginning of the task, after which there was a pause when participants could ask questions. Each trial was followed by an immediate serial recall screen where participants were required to recall verbally the nine syllables in the sequence they were presented and then press the spacebar to move to the next trial. Their responses were recorded and later scored for accuracy. A sheet of paper with nine empty grids was provided to participants to help keep track of the number of syllables they were recalling. They were instructed to say "blank" if they could not recall a particular syllable in a sequence. Overall, participants learned four critical sequences through Hebb repetition across the session, each consisting of three trisyllable groupings that overlap with existing English words (see Figure 2.2 for a typical trial design). The nonrepeated filler sequences were constructed from different syllables than the Hebb sequences and presented in a random order on each filler trial.

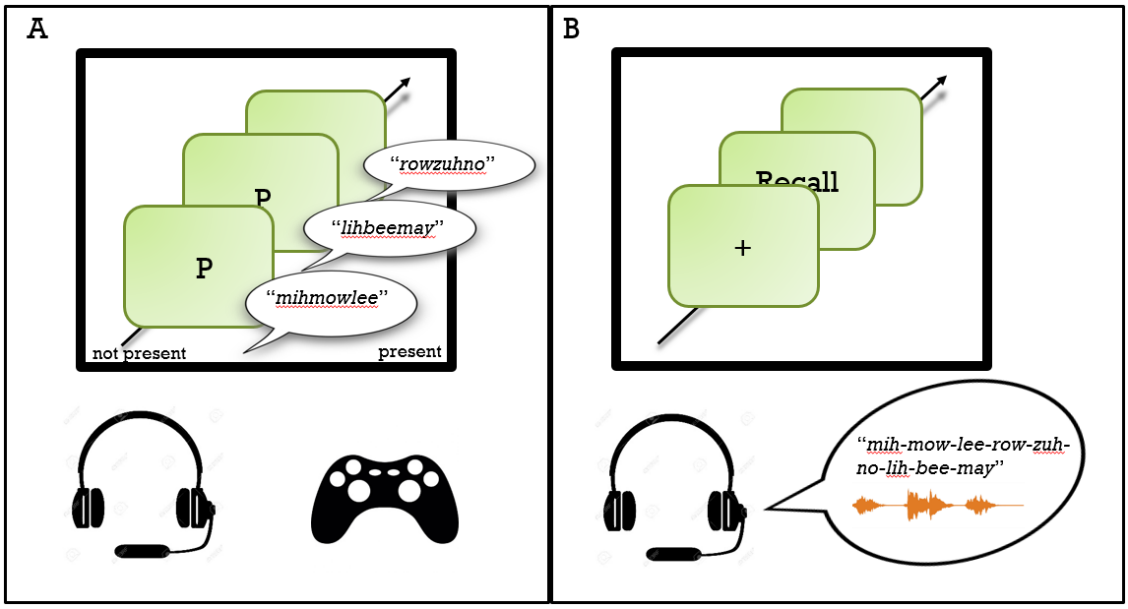

Figure 2.2. An illustration of three learning trials in the Phoneme Monitoring task (A) and one learning trial in the Hebb Repetition Task (B).

Each of the training sessions was followed by the *pause detection task*, which was intended as a measure of the extent to which the novel sequences had become lexical competitors to the base words and so could influence their recognition. Participants were required to make a speeded decision indicating whether a pause was present in each spoken stimulus by pressing one of two buttons. Stimuli comprised 24 existing words (12 with and 12 without novel competitors) and 56 fillers (40 of CVCVCV structure and 16 of a different structure). Half of the items contained a 200 ms pause inserted directly before the final CV (e.g. *biki_ni*). Four versions of the task were developed and counterbalanced across participants so that each item was equally represented in the four cells of the design (competitor, pause present; competitor, pause absent; control, pause present; control, pause absent). To encourage lexical processing, fillers were all existing words and half of them had a pause inserted at random locations. Response latencies were measured from the alignment point in the waveform that was used to mark pause onset. Participants had six seconds from stimulus onset to respond and each trial was preceded by a cross that appeared on the monitor for 500 ms. The trials were presented as a single block, ordered randomly for each participant. The task started with four practice trials.

In *cued recall* a stem completion test was used. During a typical trial participants heard the first three phonemes (e.g., *bik*-) of the novel nonwords from the exposure phase and were prompted by a cross on the screen to complete the sequence aloud using one of the new words they had encountered the previous day. Participants in the Hebb repetition condition were asked to recall the syllable sequences that were repeated more frequently than the other in the Hebb repetition task and finish the stem with the matching item. The time between the offset of the cue and the onset of the cross was 500 ms. The cross symbol remained on the screen for 6,000 ms to permit a verbal response before the next trial began. There were 12 randomised trials, each cueing one of the trained nonwords.

In the final *2AFC* test, participants heard two sequences: a novel nonword and its corresponding foil. The foils were constructed in a way that they differed from the novel word, and also its English base word, in their final syllable. For example, the novel word *bikiso* had the foil *bikita.* Participants listened to both sequences before responding with a button press to indicate which sequence had been heard during training. Participants saw an asterisk, displayed on the screen for 500 ms, and then heard the first sequence. After a 500 ms interval the second sequence was played followed immediately by a response instruction. Participants had 5,000 ms to make their response and were instructed to respond as quickly as possible. The order of novel nonword/foil pairs was randomised across trials and so was the order of items within each pair. The third session took approximately 20 minutes to complete.

2.2.2 Results

Data from 44 out of 48 participants were entered in analyses as described above, with 22 participants in each training condition.

In the *phoneme monitoring* task, all remaining participants scored at least 83% correct (mean 90%, *SE*= 1%). Of the error responses 6% were misses and 3% were false positive. There was no significant group difference across the experimental lists (p=.752). In the *Hebb repetition task*, as per standard Hebb learning protocol, a CV was scored as correct when recalled in the correct position in the sequence. For each individual participant, regression slopes were calculated for the effect of block on the Hebb sequences and filler sequences. Learning would be reflected in a steeper slope for the Hebb sequences. The gradient values were entered into a one-way repeated measures analysis of variance (ANOVA) with sequence type (filler versus Hebb) as the independent variable. There was a significant main effect of sequence type (F(1,21)=38.44, p<.001, η_p^2=.66) indicating higher improvement-gradient for Hebb sequences (M=.025, *SE*=.004) relative to fillers (M=.002, *SE*=.001). Therefore, the Hebb effect was obtained, which is a necessary precondition for considering the results of the pause detection task and the explicit tests (see Figure 2.3).

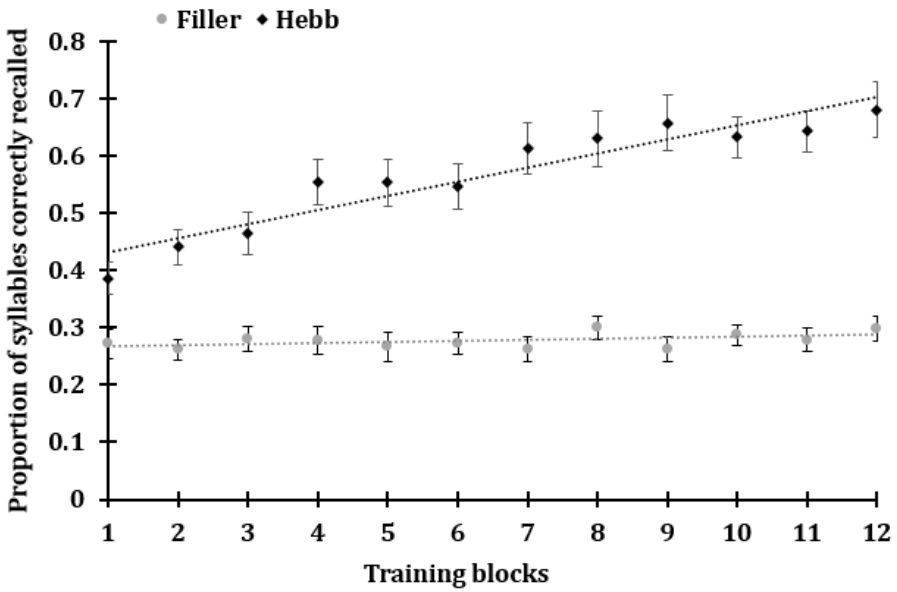

Figure 2.3. Accuracy (proportion correct) for Hebb and filler sequences in the Hebb repetition task (error bars depict standard error; regression lines illustrate the gradient of improvement in performance).

2.2.2.1 Pause detection

The data from two participants, one in the Hebb repetition task group and one in the phoneme monitoring group, were excluded from analyses due to more than 33% of

incorrect responses. RTs associated with errors, plus all RTs below 150 ms (Tamminen et al., 2010) or above 1,700 ms (Bakker et al., 2014) were removed from the data set. The RT and error data for experimental items are summarised in Table 2.1. The reported analyses focused on RTs, as is standard for this type of dependent variable.

Table 2.1
Mean Pause Detection Latencies (ms) and Error Percentages for Competitor and Control Conditions in Experiments 1 and 2.

		Experiment 1				Experiment 2	
	Training	Hebb Repetition Task		Phoneme Monitoring		Hebb Repetition Task	
	Condition	Competitor	Control	Competitor	Control	Competitor	Control
RT	0-hr	748 (36)	772 (40)	741(31)	734(32)	637 (23)	628 (30)
	12-hr	675 (32)	693 (33)	679(37)	644 (33)	546 (22)	556 (33)
	24-hr	669 (34)	656 (27)	672 (33)	665(36)	520 (21)	527 (27)
% Err	0-hr	1.6 (0.9)	2.4 (1.0)	1.2 (0.6)	1.6 (0.9)	9.0 (1.6)	5.3 (1.3)
	12-hr	0.4 (0.3)	2.8 (0.9)	2.8 (1.1)	2.0 (1.0)	9.0 (1.4)	7.9 (1.4)
	24-hr	1.2 (0.6)	0.8 (0.5)	5.2 (1.9)	1.9 (1.3)	7.2 (1.8)	7.2 (1.7)

Note. Standard error of the mean in parentheses.

RTs for pause present and pause absent trials were averaged across both trial types and RTs were analysed only for correct responses. The latencies were entered into a 2 (training task; phoneme monitoring and Hebb repetition task) × 3 (Session; 0-hr, 12-hr, 24-hr) × 2 (Competitor acquisition: competitor versus control), ANOVAs by participants and items (note that the items analyses were inadvertently left out of the pre-registration document, but are standard in this type of experiment). The analyses revealed that responses became faster over sessions ($F_1(2,80)=20.10$, $p<.001$, $\eta_p^2=.334$, $F_2(2,92)=89.86$, $p<.001$, $\eta_p^2=.661$) but there was no significant difference in responses in the competitor and control condition (Competitor acquisition, $F_1(1,40)=.16$, $p=.695$, $\eta_p^2=.004$, $F_2(1,46)=.039$, $p=.846$, $\eta_p^2=.001$). The interactions Session x Training, Session x Competitor acquisition and Session x Competitor acquisition x Training were nonsignificant ($F_1(2,80)=.69$, $p=.503$, $\eta_p^2=.017$, $F_2(2,92)=2.37$, $p=.099$, $\eta_p^2=.049$; $F_1(2,80)=.76$, $p=.471$, $\eta_p^2=.019$, $F_2(2,92)=.81$, $p=.448$, $\eta_p^2=.017$ and $F_1(2,80)=1.50$, $p=.232$, $\eta_p^2=.036$, F_2 $2,92)=0.59$, $p=.556$, $\eta_p^2=.013$ respectively). The Competitor acquisition x Training interaction was also nonsignificant ($F_1(1,40)=3.99$, $p=.053$, $\eta_p^2=.091$, $F_2(1,46)=2.45$, $p=.124$, $\eta_p^2=.051$), albeit with a slight trend towards overall stronger competition effects for phoneme monitoring than for Hebb

training. The between participants factor Training was also nonsignificant ($F(1,40)=.11$, $p=.746$, $\eta_p^2=.003$). The magnitude of the differences in the RTs to test and control base words are shown in Figure 2.4.

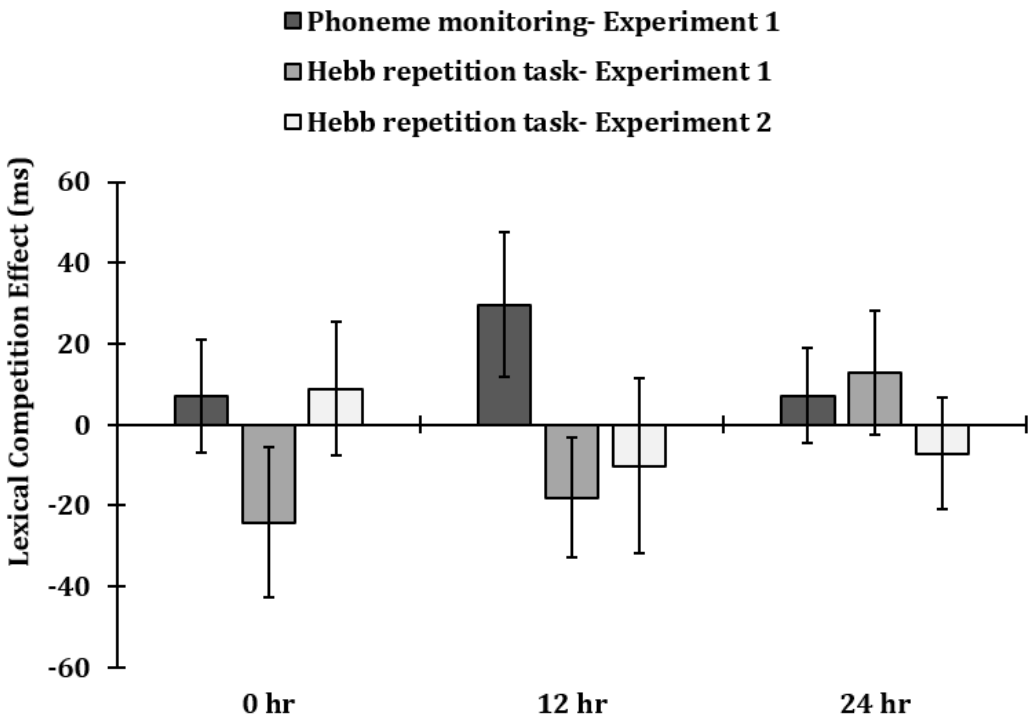

Figure 2.4. Lexical competition effect (competitor RT- control RT) across three sessions for phoneme monitoring (phoneme monitoring) and Hebb repetition (Hebb repetition task) in Experiment 1 and Experiment 2. Error bars represent standard error of the means and are not adjusted to facilitate within-participants' comparisons, given the mixed design (Cousineau & Brien, 2014).

In sum, the Hebb repetition and the phoneme monitoring groups did not show evidence of the lexical competition after delay, regardless of whether the delay contained sleep or not.

2.2.2.2 Cued recall

In the cued recall task responses were scored as accurate if first and middle syllables together with a final consonant were correct (for example, for the novel word *bikiso* the responses: *bikiso* and *bikisoo* were both scored as correct but not *bikiro*). This scoring system was motivated by two factors. Firstly, consonants arguably play a more important role in the acquisition and representation of words (Nazzi et al., 2005; Nespor et al., 2003). Secondly, participants' responses during the Hebb repetition indicated that there was some inconsistency in how participants encoded the novel words in the first place. For example,

some participants who recalled the novel word incorrectly (*bikisoo* instead of *bikiso*) repeated their mistake throughout the experiment indicating that they learned the incorrect form.

Participants' errors mostly involved the final syllable being replaced by the final syllable of another novel nonword or the final syllable of the base word. Performance in the cued recall task was relatively poor compared to other published studies (for comparison: above 40% Weighall et al., 2016; above 50% after 24 hrs in Henderson et al., 2013), with participants recalling 17% of the words heard in the training in the Hebb repetition group and 21% in the phoneme monitoring group (see Figure 2.5). The performance difference between the two groups was not significant ($t_1(40) = .59$, $p = .554$; $t_2(46) = .81$, $p = .421$).

2.2.2.3 2AFC

Mean accuracy and RT scores for the *2AFC* are presented in Figure 2.5. Participants recognised the novel nonwords at a level significantly above chance in both groups (Hebb repetition task: $t_1(20) = 22.47$, $p < .001$, $t_2(23) = 3.423$, $p = .002$; phoneme monitoring: $t_1(20) = 64.90$, $p < .001$, $t_2(23) = 23.78$, $p < .001$), with the phoneme monitoring group significantly more accurate than the Hebb repetition group ($t_1(29.43) = 8.96$, $p < .001$, $t_2(46) = 5.96$, $p < .001$). Comparison of the RTs showed that the phoneme monitoring group was significantly faster than the Hebb repetition group in recognising the novel phonological forms ($t_1(40) = 3.56$, $p = .001$, $t_2(46) = -4.21$, $p < .001$).

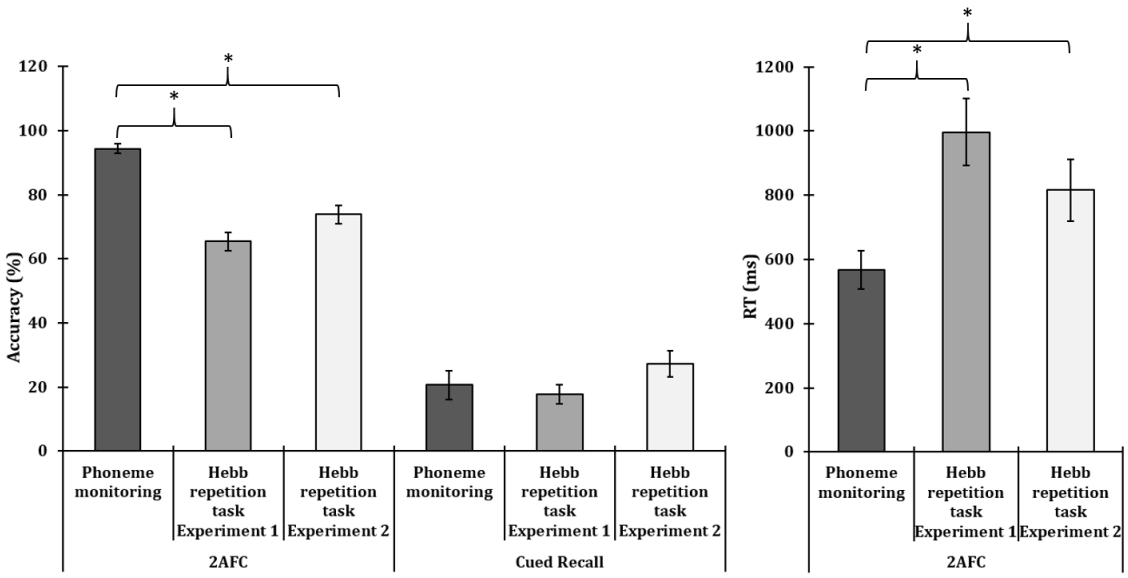

Figure 2.5. Mean percent correct on explicit tests for the Hebb repetition task and phoneme monitoring groups and mean RTs for both experimental groups in the 2AFC task. Error bars represent standard error.

In sum, although both groups recalled the novel nonwords at a low level (roughly 2 out of 12 words) the phoneme monitoring group showed superior direct recognition of the novel items in comparison to the Hebb repetition group.

2.2.3 Discussion

Experiment 1 compared the changes in dynamics of lexical competition between newly learned phonological forms and their English counterparts after two training tasks, the phoneme monitoring and the Hebb repetition task. We tested the integration of novel words at three time delays: immediately after training, after 12 hours wake period and after 24-hour period, allowing for an overnight sleep. The primary aim was to examine whether the Hebb repetition task, compared with more explicit learning, provides an opportunity for novel words to be better integrated with long-term lexical knowledge prior to sleep, as argued by Szmalec et al. (2012). The results did not support this hypothesis: there was no evidence of an engagement in lexical competition after learning via Hebb repetition. In fact, we did not observe lexical competition effects in either of the groups and regardless of whether or not the time delay included nocturnal sleep. Although the lack of lexical competition effects at any time point in the Hebb condition was a surprise, the lack of an effect for the more explicit learning condition was less so. We chose to match the level of exposure in both conditions to the relatively low level from Szmalec et al. (2012), given that this was sufficient in their Hebb paradigm. The prior evidence relating to this exposure level in explicit learning is more equivocal. For example, Gaskell and Dumay (2003b) did not find a lexical competition effect 24 hours post training when their participants were exposed to novel items 12 times, despite good recognition of the novel forms (as measured by 2AFC task). A second training session with 12 more exposures also did not lead to competition effects after a further 24 hours. Gaskell and Dumay found that the lexical competition effect only emerged after a third session, meaning a total exposure rate of 36 presentations. Later studies showed that an exposure rate of 36 allowed for the lexical competition to emerge after a time-course of 12 and 24 hours, provided that the delay contained sleep (Dumay & Gaskell, 2007; Dumay, Gaskell, & Feng, 2004). In other circumstances, however a lower exposure level seemed to be sufficient. Davis et al. (2009) found a somewhat weak lexical competition effect precisely after 12 presentations, although with a different lexical integration test (i.e. lexical decision) from the current one. It seems likely, given the current results that in an explicit learning task a relatively high level of exposure is needed to guarantee robust evidence of an impact of the novel words on the recognition of their existing neighbours, but that individual differences might contribute to the observation of an effect after weaker exposure in some cases.

As shown by the cued recall task, explicit knowledge of the novel items did not differ between two groups, which is in disagreement with our prediction based on prior studies. It was expected that the novel items encoded via the phoneme monitoring task would be better recalled than those encoded via Hebb repetition. After all, the phoneme monitoring training presented the novel items in isolation with a direct instruction to retain the forms, whereas Hebb repetition used long equally spaced sequences of isolated syllables and no explicit instruction to group the syllables or retain them in the longer term. However, both groups recalled approximately 20% of novel words. Previous studies that used explicit learning tasks typically showed above 40% accuracy in recall tasks (see Henderson et al., 2013; Weighall et al., 2016 for comparison). This indicates relatively poor knowledge of novel items in both our experimental groups. Nonetheless, as we predicted, the easier 2AFC recognition test revealed that the group that learned novel nonwords via the phoneme monitoring performed significantly better than the group that learned via the Hebb repetition task. This indicates that learning via the Hebb paradigm may lead to less explicit awareness of the repeated sequences.

Given that we did not find the expected impact of Hebb repetition learning on lexical competition, an obvious follow would be to increase the exposure level in training to a level at which we can be confident that explicit training will lead to lexical competition (e.g. Gaskell & Dumay, 2003b). The key question would then be whether Hebb repetition also shows lexical competition. However, one other possible explanation for the lack of a lexical competition effect was worth consideration. As in the standard Hebb learning protocol, Experiment 1 presented trials containing the three trisyllable sequences with no temporal cues to grouping. The desired grouping into trisyllables could only be determined from the transitional probabilities of syllable pairs (Saffran, Aslin, & Newport, 1996; Pelucchi, Hay, & Saffran, 2009; Saffran, 2002, 2003; Saffran, Senghas, & Trueswell, 2000) across Hebb blocks, due to the reordering of these fixed trisyllables in every Hebb block. However, the Hebb trials used by Szmalec et al. (2012) included a more overt cue to aid segmentation: 2,000 ms gaps between the three-syllable groupings. This methodological detail was not reported in Szmalec et al. (2012) but was clarified to us later by one of the authors. These quite long gaps could have both positive and negative aspects. In terms of segmentation, these grouping cues most likely helped to chunk the 9-syllable sequences into the appropriate word-like units. From this point of view, the cues would strengthen the ability of the implicit mechanisms underlying Hebb learning to acquire the appropriate phonemic sequences. At the same, the cues may increase awareness of the groupings as separable strings, perhaps reducing reliance on implicit learning mechanisms and increasing reliance on explicit mechanisms. Therefore, in Experiment 2 we examined whether the inclusion of these

temporal chunking cues alters the pattern of lexical engagement in the Hebb training condition. With regards to tests measuring explicit knowledge we predicted that the clearer chunking cues would enhance the declarative memory of the novel phonological forms.

2.3 Experiment 2

2.3.1 Method

In Experiment 2 we addressed the influence of the inclusion of temporal grouping cues in the Hebb repetition task on the lexical integration of novel items. Because the temporal grouping variable is only relevant to the Hebb effect style of learning, the phoneme monitoring condition was dropped for Experiment 2.

2.3.1.1 Participants

Twenty-two participants (15 females), aged between 18 and 25 (mean age 20.2 years), who hadn't taken part in Experiment 1, were trained on novel items using a new version of the Hebb repetition task. The criteria for participation were the same as in the previous experiments.

2.3.1.2 Material, design and procedure

The critical stimuli were the novel items used in Experiment 1. This time however, 2,000 ms silent gaps were inserted between the three trisyllable groupings constituting the Hebb and the Filler sequences (e.g., "*mih-moh-lee (...) roh-sah-noh (...) lih-bee-may*"). The experimental design, procedure and the experimental tasks were otherwise identical to the Hebb condition of Experiment 1. As the inclusion of the gaps was likely to make the grouping in the Hebb repetition task more transparent, upon completion of the experiment, participants additionally filled out a debriefing questionnaire to assess each participant's awareness of list repetition in the Hebb task and the objective of the experiment.

2.3.2 Results

In the Hebb repetition task, the recall accuracy and regression slopes were calculated according to the previously outlined criteria. The gradient values were entered into a one-way repeated measures ANOVA with sequence type (Filler versus Hebb) as the independent variable. There was a significant main effect of sequence type, $F(1,21)=38.96$, $p<.001$, $\eta_p^2=.65$ indicating a higher improvement-gradient for Hebb sequences (M=.025, *SE*=.004) relative to fillers (M=.004, *SE*=.001). Therefore, the Hebb effect was again obtained (see Figure 2.6).

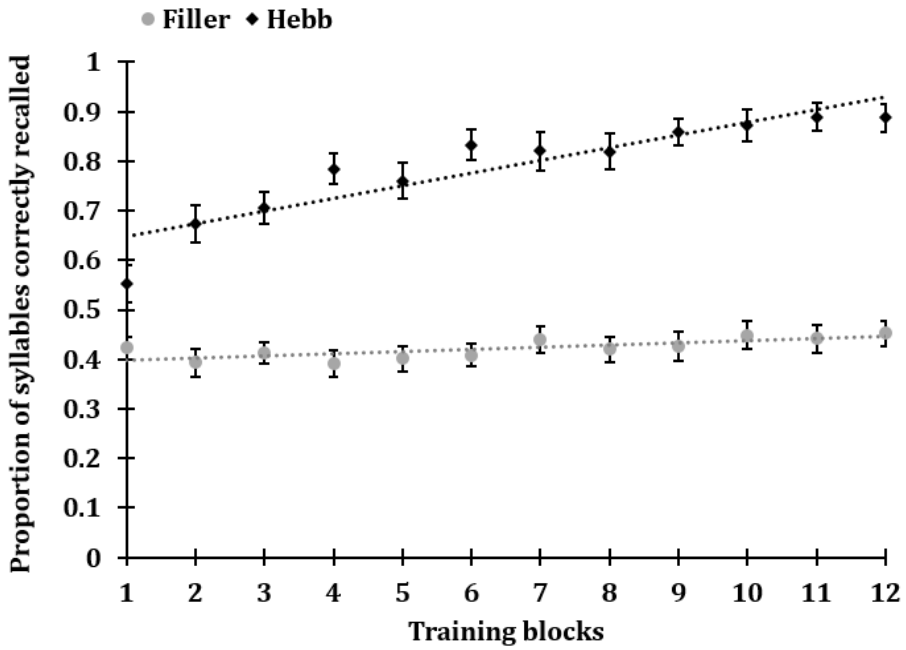

Figure 2.6. Accuracy (proportion correct) for Hebb and filler sequences in the Hebb repetition task. Values for filler trials represent the average of the two filler sequences presented between each of the Hebb sequences (error bars depict standard error; regression lines illustrate the gradient of improvement in performance).

2.3.2.1 Participant awareness

Of the twenty-two participants, fourteen (64%) were classified as being aware of syllable repetition and the study's aim on the basis of the post-experimental questionnaire. In their answers, participants either stated that they were aware of the syllable strings constituting novel nonwords or that the purpose of the Hebb repetition task was to learn novel words. Participants also listed some of the novel words in a syllabic form as examples.

2.3.2.2 Pause detection

Mean RTs and error data for experimental items are summarised in Table 2.1. The RT data were analysed using the same methodology and data exclusion criteria as in Experiment 1using 3 (Session; 0-hr, 12-hr, 24-hr) × 2 (Competitor acquisition: competitor versus control), repeated measures ANOVAs. The analyses revealed that responses became faster over sessions ($F_1(2,42)=16.69$, $p<.001$, $\eta_p^2=.443$, $F_2(2,46)=63.12$, $p<.001$, $\eta_p^2=.733$). There was no significant difference in responses in the competitor and control condition ($F_1(1, 21)=.052$, $p=.822$, $\eta_p^2=002$, $F_2(1,23)=2.76$, $p=.110$, $\eta_p^2=.107$). The interaction Session x Competitor acquisition ($F_1(2,42)=.53$, $p=.593$, $\eta_p^2=.025$, $F_2(2,46)=.04$, $p=.957$, $\eta_p^2=.002$) was nonsignificant (see Figure 2.4).

2.3.2.3 Cued recall and 2AFC

Responses in the cued recall task were scored as in Experiment 1. The inclusion of gaps between the virtual nonwords appeared to result in more items being recalled (27%) in comparison with the Hebb condition of the previous experiment, although this difference did not reach significance level ($t_1(41)=-1.95$, $p=.058$; $t_2(34.06)=-2.02$, $p=.051$). A cross-experiment comparison of recall accuracy also revealed no difference between the phoneme monitoring group from the Experiment 1 and the Hebb group in Experiment 2 ($t_1(41)=-1.18$, $p=.270$, $t_2(46)=-1.38$, $p=.175$).

In the *2AFC* task participants recognised the novel nonwords at a level significantly above the chance ($t_1(21)=25.61$, $p<.001$, $t_2(23)=5.20$, $p<.001$). Comparison between Experiment 1 and Experiment 2 in the explicit recognition test showed that despite an increased recognition level in the Hebb group in Experiment 2, the phoneme monitoring group still recognised significantly more items ($t_1(41)=6.32$, $p<.001$, $t_2(46)=4.15$, $p<.001$) and was also significantly faster in providing their responses ($t_1(41)= -2.17$, $p=.036$, $t_2(46)=-3.18$, $p=.003$). The difference in recognition scores for the two Hebb repetition groups showed that including temporal cues resulted in a significantly better recognition of novel items in the by-participants ($t_1(41)=-2.06$, $p=.046$) but not the by-item analysis ($t_2(46)=-1.32$, $p=.195$). There was no difference with regards to RTs between the two Hebb repetition task groups ($t_2(41)= 1.28$, $p=.207$, $t_2(46)= 1.60$, $p=.117$).

In sum, although provision of the temporal grouping cues resulted in a better recognition of novel items, the phoneme monitoring group was still superior in direct recognition of the novel items in comparison to the Hebb repetition group.

2.3.3 Discussion

Experiment 2 tested whether the inclusion of segmentation cues in the Hebb repetition task would support the emergence of lexical integration of novel items. Despite the inclusion of the gaps in the Hebb sequences we did not find any evidence of lexical integration of novel items. In fact, the trend for this comparison was in the opposite direction to that predicted (i.e., facilitation not competition). This result draws into question the generality of the competition effect found by Szmalec et al. (2012). The grouping of the sequences added an extra cue in favour of chunking into trisyllabic wordlike units and increased the explicitness of the task. Encouraging participants to chunk information in a specified manner may have increased task transparency and made participants notice the repetitions. Indeed, analysis of the debriefing questionnaire showed that 14 out of 22 participants (64%) noticed the patterns in syllables and showed awareness as to the task aim. Importantly, Experiment 1 and Experiment 2 provide converging evidence that despite

varying the segmentation cues available to participants, the time-course of engagement in lexical competition reported by Szmalec et al. (2012) does not apply in the current circumstances.

As Experiment 2 ruled out the possibility that grouping cues are the crucial element of the Hebb repetition task needed to show engagement in lexical competition prior to sleep, the obvious follow up was to test if an increased number of exposures would impact the pattern of lexical competition effects. As stated earlier, we know that increased exposure should lead to lexical competition after a delay including sleep for more explicit training (Gaskell & Dumay, 2003b). Perhaps an equivalent increase in exposure for Hebb repetition will be similarly beneficial. Therefore, in Experiment 3 we tested whether tripling the number of exposures to each novel word (36 presentations) would support the emergence of lexical integration in both training conditions. In this experiment, we also simplified the design of the experiment by eliminating the intermediate 12-hour test condition. Our reasoning was that if the increased number of exposures in Hebb repetition led to competition effects after 24 hours then we could run a further experiment to determine if the effect was also present after 12 hours with or without sleep. However, if the effect was not present after 24 hours then there would be no reason to think that it would emerge after 12 hours.

2.4 Experiment 3

2.4.1 Method

In Experiment 3 we tripled the amount of exposure to each novel nonword and tested immediately and after 24 hours for the emergence of lexical competition. Both Hebb repetition and phoneme monitoring training methods were used.

2.4.1.1 Participants

Sixty students from the University of York (forty-six females) participated in this experiment for course credit or financial reward (£6/hour). Their mean age was 20.5 years (ranged from 18 to 31). The criteria for participation were the same as in the previous experiments.

2.4.1.2 Materials, design and procedures

The critical stimuli were as in the previous experiments. The Hebb repetition task protocol followed that of Experiment 2 in employing grouping cues (i.e. gaps between three-syllable sequences). This time we increased the number of exposures in both tasks to 36. As mentioned above lexical integration was tested at only two time delays: immediately and

24 hr after encoding. Although the two sessions were always separated by 24 hours, the time of testing itself varied across the day, allowing participants to attend at a wider range of times. Due to the time consuming nature of Hebb repetition training, a simple tripling of the exposure session from Experiment 2 was not feasible in terms of participants' fatigue, as the Hebb repetition training would require over 3 hours to complete. Therefore, we made an adjustment to the ratio of Hebb to filler sequences. Namely, although the Hebb and the Filler sequences were still interleaved, there was only one Filler sequence following two successive but distinct Hebb sequences, each containing different sequences of syllables. Previous studies have demonstrated successful concurrent learning of several different Hebb sequences (Page, Cumming, Norris, McNeil, & Hitch, 2013; Saint-Aubin, Guérard, Fiset, & Losier, 2015). As a result, the order of the presentation of Hebb and Filler trials was: Hebb sequence 1, Hebb sequence 2, Filler sequence. As before there were 4 Hebb sequences in total (three novel words per sequence, so 12 novel words in total), which resulted in 1 hour and 45 minutes to complete the Hebb repetition task. As in Experiment 2, following completion of all experimental tasks, a debriefing questionnaire was administered to determine whether participants were aware of learning novel words. As the phoneme monitoring group was specifically instructed to memorise novel items to increase the explicitness of the training, we expected higher awareness score in this experimental group in comparison to the Hebb repetition group.

2.4.2 Results

For the Hebb repetition training, recall accuracy and regression slopes were calculated according to the previously outlined criteria (see Figure 2.7). The gradient values for Filler and Hebb trials were significantly different, $F(1,29)=46.33$ $p<.001$, $\eta_p^2=.615$ indicating a higher improvement-gradient for Hebb sequences (M=.009, *SE*=.001) relative to fillers (M=.002, *SE*=.001). Therefore, the Hebb effect was obtained. Inspecting the accuracy scores more closely, it is worth noting that, unlike the previous experiments, there was some evidence that scores were flattening out towards the end of training, suggesting that the extended training had led to participants reaching a ceiling of learning.

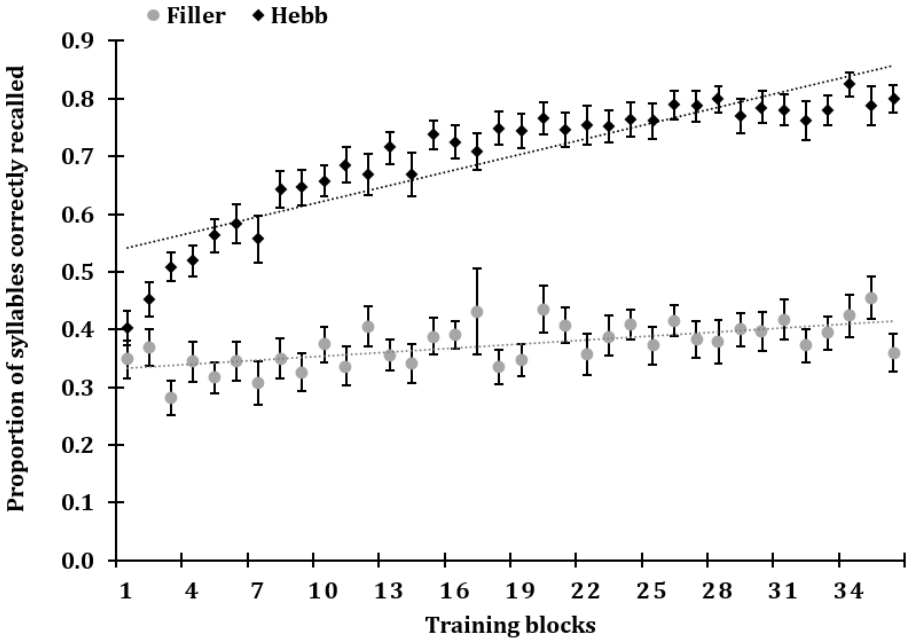

Figure 2.7. Accuracy (proportion correct) for Hebb and filler sequences in the Hebb repetition task. Values for filler trials represent the average of the two filler sequences presented between each of the Hebb sequences (error bars depict standard error; regression lines illustrate the gradient of improvement in performance).

2.4.2.1 Participant awareness

In the Hebb repetition group, twenty-one out of thirty participants (70%) reported being aware of the repetition of syllable lists and that they constituted of novel words. Participants' responses listed recognising and learning novel words as an experimental aim. In comparison, in the phoneme monitoring group 97% of all participants stated that learning new words was the aim of the experiment.

2.4.2.2 Pause detection

Mean RTs and error data are summarised in Table 2.2. As in the previous experiment only RTs were analysed for the lexical competition task.

After pre-processing as before, the response latencies were entered into a mixed-design ANOVA with the factors Session (0-hr, 24-hr) and condition (Competitor acquisition: competitor versus control), as repeated measures factors, and training task (phoneme monitoring vs. Hebb repetition) as a between-subjects but within-items factor. The analyses revealed a main effect of Session ($F_1(1,58)=49.57$, $p<.001$, $\eta_p^2=.461$, $F_2(1,46)=186.17$, $p<.001$, $\eta_p^2=.802$), whereas the main effect of training task was nonsignificant in the by-subject analysis (F_1 $(1,58)=2.70$, $p=.106$, $\eta_p^2=.044$) but significant in the by-items analysis ($F_2(1,58)=28.26$, $p<.001$, $\eta_p^2=.381$). Two interactions were also significant: Session x Competitor acquisition ($F_1(1,58)=8.65$, $p=.005$, $\eta_p^2=.013$, $F_2(1,46)=8.65$, $p=.046$, $\eta_p^2=.084$)

and Session x Training (F_1(1,58)=4.65, p=.035, η_p^2=.074, F_2(1,46)=16.46, p<.001, η_p^2=.264). As illustrated in Figure 2.8, the Session x Competitor acquisition interaction was an indication of a general shift towards stronger lexical competition after 24 hours. Although the Session x Competitor acquisition x Training interaction was nonsignificant (F_1(1, 58)=1.44, p=.235, η_p^2=.024, F_2(1,46)=0.88, p=.354, η_p^2=.019), the Session x Training interaction motivated follow-up analyses split by the type of training. For the phoneme monitoring group there was a significant effect of Session (F_1(1,29)=15.80, p<.001, η_p^2=.353, F_2(1,23)=66.94, p<.001, η_p^2=.744), with response latencies being significantly shorter in Session 2 in comparison to Session 1, and a significant Session x Competitor acquisition interaction (F_1(1,29)=9.58, p=.004, η_p^2=.248, F_2(1,23)=5.74, p=.025, η_p^2=.200) indicating that the RTs to the test base words became slower in comparison to the control base words (by 24 ms) in the second session that took place 24 hours after the initial learning phase (F_1(1,29)=5.86, p=.022, η_p^2=.168, F_2(1,23)=4.77, p=.039, η_p^2=.172).

Table 2.2
Mean Pause Detection Latencies (ms) and Error Percentages for Competitor and Control Conditions in Experiment 3

Training		Hebb Repetition Task		Phoneme Monitoring	
		Competitor	Control	Competitor	Control
RT	0-hr	747 (29)	758 (28)	666(29)	681(25)
	24-hr	622 (16)	616 (19)	615 (21)	590(17)
% Err	0-hr	7.8 (1.1)	6.7 (1.0)	6.9 (1.2)	7.8 (1.4)
	24-hr	7.5 (1.3)	6.9 (1.1)	6.6 (1.0)	5.3 (9.3)

Note. Standard error of the mean in parentheses.

The same analysis for the Hebb group, yielded a significant main effect of Session (F_1(1,29)=33.98, p<.001, η_p^2=.540, F_2(1,23)=119.29, p<.001, η_p^2=.838) however the Session x Competitor acquisition interaction was nonsignificant (F_1(1,29)=1.37, p=.251, η_p^2=.045, F_2(1,23)=.51, p=.482, η_p^2=.022), and there was no significant competition effect after a 24 hour delay (6 ms difference in RTs to test and control base words; F_1(1,29)=.45, p=.508, η_p^2=.015, F_2(1,23)=.37, p=.550, η_p^2=.016). Therefore, it appears that the shift towards stronger lexical competition after a consolidation period was driven largely by the phoneme monitoring training.

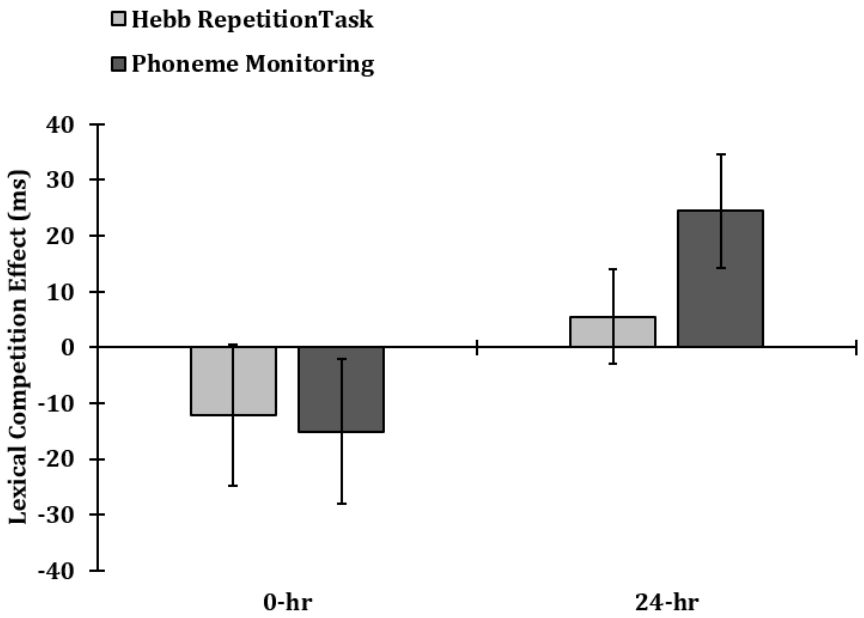

Figure 2.8. Lexical competition effect (competitor RT- control RT) across two sessions for phoneme monitoring and Hebb repetition groups. Error bars represent standard error of the means and are not adjusted to facilitate within-participants comparisons, given the mixed design (Cousineau & Brien, 2014).

2.4.2.3 Cued recall and 2AFC

The responses in the cued recall task were scored as in Experiment 1 and 2. The increased number of presentations of novel nonwords resulted in higher recall in both groups in comparison to the previous experiment where less than 30% of items were recalled. The Hebb repetition group recalled 43% of novel items and the phoneme monitoring group significantly more (58%; $t_1(58)= 2.96$, $p=.004$, $t_2(46)=2.79$, $p=.008$). Similarly, in the 2AFC task both groups scored above the chance level (Hebb repetition task: $t_1(29)=18.93$, $p<.001$, $t_2(23)=9.53$, $p<.001$; Phoneme monitoring: $t(29)=33.94$, $p<.001$, $t_2(23)=28.67$, $p<.001$), with the phoneme monitoring group recognising significantly more items (93% vs. 84%) ($t_1(58)=3.88$, $p<.001$, $t_2(46)=2.08$, $p=.043$) with shorter RTs ($t_1(58)=-4.23$, $p=<.001$, $t_2(46)=-5.89$, $p<.001$). The results of the explicit tests are illustrated in Figure 2.9.

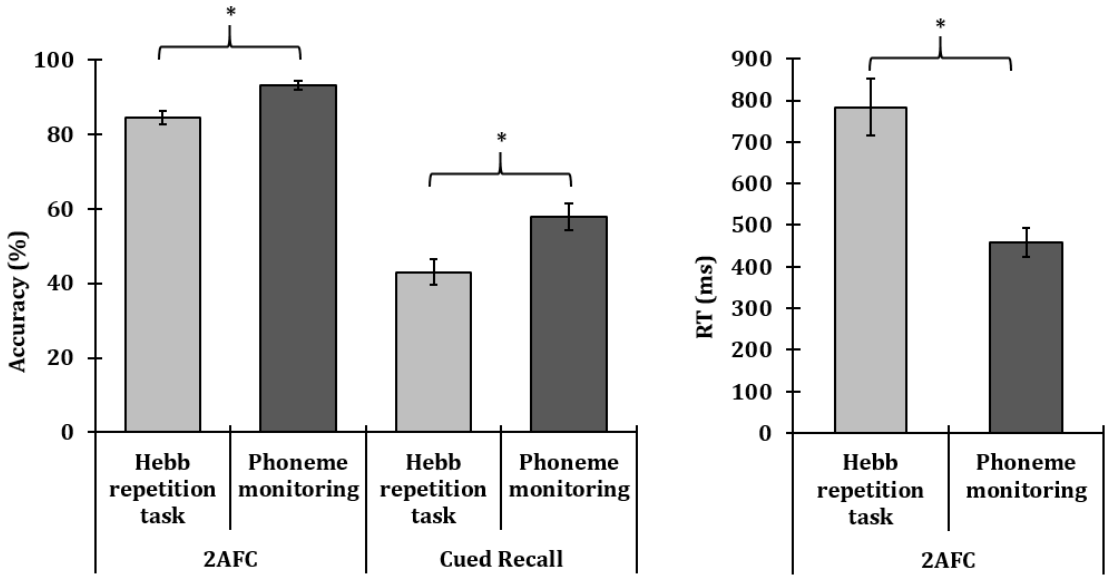

Figure 2.9. Mean accuracy in the explicit tests for the Hebb repetition task and phoneme monitoring groups and mean RTs for both experimental groups in the 2AFC task. Error bars represent standard error of the means.

2.4.3 Discussion

Experiment 3 investigated whether an increased number of exposures would lead to a better encoding of the novel nonwords and aid lexical integration of novel items. Unlike previous experiments, we found a change in the lexical competition profile over time, with stronger competition after a day than immediately after encoding. Although there was no three way interaction in the analyses, an interaction between type of training and session suggested differences in the effect of time for the two types of encoding. When the training methods were tested separately, there was evidence of lexical competition emerging only after a delay for phoneme monitoring, but no similar evidence for Hebb repetition.

The extended encoding session the Hebb repetition condition allowed 12 syllable sequences to be encountered 36 times each over a period of almost 2 hours. Despite this high level of exposure (three times that used by Szmalec et al., 2012) there was no evidence of these sequences engaging in lexical competition immediately after or 24 hours later. On the other hand, and in contrast to Experiment 1, we found a significant lexical competition effect after a 24 hour delay in the phoneme monitoring condition. This suggests that a good level of encoding and a consolidation delay that contains sleep are beneficial for lexical integration of new items learned explicitly, which stands in agreement with previous studies on novel word learning (Bakker et al., 2014; Davis et al., 2009; Dumay & Gaskell, 2007; Gaskell & Dumay, 2003b; Henderson et al., 2012).

It is possible that the observed results are not so much dependent on the different learning mechanisms utilised by the two groups, but are more a consequence of the fact that participants never encountered the new items as whole words in the Hebb task, and so the acoustic mismatch between the isolated syllables of the novel item (e.g., "*bih-kee*") and the onset of the contiguous existing word (e.g., *bikini*) was too great to influence lexical competition. This is indeed quite feasible, but it is worth noting that part of the argument underlying the Hebb task as a model of learning is that chunking will automatically and implicitly generate continuous "word" sequences. Indeed the original study by Szmalec et al. (2012) demonstrated effects of lexical competition for isolated syllables that were presented in writtten form, which clearly have even less overlap with the contiguous spoken word sequences. Therefore this cannot be the whole story. Furthermore, the performance of the Hebb group when asked to explicitly recall the syllable sequences was reasonably good (43%) and their ability to pick out these sequences from foil sequences when presented with the syllables contiguously was even better (84% correct). Based on the debriefing questionnaire, which participants filled out upon the completion of the experiment, as many as 70% of the Hebb group reported to be aware that separate strings embedded in the Hebb sequences consisted of novel words. The debriefing questionnaire results together with improved performance in the cued recall and 2AFC tasks suggest that it is unlikely that participants did not extract the novel syllable sequences in any form.

2.5 General Discussion

The research presented here is the first attempt to evaluate the lexical impact of two different approaches to word learning by comparing a largely explicit form of training utilising phoneme monitoring with a more implicit Hebb repetition paradigm. In a series of three experiments we tested whether the Hebb repetition procedure would faciliate the time course of lexical integration of novel words compared with a more explicit phoneme monitoring task. We found no evidence that the Hebb-style learning leads to better integration of novel items in comparison to explicit training. In fact, our results suggest that the novel items were not integrated well after the Hebb repetition training and argue against the Hebb repetition learning as a specific mechanism for learning new words.

Across the three experiments we manipulated the properties of the Hebb repetition task and the number of exposures to novel items. Specifically, with regard to the Hebb task, in Experiment 1 we used a version of the task which has been typically used in Hebb studies. This meant that we did not provide any temporal grouping cues to boundary locations, with only statistical information marking the potential word boundaries. This changed in

Experiment 2 where we supplemented the statistical cues with temporal cues to word boundaries following Szmalec and colleagues (2012). Finally, in Experiment 3 we employed the same temporal and statistical cues but tripled the number of exposures to novel nonwords. Despite our manipulations, in all three experiments we found no evidence that Hebb-style learning leads to accelerated integration of novel items prior to sleep. In fact, even after sleep we found no evidence of Hebb repetition leading to competition between novel and existing words.

Several studies have reported succesful lexical integration of novel words following the Hebb repetition task (Bogaerts, Szmalec, Hachmann, Page, & Duyck, 2015; Szmalec et al., 2012). Thus, it is possible that the lack of Hebb effect observed in our study reflects the failure to reach significance levels for a real but not substantial underlying effect. Thus, in order to test our findings with more statistical power, we ran a meta-analysis of all Hebb repetition learning conditions. Based on Szmalec et al. (2012), the lexical competition effect should be present after 12 hours or more regardless of whether the delay between learning and testing contained sleep. Hence, in our experiments it should be observed after both 12 and 24-hour delays in Experiments 1 and 2 and after 24 hours in Experiment 3. Therefore, we analysed the Hebb condition pause detection competition effects combined from these five conditions. The results showed that two out of the five conditions showed a numerical difference in the predicted direction (13 ms, 6 ms) and three showed a difference in the non-predicted direction (-18 ms, -10 ms, -7 ms). Overall the difference was in the nonpredicted direction (-3 ms) and was not significant ($F_1(1, 111) = .261$, $p = .611$, $\eta_p^2 = .002$; $F_2(1, 23) = .447$, $p = .510$, $\eta_p^2 = .019$).

To check the informativeness of this null result, we computed the Bayes Factor (BF; Dienes, 2014) for the overall Hebb effect of -3 ms in comparison with the effect for more explicit training found after a delay given sufficient exposure in Experiment 3 (24 ms). The BF allows statistical assessment of the strength of evidence for or against a null hypothesis, with a BF of 3 or more indicating substantial evidence against the null hypothesis and of 1/3 or less as evidence for the null hypothesis. The BF was calculated according to Dienes (2008) resulting in a value of .19 based on the participants analysis and .23 based on the items analysis. Thus our data provide substantial evidence for the null hypothesis that Hebb repetition in our study did not induce lexical competition after delays of 12-24 hours.

The three experiments looked at different factors that could impact the learning process and the emergence of lexical competition for Hebb repetition, such as segmentation cues in the Hebb repetition task, the level of exposure and the time available for consolidation. The inclusion of grouping cues and increased exposure level to novel nonwords resulted in higher transparency of the Hebb task and thus its reduced

implictness. Yet, we still did not observe any competition effects emerging in the Hebb condition. On the other hand, the level of exposure was important for the explicit condition leading to lexical competition after a 24 hour delay in Experiment 3. Similarly, the explicit measures of memory for novel items indicated better performance after the explicit training in comparison to the Hebb task. This suggest that two factors provide optimal conditions for the emergence of lexical competition: a good level of initial explicit encoding and a time delay that includes sleep. These findings are consistent with previous studies on word learning (Bakker et al., 2014; Davis et al., 2009; Dumay & Gaskell, 2007; Gaskell & Dumay, 2003b; Henderson et al., 2012) and fit well with the CLS account (Davis & Gaskell, 2009) described in the introduction. Still, we do not rule out the likelihood that in different circumstances there are other neural mechanisms that support word learning (cf. McMurray et al., 2016). Nonetheless, we do not find any evidence in this study that the implicit mechanisms that underlie Hebb repetition can lead to similar engagement in lexical competition.

A recent study by West, Vadillo, Shanks, and Hulme (2017) has shown that explicit measures of memory are indeed more relevant to language learning than implicit measures. The authors tested 7-8 year old children on a large battery of explicit and implicit memory tests to determine which were predictive of good language and literacy attainment. They showed strong associations between the explicit declarative memory tests and attainment (e.g. word list learning). The contrary was true for the implicit tests. Interestingly, explicit immediate serial recall performance—as used in the Hebb repetition task—was a good predictor of language attainment but the implicit gain attributed to Hebb repetition was a poor predictor. These results cast doubt on the fact that implicit learning skills are crucial to language learning and may underlie some language learning disorders (Ullman, 2004)

Given the differential results obtained in this study and in Szmalec and colleagues (2012) it is important to consider the underlying factors that could impact the presence or absence of this effect. There were, unavoidably, several differences between the two sets of studies. One potential explanation of these different results could be the number of words to be learnt. Szmalec et al., (2012) used six novel nonwords, whereas in our study we used twice as many (the number of exposures was kept the same in Experiment 1 and 2). It is possible that the number of words that can be learnt via the Hebb task is limited and by employing more words we overloaded the learning mechanism. However, robust Hebb effects were found in all our experiments, indicating good learning of the sequences and 2AFC recognition of the form of the novel words in this condition was reasonable (above 70% in Experiment 2; above 80% in Experiment 3) which contradicts this argument. Therefore, a more plausible explanation would be that the lexical knowledge obtained in

the Hebb task was insufficient to influence recognition of neighbouring existing words in the lexical integration test. The poorer nature of lexical representation following the Hebb task could be due to dual learning in the Hebb repetition task where errors can be learnt across trials (Couture & Tremblay, 2006). For example, the incorrect responses can be replicated increasingly over subsequent repetitions and account for the lack of sequence learning (Lafond, Tremblay, & Parmentier, 2010). Thus, the Hebb repetition effect can be related to both a response learning as well as stimulus processing. This however, argues against the Hebb repetition as an efficient way of learning new words.

Another difference that does not seem likely to be influential is the modality of presentation. Szmalec and colleagues used written syllables (in Dutch), but for English these would have been too ambiguous in pronunciation and so we opted for spoken syllables to ensure that the correct vowels were learned. But the use of spoken syllables would seem to enhance the likelihood of competition in the auditory modality, given that Bakker et al. (2014) found that transfer from written word learning to engagement in auditory lexical competition is delayed compared with the opposite transfer or intramodal effects.

An alternative explanation and most likely cause of the difference in Hebb repetition effects between studies relates to the relationship between the novel and existing words. As mentioned, similar to previous explicit word-learning studies, we used novel items that were fairly distinct neighbours of their English counterparts (i.e. deviating in the full final syllable) as opposed to the Szmalec and colleagues Hebb repetition studies, which used items that more closely overlapped with their English base words (i.e. only the final vowel deviation). In doing this, we wanted to test whether any effects of the Hebb repetition procedure would extend to competition neighbourhoods more generally. Perhaps then the minimally deviant nonwords used by Szmalec and colleagues in their studies actually activated the neighbouring words (Cutler, Sebastián-Gallés, Soler-Vilageliu, & van Ooijen, 2000; van Ooijen, 1996) in a way that led to the novel word being treated as matching the existing word, perhaps as a new phonological variant (Bürki & Gaskell, 2012) requiring less lexical processing. This automatic activation of similar sounding English neighbours would not occur in our study due to the more substantial mismatch between novel and existing words. In that way, it is the type of material to be learnt that determines the learning route.

A complementary systems account in fact predicts that both systematicity and similarity to acquired knowledge can influence the time needed to consolidate new material (McClelland, 2013; Mirković & Gaskell, 2016). For example, Mirković & Gaskell, (2016) found that learning new past tense forms that were closely overlapping with existing past tense forms did not benefit from sleep-dependent consolidation whereas learning distinct past tense forms did. Here, the sleep benefits, and hence hippocampal involvement,

depended on the overlap between new and existing language. The congruency of the new form with similar items may dictate the necessity of recruitment of the hippocampus to learn the new form, and hence the reliance on consolidation for cortical integration. The hippocampal route should be more necessary for acquiring new and distinct episodic memories, while the neocortical pathway utilises a similarity between novel and existing mappings to facilitate learning. (O'Reilly, Bhattacharyya, Howard, & Ketz, 2014). Thus we speculate that the competitors used by Szmalec and colleagues can be learned reasonably well through adjustment of existing cortical networks due to their close similarity to existing words. However, in a more typical learning context most novel words are more distinct neighbours of existing words (more than a final vowel-change). This would mean that the existing cortical network is less able to adapt to accommodate the new lexical item and so the hippocampus has a stronger role to play, implying more substantial consolidation effects post-encoding. Some evidence for this argument comes from a study of novel word learning in French. Here, Bürki, Spinelli, and Gaskell (2012) taught participants novel monosyllabic spoken forms that could potentially be reduced forms of a bisyllabic word (e.g., participants learned "plour", which might be a reduced form of "pelour"). Interestingly, the newly learnt information did not show any influence of consolidation over 24 hours. In that way, the authors showed that the type of learning experience and the similarity of the new form to an existing form can shape the need for consolidation. This and similar studies using more regular variants of exisitng words (Snoeren, Gaskell, Maria, & Di Betta, 2009) add strength to the argument that single vowel deviations from existing words might rely less on consolidation than more distinct deviations.

2.6 Conclusions

Lexical integration of novel words was tested in three experiments using the Hebb repetition task as an example of implicit statistical learning and phoneme monitoring as a more explicit means of familiarisation. We observed evidence for engagement of the novel words in lexical competition only for the more explicitly trained words, and only when the initial exposure level was high. Successful lexical integration of novel items appears to benefit from a sufficient level of explicit exposure followed by a consolidation opportunity that includes sleep. Our findings do not provide evidence for the implicit mechanisms underlying Hebb repetition as effective for learning and, particularly, integration of verbal material. While we do not doubt the value of implicit and statistical learning mechanisms for language learning more generally, it appears that explicit memory systems play a crucial role in acquiring and retaining information about word forms. Discrepancies between our

findings and previous studies of the Hebb repetition effect may be a consequence of the level of overlap between novel and existing words. When overlap is very high the requirement for consolidation may be reduced, but for the more general process of acquiring lexical neighbours, offline consolidation appears to be a crucial part of the process.

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CHAPTER 3
TARGETED MEMORY REACTIVATION IN LANGUAGE LEARNING

Reactivating memories during sleep by re-exposure to associated memory cues improves memories recall. Here, we tested whether applying non-verbal cues during sleep can improve learning of novel words as well as their integration within existing lexicon. Re-exposure to environmental sounds associated with novel words at encoding led to a better memory for cued novel words as compared with non-cued words. Analysis of electroencephalographic data revealed that successful cueing with sounds in SWS was associated with a reduced fronto-central negativity in event-related potentials and a cueing-related increase in fast spindle activity. With regards to lexical integration of novel items, the cueing in sleep not only failed to improve lexical integration of novel tokens but we did not observe any integration of both cued and non-cued words. Our results indicate that non-verbal cueing during SWS improves consolidation of episodic traces of associated memories and facilitates their later recall. The lack of lexical integration observed in our study calls for future investigations.

3.1 Introduction

Substantial evidence suggests that sleep dependent memory consolidation supports learning of new vocabulary. In the context of word learning, consolidation refers to a gradual process whereby a newly learnt word is integrated into pre-existing lexicon (Davis & Gaskell, 2009). In other words, after a sleep-supported lexical integration process has taken place, the novel word gains properties similar to already known words. Sleep is understood to play a particularly important role in consolidation of memory (Born & Wilhelm, 2012). Sleep was shown to stabilise and strengthen individual memories (Diekelmann & Born, 2010) as well as help their integration into pre-existing memory networks (Davis & Gaskell, 2009). The longstanding models of memory consolidation, such as the Complementary Learning Systems (CLS) model (McClelland et al., 1995) provide an account for these processes in which memories are supported by two systems, a hippocampal and a neocortical system. The temporary hippocampal system is fundamental to the encoding of new memories, whereas the neocortical system provides a long-term storage for consolidated memories. By the CLS account, sleep offers an ideal medium for transfer of newly encoded information from the hippocampus into the neocortex where they become embedded over time. The idea of cross-talk between the two systems is

consistent with evidence for hippocampal replay during sleep from both animal and human studies (Rudoy et al., 2009; Schreiner & Rasch, 2014; Wilson & McNaughton, 1994).

3.1.1 Memory reactivation in sleep

On the one hand, and in accordance with what was once believed to be a primary role of sleep, sleep offers a protection from retroactive interference processes whereby acquiring new information contributes to forgetting of and impeding the recall of previously learnt material. On the other hand, however, recent research has uncovered more of an active role for sleep and has shown that sleep actively contributes to memory formation via reactivation and strengthening of newly encoded memory traces.

The standard two-stage model of memory forms a basis for conceptualising the function of sleep for memory as a process supporting active system consolidation (Diekelmann & Born, 2010; Marshall & Born, 2007). According to the active system consolidation hypothesis, the beneficial role of sleep in memory consolidation is due to a spontaneous and repeated reactivation of newly acquired information taking place during subsequent night. In particular, a distinct neurophysiology of slow wave sleep (SWS) is thought to be particularly important for these consolidation processes (Born, Rasch, & Gais, 2006; Diekelmann, Biggel, Rasch, & Born, 2012; Rasch & Born, 2013). For example, time spent in SWS positively correlates with memory improvement after sleep (Diekelmann et al., 2012; Marshall et al., 2006). Likewise, a period of intense studying prior to sleep can increase the amplitude and attenuate the frequency of slow oscillations (SOs, dominant frequency of 0.7-0.8 Hz), a hallmark of SWS (Gais, Mölle, Helms, & Born, 2002). Importantly, the neural firing pattern associated with particular wake activity was observed being replayed during subsequent SWS in the hippocampus and neocortex in rodents (Wilson & McNaughton, 1994) and in humans (Peigneux et al., 2004). In agreement with the two-stage account of memory formation the hippocampal replay preceded the memory replay in neocortical sites (Ji & Wilson, 2007). This 'off-line' replay of newly encoded memories in SWS, believed to facilitate a dialogue between the hippocampus and neocortical system, was associated with memory consolidation benefits measured after sleep.

On a neuronal level, a dialogue between the neocortex and hippocampus, which facilitates systems consolidation during SWS, is driven by the neocortical SOs (Born & Wilhelm, 2012). The depolarizing up phases of the SOs drive the repeated reactivation of memory representations stored in the hippocampus. Interestingly, SOs show a temporal relationship with sleep spindle (Gais et al., 2002; Mölle et al., 2011), another aspect of sleep physiology which has also been linked to memory replay and consolidation (Schabus et al.,

2004). More specifically, the negative-going-half-wave of the SO is associated with a suppressed spindle activity and cortical silence. In contrast, the subsequent positive-going-half-wave of the SO is associated with a pronounced increase in spindle activity and a widespread depolarisation in cortical networks. The spindle activity is, on the other hand, closely grouped with another oscillatory pattern, hippocampal sharp-wave ripples. The spindles and sharp-wave ripples form the spindle-ripple events which are fundamental in facilitating memory reactivation (Born & Wilhelm, 2012; Feld & Born, 2017). Summing up, the SOs provide a global temporal frame with the depolarising up phases considered to represent a period of enhanced replay of information from the hippocampus to the neocortex (Staresina et al., 2015). In result, the finely coordinated brain activity taking place during SWS enables memory consolidation to take place and in consequence stabilise and enhance memory for newly learnt information after sleep.

The consolidation process during sleep is selective inasmuch as it does not enhance every memory. The course whereby memories are chosen for consolidation is believed to be influenced by many factors with stimulus properties (Groch, Preiss, et al., 2017), training procedure (Diekelmann, Wilhelm, & Born, 2009), motivation to remember (Wilhelm et al., 2011) and pre-sleep memory strength (Creery, Oudiette, Antony, & Paller, 2015) being just a few. Growing evidence suggests the further possibility of externally enhancing consolidation of selected memories in sleep. This direct influencing which memories are reactivated is possible due to a targeted memory reactivation (TMR) technique. TMR is believed to mimic these natural spontaneous reactivations to enable memory enhancement by selectively cueing memories in sleep. More specifically, the TMR method entails that some information is learnt during pre-sleep memory tasks and that this information contains, for example, an auditory or odour cues associated with it. During subsequent sleep, the participant's brain activity is measured and when SWS is identified the auditory or odour cues from the learning session are presented. These cues are believed to work as reminders of prior learning and prompt the endogenous memory reactivation of selective memories. Finally, the memory is tested again upon waking to assess the selective memory improvement with behavioural measures. A considerable number of studies using the TMR paradigm reported an improved memory for material cued in sleep. In a landmark study Rasch and colleagues (2007) showed that memory for spatial locations can be enhanced by presenting odorant cues, associated with those locations, during sleep. Importantly, control experiments showed that this effect did not occur when the odour was re-presented during other than SWS stages of sleep, for example REM, or waking interval. Furthermore, functional imaging data revealed an increase in hippocampal activity when odour cues were re-presented during SWS, suggesting that odour re-exposure stimulated neural replay in

memory relevant brain regions, potentially enhancing an active reorganisation of declarative information (Rasch et al., 2007).

These findings have been further extended to auditory modality. For instance, Rudoy, Voss, Westerberg, and Paller (2009) exposed participants to a visuo-spatial learning task where pictures of objects were paired with semantically related sounds (e.g. a picture of a dog and a bark sound). Half of the sounds were then re-presented during a subsequent nap. Interestingly, picture-location memory accuracy was higher for items whose associative sounds were re-presented during sleep. This suggested that the naturally occurring neural replay of individual memories had been influenced by auditory cues. Henceforth, several studies explored different factors that could impact cueing in sleep, for example, by testing different material to learn and characteristics of the cues. The TMR paradigm was shown effective for verbal and non-verbal declarative memory (Diekelmann, Büchel, Born, & Rasch, 2011; Fuentemilla et al., 2013; Oudiette, Antony, Creery, & Paller, 2013; Oudiette & Paller, 2013; Rudoy et al., 2009), emotional memory (Cairney et al., 2014) and procedural memory (Antony, Gobel, O'Hare, Reber, & Paller, 2012; Cousins, El-Deredy, Parkes, Hennies, & Lewis, 2016; Schönauer, Geisler, & Gais, 2014). Nevertheless, although fascinating, these findings are largely based on modulation observed in post-sleep behavioural performance and allow only for making indirect inferences that cueing during SWS evokes memory replay during sleep.

In sum, the TMR is a non-invasive technique using external stimuli to aid processing and consolidation of memories during sleep. Still, research on the subject has been mostly restricted to measuring cueing effects with post-sleep recall tests which are indicative of explicit knowledge only. So far, there has been little discussion about which aspects of memory consolidation are directly affected by TMR in sleep. Surprisingly, the effect of TMR on integration of memories into pre-existing memory networks, as opposed to their strengthening, has not been closely examined. One purpose of the investigations presented in this chapter was to assess the extent to which, if at all, the TMR method impacts the process of integration of newly learnt information within neocortical networks. Here, novel linguistic items represent stimuli that are specifically suitable for such investigation as numerous studies provided evidence for the beneficial role of sleep in integrating new words into the 'mental lexicon'.

3.1.2 Sleep dependent consolidation of novel words

Sleep has been shown to support word learning in children (Brown, Weighall, Henderson, & Gaskell, 2012; Henderson, Weighall, Brown, & Gaskell, 2012; Henderson,

Weighall, Brown, & Gaskell, 2013) and adults (Davis, Di Betta, Macdonald, & Gaskell, 2009; Dumay & Gaskell, 2007; Gaskell et al., 2014; Gaskell & Dumay, 2003; Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010). Importantly, studies on word learning demonstrated that sleep not only benefits the explicit memory of newly learnt items recalled next day but also that it aids the integration of new words into pre-existing networks (Dumay & Gaskell, 2007; Gaskell & Dumay, 2003). This succesful integration was shown to be associated with increased spindle activity during post-learning sleep (Tamminen et al., 2010) and theta activity during later recognition tests (Bakker et al., 2014). This sleep-mediated integration of new linguistic representations into the pre-existing lexicon was interpreted within the Complementary Learning System account (McClelland et al., 1995). Based on the CLS model, Davis and Gaskell (2009) proposed a CLS framework for word learning, closely linked with the active systems theory of memory consolidation in sleep (Born & Wilhelm, 2012). Drawing on principles of the CLS account, the model differentiates between two stages of learning and lexical integration of new words. Firstly, the hippocampal system allows for initial rapid familiarisation with novel words. This is due to the fact that the presence of the hippocampal system offers plasticity and a rapid acquisition of new lexical representations without interference from previously or subsequently learnt knowledge. The representations temporarily stored here are sparser and more independent; therefore, they can be learnt swiftly and used to support the slower and interleaved learning within the second, cortical system. A central part of the model is the proposal that learning involves sleep-associated consolidation processes to mediate between fast-learning hippocampal and slow-learning neocortical systems. Due to this hippocampal mediation, which entails the memory replay in sleep, the novel lexical representations become redistributed to and integrated within neocortical long-term memory networks. In that way sleep-dependent consolidation aids the integration of newly learnt words into lexicon allowing them to behave like other already known words. As a result, the newly learnt items can compete in the automatic recognition process with other phonologically overlapping familiar words (Davis & Gaskell, 2009).

The engagement in lexical competition process quantifies the behavioural differences between newly learnt and consolidated novel items. The lexical competition process has been extensively researched in word learning studies (Bakker et al., 2014; Brown et al., 2012; Davis et al., 2009; Dumay & Gareth Gaskell, 2012; Dumay & Gaskell, 2016; Gaskell & Dumay, 2003; Gaskell & Marslen-Wilson, 2002; Henderson et al., 2012; Lindsay & Gaskell, 2012; Lindsay, Sedin, & Gaskell, 2012; Szmalec, Page, & Duyck, 2012). Still, very little is known about the importance of memory reactivation in sleep for successful learning and integration of novel spoken forms. For example, if replay of

memories during sleep is a vital factor that supports word learning, in the same way as learning other non-linguistic information, then TMR in sleep should bring significant improvements in memory for novel words. This logic was applied in a recent study by Schreiner and Rasch (2014) who tested whether the re-exposure to complex verbal cues during sleep will induce reactivations of newly learned vocabulary and hence improve their recall at the post-sleep test. By doing so the authors tested whether TMR would improve memory for novel words as measured by their explicit recall next morning. The authors asked their German participants to learn new Dutch words and their German translations before going to sleep. During subsequent NREM sleep the learned Dutch words were replayed in order to investigate whether this will enhance the memory of their German translations. In the morning, participants completed the recall test where they were asked to provide the German translations to newly learned Dutch words. Notably, the recall of German translations of the Dutch words replayed in sleep showed a significant improvement in memory as compared to the Dutch words that were not replayed in sleep. The researchers also evaluated whether the TMR benefits for cued items adversely affected the memory for non-cued words by comparing the performance to the control group that did not undergo cueing in sleep. The comparison revealed no differences between the recall of the control group and the experimental group of non-cued items indicating that cueing in sleep did not disrupt the ongoing consolidation of non-cued items (Schreiner & Rasch, 2014). Moreover, it suggested that presentation of cues in sleep induced memory enhancement for novel words that exceeded the typical sleep consolidation benefits.

The study by Schreiner and Rasch (2014) was the first to show that explicit recall of newly learned novel words can be aided by TMR. However, this study did not investigate the lexical processing of novel words, i.e. it did not examine whether the novel words have been integrated within the lexicon, thus leaving the question of whether TMR can also support lexical integration of novel phonological tokens, open. Moreover, the properties of stimuli used in their study could potentially impact the way the novel words were learnt. As mentioned before, the authors asked participants to learn novel Dutch words and their German translations which often shared the phonological, semantic and orthographic form, for example *watten* → *watte* (English translation: *cotton*) or *amandel* → *mandel* (English translation: *almond*). Undeniably, Dutch and German share some semantic and phonological cross-linguistic overlap with a relatively high number of phonetically identical cognates (i.e. words having the same linguistic derivation as translation equivalents), with an average cognate percentage of 60% (Schepens, Dijkstra, Grootjen, & van Heuven, 2013). The form and meaning similarity of cognates (e.g. *flamme* in French and *flame* in English) has been shown to facilitate learning of additional languages (Otwinowska & Szewczyk, 2017;

Schepens et al., 2013) even when words are only phonologically similar and semantically dissimilar (Dijkstra, 2007). In fact, our recent work has shown that phonological overlap between new and old words can directly affect the trajectory of novel word learning and their lexical integration, for example, by limiting a need for the sleep-dependent consolidation process (Sobczak & Gaskell, submitted; see also Chapter 2).

Furthermore, other properties of experimental design used in Schreiner and Rasch (2014) could further affect the results. Namely, by providing German translations to their newly learned Dutch counterparts the study introduced a semantic element. Hence, the cues used in sleep could trigger an engagement of semantic networks. Indeed, a recent study by Cairney, Sobczak, Lindsay, and Gaskell (2017) has indicated that the verbal cues used in sleep may be processed on a more complex level than just acoustically. The authors exposed their participants to verbal cues associated with target English words in the learning phase and then re-played the target-associated cues during subsequent SWS. Crucially, although the word cues presented during the encoding and in sleep were the same, they were spoken by speakers of different gender. By doing so, the experimenters created an acoustic mismatch between the cues presented at encoding and replayed in sleep but retained their semantic content. Strikingly, the results showed that the acoustic mismatch between the cues reduced forgetting of both cued and non-cued memories as measured by the post-sleep test. The possible interpretation of this finding could be that TMR with non-identical verbal cues may utilise linguistic decoding mechanisms, resulting in widespread reactivation across a broad category of memories. It would also indicate a deeper level of processing of lexical cues during sleep, potentially due to their more complex properties including semantics.

One recent TMR study has shed some light on the influence of cueing in sleep on lexical integration of novel phonological forms (Tamminen, Lambon Ralph, & Lewis, 2017). In this study the authors asked participants to learn novel spoken words (e.g. *cathedruke*) together with their meanings and then tested the knowledge and a lexical integration of novel words with a free recall, recognition and lexical competition tasks, respectively. The tests were applied before and after participants took a nap during which half of the novel words were cued once. Surprisingly, the results showed that cuing in sleep did not affect the performance in behavioural tests. Playing the novel words in sleep not only failed to improve the performance on the free recall or recognition tasks but in fact made it worse. As for the lexical integration test, the authors observed the lexicalisation of novel words in both the sleep and wake control groups with no statistical difference observed between cued and non-cued items in the magnitude of elicited competition effects. Nonetheless, the

study found an indirect relationship between cueing and time spent in the REM stage of sleep. This was taken as evidence that the impact of TMR on lexical integration is mediated by time spent in REM sleep (Tamminen et al., 2017). In fact, changes in REM associated with cueing in sleep have been previously reported (Cousins, El-Deredy, Parkes, Hennies, & Lewis, 2016). It was suggested that SWS and REM play complementary roles in memory formation (Diekelmann & Born, 2010) and that cueing in SWS can modulate the role of REM in the consolidation process. Another recent study has also indicated the REM stage as having important benefits for word learning (Batterink et al., 2017). However, some objections can be raised with regard to those studies. Firstly, studies indicating the importance of REM in word learning provided participants with meanings for newly learned items during learning. In fact, as pointed out by Tamminen et al. (2017), the REM stage of sleep activates broad semantic networks and allows the integration of new memories with remotely related existing knowledge. Thus the correlation observed between larger increases in lexical competition and time spent in REM could be due to a semantic content provided at encoding. Moreover, these studies utilised an afternoon nap instead of a full night of sleep. It is possible that sleep characteristic and physiology during a nap are different in comparison to nocturnal sleep (Lo, Dijk, & Groeger, 2014; Lynn et al., 2016; Tucker et al., 2006). Additionally, thus far the learning-related cues used in TMR studies were the associates of tokens to remember whereas in Tamminen et al. (2017) the actual tokens were used which cannot rule out their differential processing.

Lastly, it is worth noting that, thus far, a vast majority of TMR studies focused on associative memory of items which are already familiar to participants (for example, a sound and a semantically related or not, but already known object). Thus, there remains a paucity of evidence on how TMR would affect learning of completely new, and therefore still unconsolidated, information. This calls for further investigations which could help to determine whether the TMR paradigm would be equally successful when learning unknown material such as novel words. For example, using more semantically ambiguous non-verbal cues and novel words, the stimuli with limited semantic properties, would help to further uncover the rules that govern the overnight memory reactivation.

Drawing upon research outlined above, this chapter seeks to examine the impact of selective cueing in sleep on memory for newly learned unfamiliar items, their consolidation and integration within neocortical networks. Taken together, whilst offline consolidation clearly plays an important role in learning new words, the existing evidence failed to provide a consistent account of how learning and integration of novel information, such as novel words, can benefit from TMR technique and, in a broader sense, memory replay in

sleep. By employing novel linguistic tokens, a material particularly suitable to investigate integration processes, the study provides an important opportunity to advance our understanding about the scope of cued reactivation in sleep and mechanisms that underlie sleep-related consolidation. In the next sections I will present the principal findings on neural underpinnings of TMR before I move to outline the aims of the current study in more detail.

3.1.3 Neural correlates of TMR in sleep

Oscillatory parameters of brain activity associated with successful memory reactivation during sleep have provided first insights into plasticity processes supporting stabilization, strengthening and integration after reactivation during sleep. For example, Schreiner and Rasch (2014) provided evidence that successful cueing in sleep, as compared to an unsuccessful one, resulted in an increase oscillatory theta activity (4-7Hz). In particular words not remembered before sleep, but successfully retrieved after cueing (and subsequently labelled *gains*) seem to be strongly related to an increased theta power as well as an elevated slow spindle activity (11-13 Hz). Interestingly, presenting correct or incorrect feedback immediately following the cues cancelled these theta power increases and the subsequent memory benefits (Schreiner, Lehmann, & Rasch, 2015; Schreiner & Rasch, 2017). This suggested that, in line with the active systems consolidation theory, cueing benefits may depend on timing of slow oscillation/K-complexes. Indeed, recent work suggests that most successful cue presentation is timely related to the slow oscillation up-states (Antony, Piloto, Paller, & Norman, 2014; van Poppel, Korjoukov, & Talamini, 2016). It is therefore possible that the synchrony between SOs up-state and theta activity underlie the plasticity related to the memory reactivation in sleep (Schreiner & Rasch, 2016). Interestingly, theta activity was also reported to play a crucial part in speech perception (Luo & Poeppel, 2007; Luo, Tian, Song, Zhou, & Poeppel, 2013). This may indicate that the increase in theta activity observed by Schreiner and Rasch (2014) can be related to an effective processing of verbal cues presented in sleep instead of the memory reactivation process itself. As a matter of fact, another study that also observed theta increases associated with successful TMR (Groch, Schreiner, Rasch, Huber, & Wilhelm 2017) likewise used verbal cues as reminders replayed during sleep albeit in a non-linguistic context.

Oscillatory activity in theta range has also been indicated in studies investigating successful encoding and retrieval during wakefulness (Nyhus & Curran, 2010). Theta as well as gamma activity are associated with processes of long term potentiation (LTP) and synaptic plasticity, thereby facilitating the encoding of new memories (Hasselmo & Stern, 2014; Hyman, Wyble, Goyal, Rossi, & Hasselmo, 2003). For example, theta activity is

typically increased for correctly recognised words as opposed to correctly rejected new words (Osipova et al., 2006). Similarly, Schreiner, Göldi, and Rasch (2015) showed theta power increases during a recognition task following cueing in sleep with stronger theta activity for successfully cued words as compared to non-cued words. It is worth noting that these theta increases during the post-sleep recognition task, were not reflected in behavioural measures as no significant difference was noted between cued and non-cued items in the recognition task (Schreiner, Göldi, et al., 2015). One plausible explanation ties the increase in theta power with successful integration of newly learnt words into the mental lexicon. For example, studies investigating neural signatures of successful word integration have reported increased theta activity during post-sleep wakefulness (Bakker et al., 2014) along with a longer time spent in SWS (Peigneux et al., 2004; Takashima et al., 2006) and sleep spindles density (Tamminen et al., 2010), as prominent signatures of sleep physiology participating in integration processes. Bakker et al. (2014) showed that novel words learned 24 hours before testing, and therefore having an opportunity to undergo sleep-related consolidation, elicited more word-like oscillatory responses in comparison to novel words that did not have a chance to get consolidated. Interestingly, it was the increased power in theta band that was similar for existing and newly learnt consolidated words. The authors suggested that an increase in theta power reflects lexical access and thus indicates that sleep-related consolidation enables novel words to acquire lexically integrated word-like neural representations (Bakker et al., 2014).

3.1.4 Current study

Here, we report a study that examined how cueing during sleep affects explicit memory of newly learnt phonological forms and their lexical integration by using an explicit recall task and a pause detection task (Mattys & Clark, 2002), a well-established measure of lexical integration. Although this has been previously examined (Tamminen et al., 2017) we introduced several changes in order to provide more insight into consolidation, lexical integration and cueing processes. We used similar non-words as in Tamminen et al. (2017; *e.g. cathedruke*) that closely overlapped with existing English base-words (*cathedral*). However, in contrast to Tamminen et al. (2017) we did not introduce the meanings of novel items by providing their semantic definitions. This allowed us to investigate purely phonological learning but also retain consistency with previous work on word learning when meanings of novel words were not supplied (Dumay & Gaskell, 2007; Gaskell & Dumay, 2003b). Additionally, limiting the semantic information would enable us to test whether the TMR paradigm would apply to material with no existing semantic connotations.

As cueing in sleep appears to be most successful for hippocampally-dependent associative memories, the cues which were associated with new words were used instead of actual novel words. As sounds were previously indicated to be as successful in cueing as words (Cairney et al., 2017) we used environmental sounds, the same as those used in previous TMR studies (Cairney et al., 2016; Rudoy et al., 2009). The choice of sounds as TMR cues was additionally motivated by the fact that non-verbal cues allowed us to restrict semantic information carried by the verbal cues. At the same time, they offered some, although more abstract, reference to prior knowledge- a vital pre-condition for successful cueing in sleep (Groch, Schreiner, et al., 2017). We expected that using the sound cues would limit the need for complex linguistic processing during TMR, which may also alter the evoke and induced brain response to cue reminders, in particular with regard to theta activity.

Based on the previous studies we hypothesised that cueing during sleep would affect the memory for newly learnt novel words with cued words being remembered better than non-cued words. Following previous studies, we also included the old/new categorisation test; however, as neither of the TMR studies reported any cueing effect on recognition of new items, we predicted that recognition of cued and non-cued items would be at a similar level (Ashton, Cairney, & Gaskell, 2017). With regards to the lexical integration of novel items, the picture drawn from the previous reports is unclear. For example, Tamminen et al. (2017) demonstrated successful integration of both cued and non-cued words, with the time spent in REM mediating the integration of the cued items. However, the study showed no effect of cueing on explicit recall of new items. These results imply a potential dissociation between strengthening the explicit memory of individual tokens by TMR and their integration. It is plausible that successful cueing in sleep would hinder the integration process. Tamminen et al. (2017) could have observed the integration of both cued and non-cued items because the strengthening of individual memories with TMR failed. In fact, a recent study has shown that a rule extraction, a process typically benefiting from sleep, is not only not susceptible to but in fact may be hindered by TMR (Hennies, Lambon Ralph, Durrant, Cousins, & Lewis, 2017). However, the reverse is also possible: Tamminen et al. (2017) could have observed lexical integration of all items regardless of unsuccessful cueing in sleep. In that way, the cueing in sleep, and consequently memory reactivation, may play little or no role in the integration process of novel words. For example, replaying associated cues in sleep may merely result in the strengthening of individual lexical entries but has little impact on their integration within lexicon. Hence, the inter-dependency of these processes and how they are influenced by TMR in sleep is currently unclear.

Nonetheless, sleep has been widely shown to support novel word integration (Dumay & Gaskell, 2007; Gaskell & Dumay, 2003b). This suggests that TMR should enhance the naturally occurring sleep-dependent lexical integration process. It is possible that the amount of lexical competition elicited by cued and non-cued words in Tamminen et al. (2017) could have been indistinguishable due to, for example, overtraining the items. It has been previously shown that the memory enhancement induced by TMR is most beneficial for weakly coded memories (Cairney et al., 2016; Creery et al., 2015). Based on this, providing that we observe a TMR effect in explicit recall of novel items, in order to assess the extent of the contribution of TMR towards lexical integration processes some modulation of lexical competition processes is needed.

One way to manipulate the amount of lexical competition elicited by novel items is to choose fewer exposures to novel items. A limited number of exposures (i.e. 12 exposures) have been previously reported to be insufficient for generating reliable lexical competition effects (Gaskell & Dumay, 2003b; Sobczak & Gaskell, submitted). Therefore, it is likely that a relatively low level of exposure could not guarantee robust integration of newly learnt tokens after a night of sleep. Yet, if the TMR indeed facilitates the integration process, we should observe a better integration of the cued items after sleep, despite the low exposure level. In contrast, we may not see a successful integration for the uncued words. In order to capitalise on this fact, we exposed our participants to novel items 13 times in the training phase (12 times during the exposure task and once during a stem completion with feedback, see the experimental design). On the basis that a low level of exposure may not suffice to show the effect of lexical competition, we hypothesised that if cueing in sleep additionally supports lexical integration, we will observe differences in lexical competition effects elicited by cued and non-cued items with cued items eliciting more lexical competition and non-cued items eliciting less or no lexical competition.

As previous studies reported different brain responses to successfully cued and unsuccessfully cued items (Schreiner & Rasch, 2014) we also expected to see differences in brain waveforms with regard to cueing effect. The examination of cue-evoked neural responses will also allow for quantification of successful TMR in sleep. Similar to the event-related responses in sleep, the oscillatory activity in theta range was also reported as being related to effective cueing (Groch, Schreiner, et al., 2017; Schreiner & Rasch, 2014). Alternatively, it is possible that the observed theta increases were instead related to processing of verbal cue reminders in sleep. Therefore, had we successfully obtained a TMR effect with non-verbal cues, if theta activity reflects the successful memory reactivation in

sleep, we would expect this improvement to manifest itself in increased theta activity with regards to the successfully cued items.

By employing similar event-related response and time-frequency analyses we aimed to further explore the neuro-correlates of successful reactivations of memories in sleep. Additionally, since previous reports indicated a positive correlation between time spent in SWS and subsequent increase in declarative memory performance (Plihal & Born, 1997), the spindle density and lexical integration of novel words (Tamminen et al., 2010) as well as association between both increased SWS and spindle activity with successful cueing (Schreiner & Rasch, 2014), we anticipated increases in these sleep physiological measures to accompany memory benefits if such were found.

Lastly, as some studies indicated that cueing in sleep can alter the brain activity in the following wakefulness and without explicit behavioural effects (Schreiner et al., 2015) we also collected EEG responses during a passive listening task performed in the morning, after a night of sleep (see Appendix B).

Participants were taught the sound-novel word paired associates (e.g. a sound of a cutting saw and a novel word *cathedruke*) during the exposure task. Immediately after training participants completed a lexical integration test, the pause detection task. Following this, their memory for the novel words was tested by a stem completion and a recognition task prior to sleep. During the subsequent sleep, half of the sounds associated with novel words were replayed to participants during their SWS. In the morning, the lexical integration and participants' memory of novel items was again assessed by the same set of tasks. In addition to those tasks, participants also underwent the passive listening task when their brain responses were recorded with Electroencephalography (EEG; see Figure 3.1).

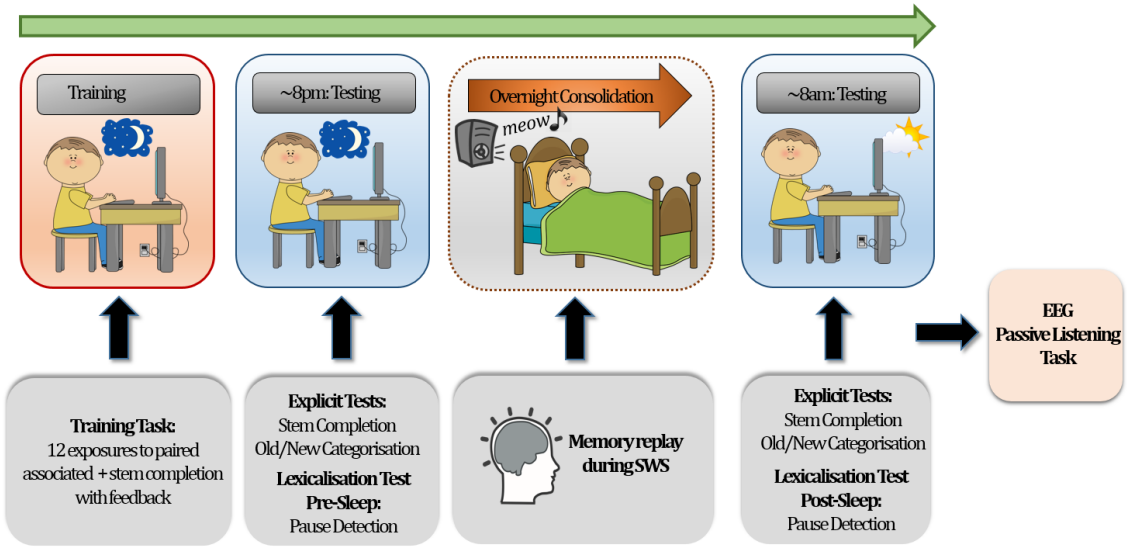

Figure 3.1. Experimental procedure for the TMR experiment. In the first session, prior to sleep, participants encoded 40 sound-novel spoken word associates before completing a pause detection, a cued recall and an old/new categorisation task for all learned novel words. During a sleep delay, half of the sounds associated with newly learned novel words were replayed via a loud speaker during slow wave sleep (SWS). In the second, post-sleep session participants completed the same three tasks as in session one and an additional EEG listening task.

3.2 Material and Methods

3.2.1 Participants

Sixty-three participants (forty-seven females, aged 18-25) were recruited on a voluntary basis at the University of York in return for either a course credit (Psychology undergraduate students) or a £30 payment reward. However, seven of these participants were excluded for the following reasons: computer malfunction (2), experimenter error (3), inability to sleep (1), poor task performance (1). In results, data from fifty-six participants was analysed (forty-two females, mean ± SD age, 19.89 ± 1.75 years). Each participant was screened prior to the study for any sleep psychiatric or neurological disorders, use of psychologically active medication and any alcohol and caffeine consumption for the 24-hour period that preceded the experiment. All recruited participants were non-smokers. Participants' pattern of sleep across the month preceding the study was evaluated with Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynold, Monk, Berman, & Kupfer, 1989). Written informed consent was obtained from all participants in line with the Research Ethics Committee of the Department of Psychology, University of York.

3.2.2 Stimuli

3.2.2.1 Novel spoken words

Critical stimuli consisted of 60 word-triplets taken from Tamminen and Gaskell (2008) and Dumay and Gaskell (2012). The triplets consisted of familiar words (e.g., *cathedral*), a fictitious novel word derived from the base words (e.g., *cathedruke*), and a non-word foil of similar sound to the novel word to be used in the old/new categorisation task (e.g., *cathedruce*).

3.2.2.2 Environmental sounds

Sixty-five environmental sounds (e.g., a whistle of a kettle, a bark of a dog) were adopted from two prior studies of memory reactivation in sleep (Oudiette et al., 2013; Rudoy et al., 2009) and the internet (freesound.org). The sounds ranged from 200–569 ms in length (mean ± SD, 460.76 ± 67.03 ms).

3.2.2.3 Paired associates

Each novel spoken word was paired with a sound. Care was taken that the sound used for each novel word-sound pair was not related in any way to the English base word (e.g., *cathedruke*→ a sound of a cutting saw). The resulting sixty paired associates were divided into 3 sets, twenty pairs each. Each participant was trained on the novel items from two sets, therefore their training involved learning 40 sound-novel spoken word pairs with the novel words and the sounds from the third set acting as controls in the lexical integration task (control English base words) and overnight replay (control sounds). The assignment to item sets was counterbalanced across participants (i.e. for some participants the test items were the control items and *vice versa*).

3.2.3 Procedure

The experimental procedure and tasks are outlined in Figure 3.1. The experiment took place in the Sleep, Language and Memory laboratory, Department of Psychology, University of York. Participants entered the laboratory at 7.30pm (± 45 minutes). Participants were informed that they would take part in the sleep and memory experiments and their written consent was obtained. Two experimental sessions were separated by overnight sleep delay. Participants were not informed that TMR will be used during the sleep phase. The session began with the application of the electrodes for standard polysomnography (PSG), including: electroencephalography (EEG, 7 channels: F3, F4, C3, C4, O1, O2 and a ground reference), electromyography (EMG, 3 channels) and electrooculography (EOG, 2 channels) recordings plus recording from mastoids used for referencing purpose (2 channels). Additionally, upon awaking 5 further electrodes were

added (Fpz, F7, F8, T3, T4) to monitor the brain activity during the last experimental task (i.e. EEG passive listening task, see Appendix B). Participants were connected to the PSG sleep monitoring system in the bedroom where they slept. After the electrodes application and the training session but before completing the testing phase participants were asked to complete the Stanford Sleepiness Scale (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973). Participants were asked to complete the Stanford Sleepiness Scale (Hoddes et al., 1973) for a second time in the morning before they began the testing phase.

3.2.3.1 Session one: training

The training involved two tasks: firstly, an *exposure task* where participants listened to the sound-novel spoken word pairs and secondly, a *stem completion task with feedback*. The order of the tasks was fixed across participants. Each participant was provided with printed instructions prior to starting the training where the importance of learning new words and associations between novel words and sounds was emphasised. Participants were encouraged to ask questions if something was unclear.

In *the exposure task*, each trial began with a black fixation cross placed in the centre of a PC screen for 1,500 ms, to indicate the onset of an auditory stimulus, which was followed by a sound presentation. After 1,500 ms, a novel spoken word was played over the headphones. This was followed by a 5,000 ms break when, in order to facilitate learning, participants were instructed to memorise the novel word and try to associate it with the sound stimulus. They were encouraged to use mental imagery to help them form associations. Each sound-novel spoken word pair was presented 12 times over the total of 12 blocks of trials, i.e. once per block. In order to maintain participants' attention on the task, one third of all trials per block were catch trials (12 catch trials and 40 typical trials/block) when participants were required to provide a response with relation to a word or a sound they had heard immediately before the catch trial. In half of the catch trials participants were asked to monitor the novel spoken word for a visually presented target phoneme that was displayed in the middle of the screen on that trial (overall, six target phonemes were used: *"n"," d"," k"," l"," t"," p")* (Dumay & Gaskell, 2007; Gaskell & Dumay, 2003b). In the other half of the catch trials participants were presented with an environmental sound and had to decide whether it was the same sound that they heard in the previous trial or a different sound. The type of catch trial was randomised within a block. Half of the catch trials required a *yes* and half a *no* response with the order of the *yes/no* trials randomised per block. The catch trials referred to a novel spoken word or a sound presented on the last trial preceding it; thus they began after a 5,000 ms interval which participants were given to memorise the sound-novel word pairs. Each catch trial began

with a 250 ms pre-stimulus interval marked by a blue cross displayed in the middle of the screen and followed by the presentation of either a sound or a phoneme. Participants were instructed to press the right button on the game controller if they thought the phoneme was presented in the novel spoken word they had heard on the last preceding trial/the sound was the same as the one played on the last preceding trial, or to press the left button otherwise. Unlimited time was given to respond to the catch questions. Before the start of the task participants completed a series of practice trials where they had a chance to practise the typical trials and both types of the catch trials. During the practice part of the task the experimenter was present in the room to ensure that participants understood the task correctly and to answer participants' questions. The exposure task was split into two parts with each part taking approximately 45 minutes to complete (90 minutes in total) and with a break in between. Each part of the task had a self-paced break in the middle to allow for rest and to help maintain participants' attention throughout the task.

In the second training task, *stem completion with feedback,* participants were presented with the environmental sound first and then prompted auditorially with the initial syllable of the newly learned spoken word associated with that sound, as a cue for recall. For example, if participants learned the novel word *cathedruke* in association with a sound of a motorbike, they first heard the sound and then they heard the stem cue *ca-*, played over the headphones. Participants were instructed to vocalize their responses as quickly and accurately as possible, and their responses were later scored for accuracy. Participants were given a visual signal ("+") that appeared on the screen for 500 ms before hearing the sound and the stem cue. They were given 10 seconds to recall and produce the novel word (Tamminen et al., 2010). If participants recalled the novel word they could either wait until the next trial started or move to the next trial by pressing the spacebar. After each trial, regardless of their response, participants heard auditory feedback of the novel word that they should have produced (Lindsay & Gaskell, 2009).

Before the start of the training tasks participants were informed that a test phase would follow immediately after the learning phase, and that they would have to recall the novel words associated with the sounds.

3.2.3.2 Session one: tests

In order to assess the immediate explicit knowledge of the novel spoken words and their integration within lexicon, three tests were used: *pause detection, stem completion and old/new categorisation*. All tasks were presented in a fixed order to assure that the old/new categorisation task was completed last, as it involved the presentation of the novel spoken words.

The experiment employed *the pause detection task* in order to measure the level of lexical integration of the novel words. The pause detection task (Mattys & Clark, 2002) had been previously used as a measure of inter-lexical inhibition in studies targeting consolidation processes in novel word learning (Dumay & Gaskell, 2007, 2012). For example, Gaskell and Dumay (2003b) and Dumay and Gaskell (2007) showed that participants who learned fictitious novel phonological forms such as *cathedruke* (designed to overlap strongly with existing words) needed more time in processing their existing neighbours (e.g. *cathedral*), but only after overnight consolidation had taken place. Longer RTs in detecting the pause in the English counterparts of the novel words was taken as an index of the engagement of the novel word in lexical competition with existing neighbours and therefore marked their successful lexical integration. In *the pause detection task*, which was intended to measure whether the novel words became competitors of their English neighbours, participants were asked to make a speeded decision as to whether the aurally presented words contained a short 200 ms long pause or not, by pressing one of two buttons on the game controller. Stimuli comprised of 60 existing words (40 test base English words and 20 control base English words) and 80 filler words. Half of the items contained a 200 ms pause inserted before the uniqueness point (UP). To encourage lexical processing, fillers were all existing words and half of them had a pause inserted at random locations. 9 versions of the task were developed for each one of the three stimuli sets and counterbalanced across participants so that each item was equally represented in the eight cells of the design (reactivated competitor, pause present (1); non-reactivated competitor, pause present (2); reactivated competitor, pause absent (3); non-reactivated competitor, pause absent (4); reactivated control, pause present (5); non-reactivated control, pause present (6); reactivated control, pause absent (7); non-reactivated control, pause absent (8)). As the motivation for the study was to investigate the potential influence of the TMR on lexical integration of novel words the task compared twenty novel items that were learned and reactivated and twenty novel items that were learned but not reactivated against twenty control items (regardless of their reactivation as no effect was assumed). Response latency was measured from pause onset. Participants had 3 seconds from stimulus onset to respond and each trial was preceded by a cross that appeared on the monitor for 500 ms. The inter stimulus onset was 1,000 ms. Participants completed one block of trials, arranged randomly for each participant. The task started with four practice trials.

The second testing task was *the stem completion task* which was identical to the stem completion task used in the training phase with the exception that this time there was no feedback provided.

In *the old/new categorisation task* the novel words and the foils were presented (e.g. *cathedruce*) over the headphones. Participants were asked to listen to the words and indicate whether the word was a word they learned before (an *old* one) or a similarly sounding foil (a *new* one). Half of the items were reactivated and half were not. The RTs were measured from word onset and participants had 3,000 ms to decide.

We informed participants that they would complete the same tests again in the morning after sleep with the expectation that this knowledge would increase the salience attributed to the learned material, and thereby enhance sleep-dependent consolidation (Fuentemilla et al., 2013; Wilhelm, Prehn-Kristensen, & Born, 2012).

3.2.3.3 TMR stimuli

The TMR stimuli consisted of half of the sounds from the forty sound-novel spoken word pairs that participants learned in the training session (twenty experimental sounds) and 10 sounds not previously heard in the experiment (control sounds taken from experimental set that participant did not learn). The reason behind including the control sounds in the stimuli set used for TMR was two-fold: firstly, the presentation of the control sounds would allow for attenuation of the neural response to the sound cues and secondly, it enabled to control for any perceptual processing of replayed sounds in sleep. For example, had the experimental and control sounds been processed on a different level we should observe dissimilar waveforms evoked in response to these two types of sound cues. There were 9 reactivation lists created for each out of three sets of stimuli to ensure that items that underwent reactivation during sleep were counterbalanced across participants (such as each word was being reactivated a similar number of times across the participants group).

3.2.3.4 Sleep and TMR

At approximately 11pm, participants went to bed and were left to sleep. To habituate participants to auditory stimulation during sleep, background white noise was played via a speaker in the bedroom at an unobtrusive sound-pressure level of 39 dB throughout the sleep period. After participants had exhibited at least 2 min of sustained SWS (as determined via online PSG monitoring), the TMR set was replayed. The TMR stimuli was played interleaved with the control sounds and the order of all sounds was randomised. The cues were presented 4, 5 or 6 seconds apart, with the length of the inter-cue interval randomised. The different lengths of the inter-cue interval were to prevent the cues appearing in the predictable fashion that could cause any entrainment of the brain oscillatory activity. However, in order to prevent the habituation to the sounds played during stimulation interval, the null events were randomly interspersed between the cues

(silence trials). The total stimulation time was identical for all participants. The TMR set was replayed repeatedly throughout the first two cycles of SWS with a 1 min interval separating each repetition (Oudiette et al., 2013). The cues were immediately stopped if participants left SWS or showed signs of micro-arousal or awakening, but restarted if they returned to SWS. Participants were woken up at approximately 7am, unless they were exhibiting SWS or REM, in which case they were allowed to sleep until either awakening or entering sleep stage I or II. To attenuate the effects of sleep inertia, participants were given a break of ~20 minutes after waking when they had something to eat and drink and watched a silent movie whilst extra electrodes were being placed on their scalp.

3.2.3.5 Session two: tests

Participants completed the Stanford Sleepiness Scale (Hoddes et al., 1973) for a second time before carrying out post-sleep tests that were identical to the pre-sleep tests. After they finished the behavioural tasks they were asked to lie down on a bed again and they were once more connected to the PSG monitoring system to complete the EEG passive listening task (see Appendix B). After the task ended, the PSG electrodes were removed and participants were informed of the true purpose of the experiment and asked if they had been aware of any auditory stimuli during the sleep period.

3.2.4 Equipment

3.2.4.1 Experimental tasks

All of the experimental tasks were implemented on a PC with E-Prime version 2.0 (Psychology Software Tools, Inc.). Auditory stimuli were presented via headphones (Beyerdynamic DT 234 PRO) while visual stimuli were presented ~0.5 m from participants on a 23" flat screen LCD monitor (resolution = 1920 x 1080 pixels) positioned at eye level.

3.2.4.2 Polysomnography (PSG) acquisition

An Embla N7000 PSG system with RemLogic version 3.4 software was used to monitor sleep. After the scalp was cleaned with NuPrep exfoliating agent (Weave and Company), gold-plated electrodes were attached using EC2 electrode cream (Grass Technologies). EEG scalp electrodes were attached according to the international 10-20 system at six standardised locations: frontal (F3, F4) central (C3, C4) and occipital (O1, O2), and each was referenced to an electrode on the contralateral mastoid (A1 or A2). Left and right electrooculography electrodes were attached, as were electromyography electrodes at the mentalis and submentalis bilaterally, and a ground electrode was attached to the forehead. Each electrode had a connection impedance of < 5 kΩ and all signals were digitally

sampled at 200 Hz, with the exception of the listening task where the sampling rate was 500 Hz.

Sleep scoring. Online sleep scoring was conducted on the referenced central electrodes (C3-A2 and C4-A1). Subsequent offline scoring in accordance with the criteria of the American Academy of Sleep Medicine (Iber, Ancoli-Israel, Chesson, & Quan, 2007) confirmed that TMR had taken place in SWS. Sleep data, scored offline, was partitioned according to the percentage of total sleep time spent in sleep stage I, stage II, SWS and REM. PSG epochs scored as either stage II or SWS were extracted from all six EEG channels for spindle analysis. Artefacts were then rejected from the data using EEGLAB version 13.6.5b (Delorme & Makeig, 2004) before a linear finite impulse response filter was used to bandpass filter each channel at 12-15 Hz. An automated detection algorithm (Ferrarelli et al., 2007) counted discrete spindle events as amplitude fluctuations within the filtered time series that exceeded a threshold of eight times the mean channel amplitude. Spindle density (counts per minute) was then calculated on all reference EEG channels (F3-A2, F4-A1, C3-A2, C4-A1 O1-A2, O2-A1) for each participant. Several studies have used this method to investigate the role of spindles in sleep-dependent memory consolidation (Cairney et al., 2014; Tamminen et al., 2013, 2010).

EEG pre-processing and analysis. In order to examine the event related responses to the cues presented in sleep we analysed the brain signal collected from 6 EEG electrodes (F3, F4, C3, C4, O1, O2). EEG pre-processing (triggers re-coding, filtering, re-referencing, data segmentation and artefacts rejection) was done using the EEGLAB toolbox for MATLAB (Delorme & Makeig, 2004) and a combination of standard and custom-made MATLAB scripts. The signal was re-referenced offline to the averaged left and right mastoids and band-pass filtered at 0.1-30 Hz. Epochs of 200 ms before to 2,000 ms after the onset of the stimulus. The 200 ms interval before the stimulus onset served as a baseline and it was used for base-line correction. Trials containing muscle, eye-blink and other artefacts were removed manually (<10%). Noise channels were interpolated using the averaged signal of neighbouring channels. Following Schreiner and Rasch (2014) epochs were categorised based on performance between pre- and post-sleep tests (see Results for details). This resulted in the following categories of the event-related response to cues: the words *remembered* and *not remembered* at the post-test. In addition, the words remembered at the post-test were separated into: *Gain*, words not remembered at the pre-sleep test, but remembered at the post-sleep test, *Hit,* the words remembered at both the pre-and post-sleep tests. The words not remembered at the post-test were also split into two further categories: *Loss*, the words remembered at the pre-sleep test but forgotten at the post-sleep

test, and *Miss*, the words that were recalled at neither the pre-nor the post-sleep tests. As the TMR stimuli contained sounds that participants never encountered during both the training and test (control sounds), these trials were labelled *Control*. Additionally, in order to provide a baseline when no event-related response is expected, we randomly sampled 10 trials during SWS for each participants where no stimulus was presented. These trials formed the category *Silence*. Only participants with trials in each condition were considered for further analysis (26 participants in total). Signal averaging was carried out separately per subject and per condition and grand averages of all conditions were calculated.

Analysis of power changes. The analysis of power changes was performed using FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). In order to avoid edge effects, data were epoched into segments of 1,000 ms pre and 3,500 ms post-stimulus onset. An interval of 500 ms at the beginning and the end of the trials was discarded afterward. Frequency bands corresponding to slow wave activity (0.5–4 Hz) were not measured because of the limited number of possible cycles in the short trial length and border effects. Time frequency analysis was computed for each trial by using 5-cycle Morlet wavelet decomposition, ranging from 5 to 20 Hz in 0.5 Hz steps. A sliding window with a step size of 10 ms was applied across the entire length of the epochs. Single trials were normalized with respect to a pre-stimulus time window ranging from − 500 ms to – 100 ms.

3.2.4.3 TMR

TMR was implemented with E-Prime version 2.0 (Psychology Software Tools, Inc.). Auditory cues were played via a speaker mounted ~1.5 m above the bed, which was connected to an amplifier in a separate control room. Participants were instructed to not use the earplugs during the night and to not place the pillow/duvet over their heads.

3.3 Results

3.3.1 Alertness

Subjective ratings of alertness obtained with the Stanford Sleepiness Scale (Hoddes et al., 1973) were comparable at the pre-test (evening) and post-test (morning) sessions (mean ± SEM, pre-test = 3.57 ± 0.25; post-test= 3.55 ± 0.26, $t(55) = 1.00$, $p = .322$). There was also no significant correlation between time spent in SWS and mean response times in the old/new categorisation task ($r = -.06$; $p = .660$) or the pause detection task ($r = .07$; $p = .629$) in Session 2, suggesting that behavioural effects were not influenced by differences in homeostatic sleep pressure (Cairney, Durrant, Power, & Lewis, 2015; Durrant, Cairney, & Lewis, 2013; Durrant, Taylor, Cairney, & Lewis, 2011).

3.3.2 TMR cycles

The number of full TMR cycles in sleep ranged from 7 to 14 with mean (± SD) number of full TMR cycles = 10.14 (±1.83). As expected, the number of cycles was positively correlated with time in SWS (r=.32, p=.017) which meant that participants who displayed more SWS received proportionally more TMR cycles. The number of full TMR cycles did not correlate significantly with participants' alertness in the morning (r=-.07, p=.611) suggesting that the overnight sound replay did not influence their sleep quality.

3.3.3 Behavioural measures

RTs were analysed for the lexical competition task, whilst accuracy data were analysed for the stem completion and the old/new categorisation task.

3.3.3.1 Stem completion

Performance in the stem completion task in Session 1 was taken as a pre-retention learning performance. In Session 1 participants recalled on average (± SEM) 19.36 (±1.23) novel words correctly (recall performance 48.40%). We observed no difference in the pre-sleep recall performance between later cued and non-cued words in the participants' group (t_1(55)=.43, p=.667; t_2(59)= .50, p=.621). As an index of the cued recall improvement for novel words we calculated the difference between the number of correctly recalled novel words before and after the retention interval. The indices were calculated separately for cued and non-cued items. Overall, the performance in Session 2 increased overnight with participants recalling on average (± SEM) 22.52 (± 1.16) novel words. The difference in improvement in recall between cued and non-cued items was assessed by repeated measure analysis of variance (ANOVA) conducted on stem completion scores. An ANOVA with two independent factors, session (Session 1 and Session 2) and TMR condition (cued *versus* non-cued), revealed the main effect of a session F_1(1,55)=48.72, p<.001, η_p^2= .470; F_2(1,59)==73.52, p<.001, η_p^2=.555), no effect of TMR condition (F_1(1,55)=.22, p=.643, η_p^2=.004; F_2(1,59)=.75, p=.390, η_p^2=.013) and a significant session x TMR condition interaction (F_1(1,55)=4.34, p=.042, η_p^2=.073; F_2(1,59)= 8.16, p=.006, η_p^2=.121). Firstly, these results suggest that recall of both cued and non-cued items improved overnight beyond baseline levels. Crucially, the recall of items cued in sleep was significantly better than the non-cued items indicating that TMR had a significant impact on memory task performance in the post-sleep test (see Figure 3.2). On an individual level, 43 participants (out of 56) benefited from the cueing (range +1 to +8) and 13 did not (range -2 to 0).

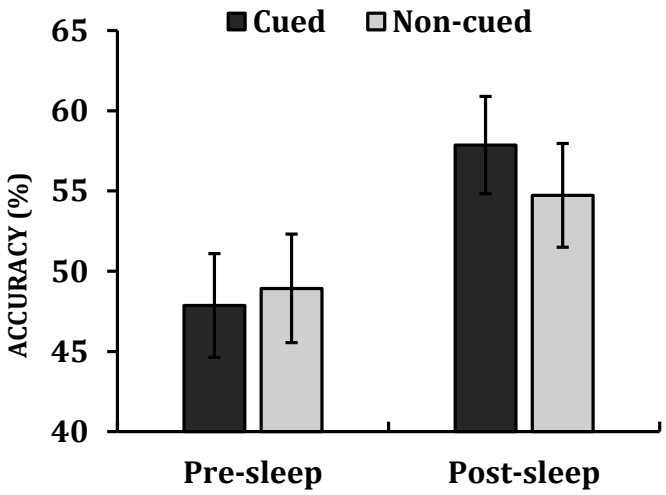

Figure 3.2 Stem completion accuracy results in the TMR experiment. Accuracy score for cued and non-cued items in the stem completion task before and after cueing in sleep show a significantly greater increase in accuracy for cued items in comparison to non-cued items (error bars indicate SEM).

Previous reports indicated that the benefit of cueing in sleep depends on the degree of accuracy in the pre-sleep tests (Cairney et al., 2016; Creery et al., 2015), therefore we assessed whether the initial performance in the Stem Completion task correlated with overnight improvement. We found that initial performance in the task was negatively correlated with the improvement shown overnight (measured as a difference score between the pre- and post-test performance r=-.33, p=.014; see Figure 3.3). We assessed this correlation separately for cued and non-cued items and found a similar negative correlation for both (r_1=-.36, p=.007; r_2=-.33, p=.013, respectively). This is in line with the sleep literature that points to a prominent role of sleep in rescuing poorly encoded memories (Diekelmann & Born, 2010).

Hits, gains, losses and misses

In order to gain more insight into the process of memory cueing in sleep, we separated words recalled in Session 2 as *Hits* (novel spoken words remembered before and after sleep), *Gains* (novel spoken words remembered after, but not before sleep). We also separated the items which were not successfully recalled in Session 2 into *Losses* (the novel words remembered before but forgotten after sleep) and *Misses* (items that were not recalled before and after sleep). Comparisons of these measures between cued and non-cued items showed no significant differences between the two (except for a nonsignificant

trend towards more *Gains* in the cued items category, $t(55)=1.79$, $p=.079$; see Table 3.1), suggesting that the benefits were spread across the full range of response types.

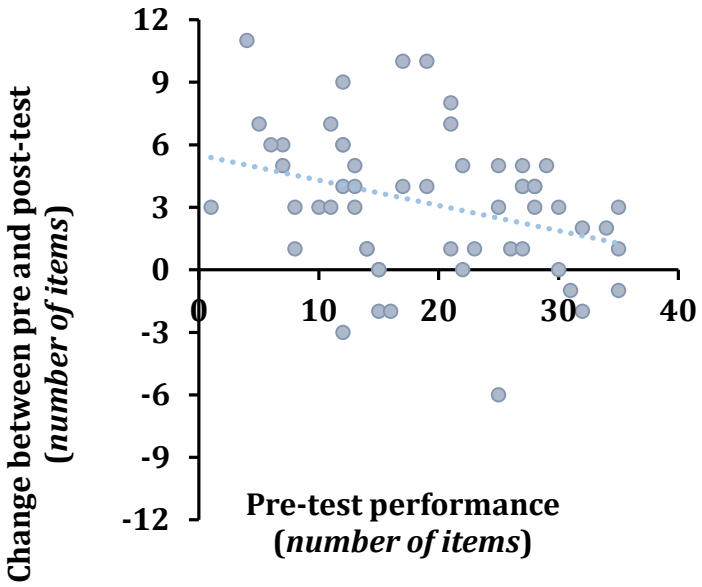

Figure 3.3. Correlation between performance at the pre-test and an overall change in accuracy between the pre and post-test (cued and non-cued items).

Table 3.1
Hits, Misses, Gains and Losses in Cued Recall task (data are shown as mean ± SD).

	Cued	**Non-cued**	**All**
Hit	8.64 (±4.93)	8.54 (±5.19)	17.18 (±9.41)
Miss	7.50 (±4.49)	7.80 (±4.67)	15.30 (±8.55)
Gain	2.93 (±2.00)	2.41 (±1.70)	5.34 (±3.02)
Loss	.93 (±1.01)	1.25 (±1.63)	2.18 (±9.41)

3.3.3.2 Pause detection

RTs for pause present and pause absent trials were averaged across both trial types and analysed for correct responses (see Figure 3.4). The responses below 200 ms were removed from analysis (0.8% of data points). We calculated an individual participant threshold for outliers' detection and removed all data points that were below or above 2.5 SD from the participant's mean per session per condition (3.1%). The remaining data points were entered into a two-way repeated measure ANOVA with factors session (2 levels: Session 1 and Session 2) and competitor condition (3 levels: cued and non-cued items with novel competitors and items without novel competitors). The ANOVA on RTs revealed a main effect of session ($F_1(1,55)= 5.02$, $p=.013$, $\eta_p^2=.084$; $F_2(1,59)= 26.14$, $p<.001$, $\eta_p^2=.307$, results per subject and per items respectively), meaning that the RTs became shorter overnight. There was no main effect of condition ($F_1(2,110)=.57$, $p=.566$, $\eta_p^2=.010$; $F_2(2,118)= .62$, $p=.538$, $\eta_p^2=.010$) and the interaction between factors was nonsignificant ($F_1(2,110)= .90$, $p=.410$, $\eta_p^2=.016$; $F_2(2,118)= 1.41$, $p=.247$, $\eta_p^2=.023$).

Based on these results, we did not observe any significant lexical competition effect elicited by newly learnt items after acquiring novel competitors. It is worth noting that although the pause detection competition effects at the post-test did not emerge as significant ($F_1(2,110)= 1.4$, $p=.247$, $\eta_p^2=.025$; $F_2(2,118)= 1.82$, $p=.167$, $\eta_p^2=.030$) the numerical difference was in the predicted direction (17 ms for cued and 20 ms for non-cued items; see Figure 3.4a and 3.4b).

In sum, the analysis of response latencies in the lexical integration test showed that the lexical competition effects did not emerge after a night of sleep. In consequence, we found no evidence that newly acquired novel items became integrated within the pre-existing lexicon after a sleep delay. If cueing in sleep was to help to facilitate the lexical integration of novel phonological forms, then stronger lexical competition effects should be evident for cued as opposed to non-cued items. However, the response latencies to cued and non-cued novel items showed no significant difference.

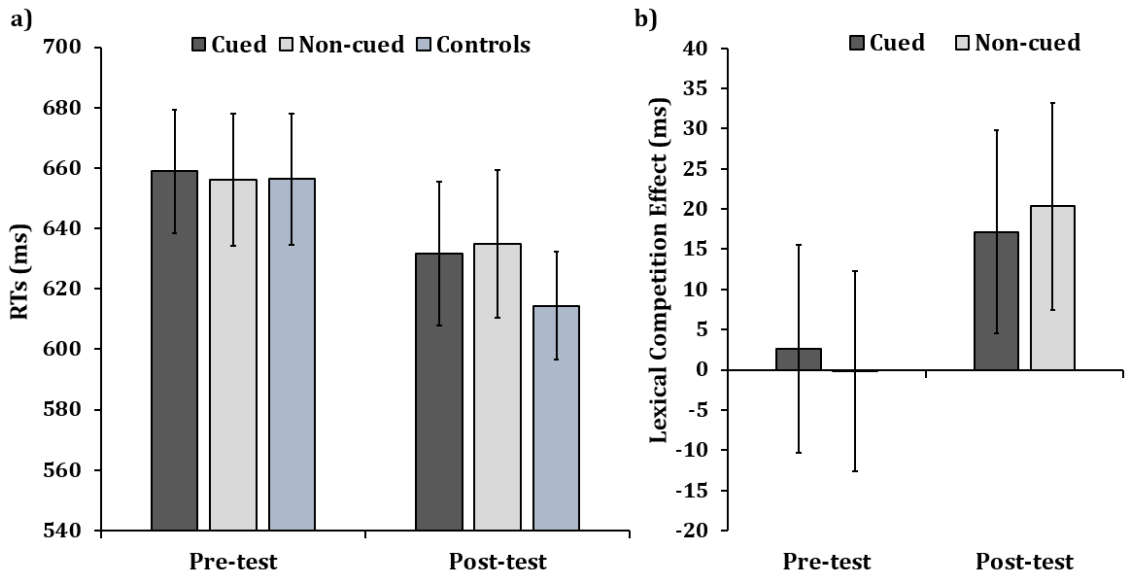

Figure 3.4. Lexical competition results in the TMR experiment. a) mean RTs to cued and non-cued test (novel competitor) and control (no novel competitor) base-words in the pause detection task. b) Lexical competition effect calculated as a mean difference between RTs to test base-word minus control base-word in Session 1 (pre-test) and Session 2 (post-test). Values above 0 indicate the presence of increased lexical competition for test-base-words. Error bars represent standard error of the means and are not adjusted to facilitate repeated measures comparisons (Cousineau & Brien, 2014).

3.3.3.3 Old/new categorisation task

As d' score reflects the sensitivity of the detector the measure was analysed per subject only. Accuracy was calculated per subject per session. To take response bias into account, accuracy was analysed by calculating signal detection measures (d'). We calculated a measure of hits, false alarms and misses as well as correct rejections (Tamminen et al., 2017) and the d' from z scores on hits and false alarm rates using NORMSINV function in Excel (Microsoft). To deal with 0 and 1 values the following approach was undertaken: 0.5 was added to both the number of hits and the number of false alarms, and 1 added to both the number of signal trials and the number of noise trials as per the loglinear approach (Hautus, 1995). A repeated measures ANOVA on d' measures for cued and non-cued items in Session 1 and 2 revealed a significant effect of session ($F(1,55)=4.16$, $p=.046$, $\eta_p^2=.070$) meaning the categorisation judgments improved overnight. There was no effect of condition ($F(1,55)=3.32$, $p=.074$, $\eta_p^2=.057$) and no interaction (session x condition; $F(1,55)=1.30$, $p=.260$, $\eta_p^2=.023$).

In sum, the analysis of d' measure showed that although participants recognised the learnt items at a better level after a sleep delay there was no significant difference between

cued and non-cued items, suggesting that cueing in sleep did not influence the recognition process (see Figure 3.5).

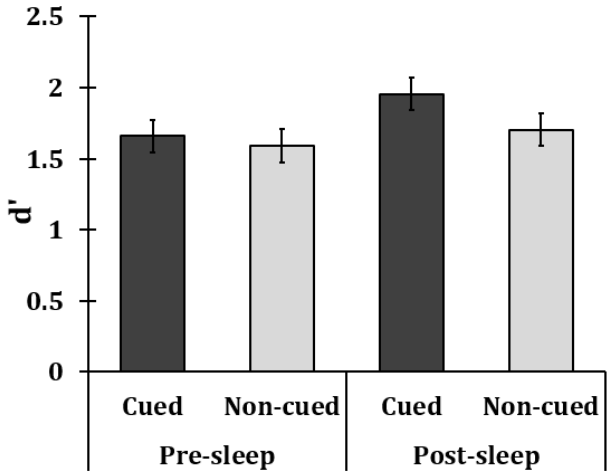

Figure 3.5. Sensitivity measures in the old/new categorisation task. Sensitivity measures were calculated as a function of whether the word was cued in sleep or not with an associated sound. Error bars represent standard error of the means and are not adjusted to facilitate repeated measures comparisons (Cousineau & Brien, 2014).

3.3.3.4 Sleep stages and spindle density

Sleep stage and spindle density data can be found in Tables 3.2 and 3.3 respectively. Sleep spindle density was calculated across Stage 2 sleep and SWS using the algorithm developed by Ferrarelli et al. (2007). Overall, when controlling for a difference in score in the stem completion task at pre- and post-test (the difference in the number of items recalled pre- and post-sleep), we found that the number of novel words recalled at the post-test positively correlated with the percentage of sleep time spent in SWS (partial correlation: r=.38, p=.004, Bonferroni corrected p value threshold was .008; see Figure 3.6).

With respect to the cueing in sleep, with a difference score in the stem completion task at pre- and post-test entered as covariates, both the non-cued and the cued items showed similar positive correlation. However, only the relationship between non-cued items and percent of time spent in SWS survived the multiple comparison correction (non-cued items: r=.37, p=.006; cued items: r=.35, p=.010). The cueing in sleep was not significantly correlated with the time spent in any other stage of sleep or spindle density averaged across all EEG channels (all p > .05). In sum, there was an overall benefit of SWS but not related to cueing.

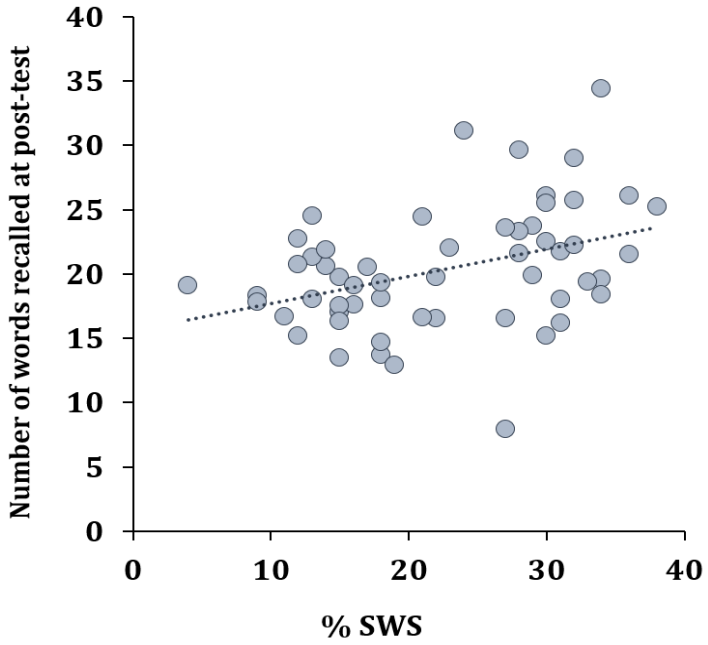

Figure 3.6. Correlation between the number of words recalled at the post-test and percentage of time spent in SWS (cued and non-cued words analysed together).

Table 3.2
Percentage of Total Sleep Time (TST) Spent in Each Sleep Stage.

Sleep Stages	**TST(min)**	**Stage I**	**Stage II**	**SWS**	**REM**
Mean Duration(min)	433.23	3.26	56.41	20.35	19.00
±SD	± 3.94	± .25	± .85	± .63	± .62

Note. REM=rapid eye movement; SWS= slow wave sleep

Table 3.3
Mean of Spindle Density (±SD) per Channel.

Spindle Density	**Mean**	**F3**	**F4**	**C3**	**C4**	**O1**	**O2**
Count/min	.69	1.11	1.06	.73	.65	.27	.32
±SD	(± .03)	(± .05)	(± .08)	(± .03)	(± .03)	(± .02)	(±.04)

Note. Sleep spindle density (counts per minute, 12 – 15 Hz) for each EEG channel.

3.3.4 Neural correlates of cueing in sleep

3.3.4.1 Event-related responses to cues

The statistical analyses were performed in Mass Univariate ERP Toolbox (OpenWetWare, 2017) using the non-parametric permutation method that allowed for exploratory investigation into a longer time window. With regards to time window of interest we excluded periods of time during which it was unlikely that effects would occur (before 200 ms and after 1,200 ms post stimulus onset; Groch, Schreiner, et al., 2017; Schreiner & Rasch, 2014). To determine when and where the event-related responses to cues differed, they were submitted to a repeated measure, two-tailed permutation test based on the tmax statistic (Blair & Karniski, 1993) using a family-wise alpha level of .05. Repeated measures t-tests were performed for each comparison using the original data and 2,500 random within-participant permutations of the data. The most extreme t-score in each of the sets of tests (i.e., the "tmax" of each set of tests) was recorded and used to estimate the tmax distribution of the null hypothesis (i.e., no difference between conditions). Based on this estimate, critical t-scores were derived and any differences in the original data that exceeded a t-score were deemed reliable (see Figure 3.7). The permutation test analysis was used in lieu of more conventional mean amplitude ANOVAs because it provides much better spatial and temporal resolution than conventional ANOVAs while maintaining a desired family-wise alpha level (i.e., it corrects for the large number of comparisons). Moreover, the tmax statistic was chosen for this permutation test because it has been shown to have relatively good power for data (like ERPs) whose dimensions are highly correlated (Hemmelmann et al., 2004). 2,500 permutations were used to estimate the distribution of the null hypothesis as it is over twice the number recommended by Manly (1997) for a family-wise alpha level of .05.

The EEG analysis of the average amplitudes of event-related responses to cues did not show any differences between items that were remembered and not remembered at the post-test (all p>.05). We further explored the waveforms by separately analysing hits and misses as well as gains and losses following analyses outlined in Schreiner and Rasch (2014). Comparison between hits and misses did not show any significant differences between the two waveforms. However, the comparison between gains and losses showed a significantly more pronounced negativity for losses as compared with gains within the right fronto-central distribution in the time interval from 390-550 ms after presentation of the cue (t(25)= +/-3.49, all p<.043, corrected for multiple comparison; see Figure 3.7).

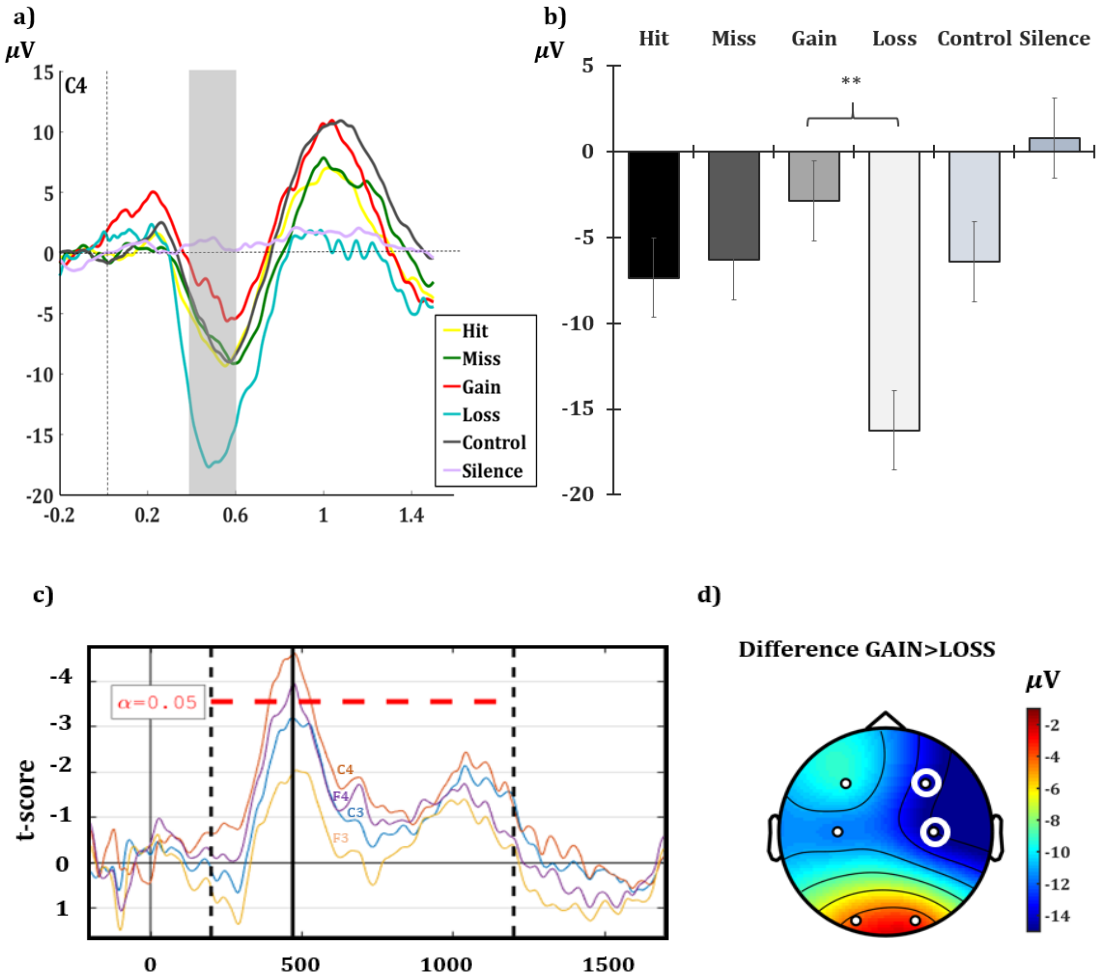

Figure 3.7. Electrophysiological results in the TMR experiment illustrating the event-related brain responses to cues recorded during sleep. a) Successful cueing was associated with less negativity at right fronto-central sites (for illustration of the results, we present the electrode with the highest significance, C4). The shaded area illustrates the time window where the brain responses to gains and losses were significantly different (390-550 ms post stimulus onset); b) The averaged event-related amplitudes in response to cueing for different trial types at the significant time window (corresponding to shaded area; for illustration of the results, we present the electrode with the highest significance, C4); c) The t-scores of comparison between brain responses to gains and losses are plotted for electrodes (C4, C3, F4, F3; the red dotted line shows significant difference between two categories below the 0.05 cut-off point); d) Scalp map representing the topographical distribution for the difference between gains and losses in the time window corresponding to the shaded area and indicating a pronounced right fronto-central negativity for losses; white circles indicate the significant electrodes: C3 and F4 at p<.05, corrected for multiple comparisons.

In sum, the results suggest that the cueing in sleep elicited differential neural responses to item categories that reflect a clear behavioural change pre and post-cueing i.e. gains and losses with losses showing significantly more negative deflection post-cue presentation.

3.3.4.2 Time-frequency analysis

Statistical analyses of the EEG data were performed with a nonparametric randomization test using cluster correction as implemented in FieldTrip (Oostenveld et al., 2011). The cluster alpha was set to .05 and 500 randomizations were conducted for all tests. Clusters were considered significant at $p < .05$ (two-sided).

Following previous work (Groch, Schreiner, et al., 2017) which demonstrated a role of theta (~5-8 Hz) and fast spindle (~14-16 Hz) in response to cues associated with items successfully recalled after sleep (in comparison to items that were not recalled and despite the absence of any evoked power, i.e. event-related responses), we firstly compared the oscillatory response to cues associated with novel words that were remembered (hits and gains) and not remembered (misses and losses) at the post-test. In accordance with Groch, Schreiner, Rasch, Huber, and Wilhelm (2017), the time frequency analysis revealed that the items that were remembered at the post-test differed from items that were not remembered in a frequency band reflecting the fast spindle range (~14-17Hz). More specifically, the two categories differed, in a time-cluster 1,200-1,500 ms after cue onset (p=.028, corrected for multiple comparisons; see Figure 3.8) at the left central electrode. In contrast to Groch, Schreiner, et al. (2017) we did not observe any significant differences between items remembered and not remembered at the post-test in theta frequency range (5-8 Hz).

In order to gain a more fine-grained picture about the possible differences in the time frequency domain we compared the differences in response to hits and misses and losses and gains in time-frequency space. Here, the difference in theta band (5-8 Hz) for the categories that reflect a clear behavioural change after cueing, namely gains and losses, was previously reported (Schreiner & Rasch, 2014), with gains showing significantly more increases in this frequency band.

Firstly, the comparison of power changes in response to hits and misses showed no significant differences in the theta and spindle frequency bands (all identified clusters $p>0.05$). Similarly, and in contrast to our hypotheses and previous reports, the time-frequency analysis revealed no significant differences in theta or spindle frequency bands related to gains versus losses. More specifically, none of the time clusters found in the data were significant (all p>.05).

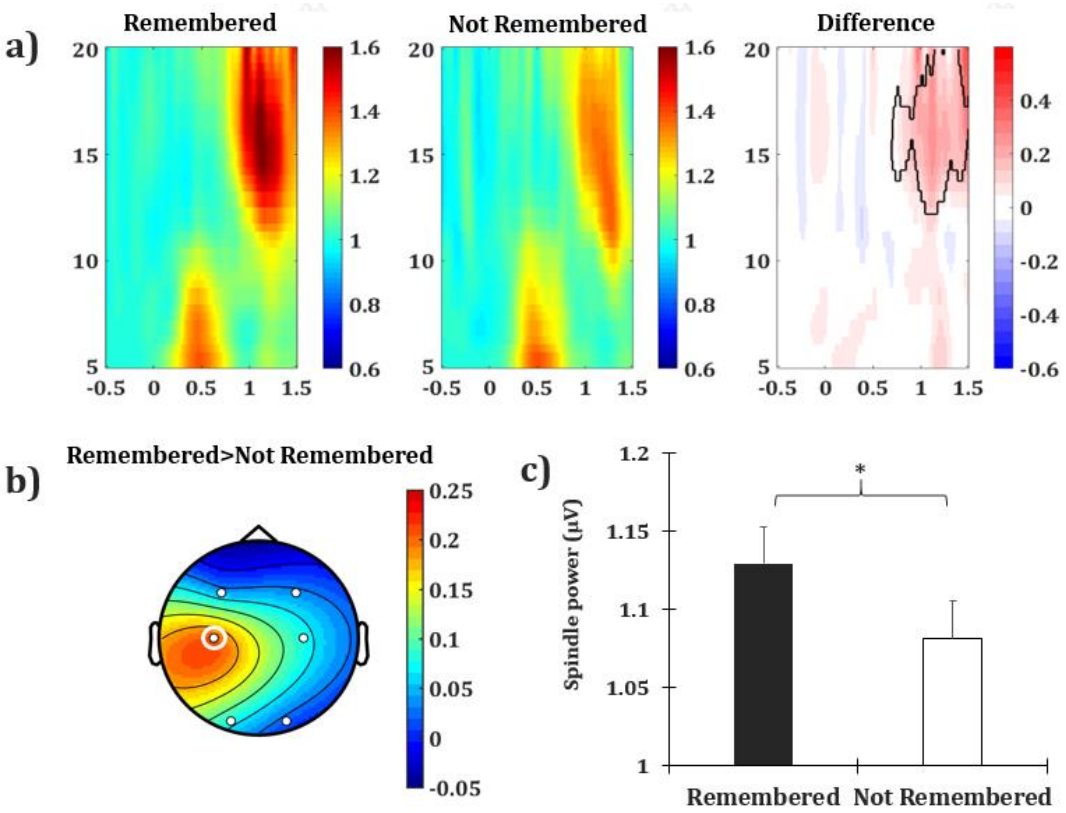

Figure 3.8. EEG activity in response to memory cueing. a) Time-frequency plots for items that were remembered and not remembered at the post-test and the difference between the two. The significant field is outlined in the Difference graph and corresponds to 14-17 Hz frequency band (for illustration of the results, we present the time-frequency data for electrode with the highest significance, C3). b) The topographical distribution of the difference between stimuli that were remembered and not remembered averaged across the time window where the brain responses were significantly different (time interval between 1,100-1,500 ms after cue onset; significant electrode C3 circled in white). c) Mean fast spindle power (14-17 Hz) at significant electrode C3 averaged across the time interval between 1,100-1,500 ms after cue onset.

In sum, the time-frequency analysis showed a pattern of results for items remembered and not remembered at the post-test in fast spindle frequency band similar to previous reports (Groch, Schreiner, et al., 2017). Here, the items that were cued in sleep and correctly recalled at the post-test showed increased fast spindle activity. In contrast to previous research (Groch, Schreiner, et al., 2017; Schreiner & Rasch, 2014) however, we did not observe any differences between gains and losses in theta frequency band.

3.4 Discussion

We investigated whether replaying the auditory cues in sleep will benefit recall and lexical integration of newly learned novel nonwords. We found that replaying

environmental sounds in sleep aided memory recall for cued (versus non-cued) novel items associated with these sounds at the learning phase. This finding stands in agreement with literature as several reports have shown the enhancing role of TMR on explicit memory for cued tokens. However, against our predictions we did not observe any TMR effect on integration of novel words as assessed with the implicit pause detection task. Similarly, TMR had no effect on recognition of novel items. With regards to neuro-correlates of successful cueing in sleep, we found that successful cueing was marked by increased activity in fast spindle frequency range. This is consistent with other research that demonstrated increased fast spindle activity following effective cueing in sleep (Groch, Schreiner, et al., 2017). In contrast to earlier findings however, no evidence of enhanced theta activity associated with successful TMR was detected in this study. Likewise, the analysis of brain responses to cues presented in sleep did not support the previous research. Here, the unsuccessful cueing, which resulted in later memory losses, was associated with an increased early negativity whereas previous research indicated an opposite trend with more pronounced negativity, albeit at a later time, being related to memory gains (Schreiner & Rasch, 2014).

3.4.1 Behavioural evidence

The findings of this experiment are in keeping with growing literature, which indicates that TMR delivered in SWS improves subsequent memory performance for cued (vs. non-cued) memories as measured by the cued recall test. The beneficial effect of cueing in sleep on memory is consistent with the active systems consolidation model which proposes that naturally occurring spontaneous memory reactivations in sleep are vital for memory consolidation. It also suggests that the TMR technique is an effective way to enhance natural overnight consolidation processes for newly learned novel words.

While previous research has investigated the memory effects of verbal TMR on acquiring new vocabulary (Schreiner & Rasch, 2014; Tamminen et al., 2017), here we go a step further by showing that cueing in sleep strengthens memory for highly novel material, i.e. novel phonological forms. This is a finding that goes beyond previous reports (Schreiner & Rasch, 2014) that used foreign words but phonologically similar to already known ones (e.g. Dutch and German). In addition, we showed that non-verbal cues can be equally effective in reactivating novel vocabulary in sleep as verbal cues are. It is worth noting that although verbal and non-verbal cues have been shown equally effective for TMR, evidence suggests that verbal cues may be potentially processed in a different way to non-verbal cues (Cairney et al., 2017).

The novel words used in our experiment were previously unfamiliar to our participants. In contrast to previous studies (Tamminen et al., 2017) they were not assigned any meaning during the training phase. This is an important difference, given that learning novel words with meanings has been shown to activate neocortical as well as hippocampus areas to a greater degree in comparison to learning words without meaning, due to both episodic and semantic memory systems being involved (Takashima, Bakker, van Hell, Janzen, & McQueen, 2016). Therefore, by providing novel word definitions or using meaningful associates (such as translations in the native language), the trajectory of learning of novel words could be changed and result in faster consolidation. For example, the use of Dutch words in Schreiner and Rasch (2014), which were intentionally phonologically similar to their German translations, introduced a close overlap between new material and known vocabulary. Our previous work suggests that the high phonological overlap between new and known words can alter the course of learning and results in a swifter consolidation of novel items (Sobczak & Gaskell, submitted).

Similarly, the presence of prior knowledge associated with newly acquired memories (i.e. the semantic definition of novel words) can accelerate their consolidation and integration (Sommer, 2017). For example, on this account Groch, Schreiner, et al., (2017) using the TMR paradigm demonstrated that prior knowledge is a prerequisite for successful reactivation of memories during sleep. Our study further expands on these findings by using memory cues that only loosely referred to existing knowledge, i.e. environmental sounds. We intentionally avoided assigning any explicit meanings to the novel items and merely encouraged participants to use their mental imagery in order to form associations between novel items and sounds. We believe that by doing so we prevented a strong semantic link with prior knowledge to be formed yet provided sufficient existing associations to prior knowledge for reactivation to take place. This allowed us to further explore the underlying processes of TMR.

In contrast to the beneficial role of cueing during sleep on recall of novel words the recognition of novel items was not affected. This finding is in keeping with previous research that also reported no effect of cueing in sleep on recognition performance (Schreiner, Göldi, et al., 2015; Schreiner & Rasch, 2017). The null effect on recognition confirms that the cueing benefits were not dependent on higher familiarity with the cued items. Similar to the results in the stem completion task, sleep in general improved the recognition performance for both cued and non-cued items (i.e. the main effect of session). This dissociation between two explicit memory tests, recall and recognition, indicates a

broader role of sleep in memory consolidation with only part of it being susceptible to cueing.

Although we observed an enhancing effect of cueing on items' recall we did not see such effect on lexical integration of novel words. In fact, novel items were not integrated well after sleep delay as assessed with the implicit pause detection task. This pattern of results is perhaps unsurprising as we specifically used a low number of exposures to novel items in order to boost any potential cueing impact on lexical integration. Thus, one explanation could be that the items were not learned well enough to induce the lexical competition effect due to a small number of repetitions. Previous studies of word learning mostly used higher numbers of repetitions (Bakker et al., 2014; Davis & Gaskell, 2009; Dumay & Gaskell, 2007; Gaskell & Dumay, 2003; Henderson et al., 2012; Tamminen et al., 2010). Nonetheless, the accuracy in the cued recall task was high (above 48%) and matched the accuracy reported in the previous studies which observed reliable competition effects after sleep (above 40 %; see Henderson et al., 2013; Weighall, Henderson, Barr, Cairney, & Gaskell, 2016 for comparison). Another, yet rather speculative interpretation would be that cueing in sleep enhanced some aspects of consolidation of novel material, measured by the memory recall, but hindered others, for example its integration within pre-existing networks. In that situation we would not see any lexical integration which is exactly the case in our study. That would assume some dichotomy within the consolidation processes, potentially with regards to different properties of learnt material. Indeed, although previous studies did not report any differences in integration measures of cued and non-cued items, the RT latencies for both categories seem to be consistent with the results obtained in our study. The cued items in Tamminen et al. (2017) elicited critically less lexical competition change from pre to post-sleep test (+5 s) than non-cued items (+34 s). Therefore, the lexical competition effect reported there, seems to be driven by items that were not cued in sleep. Besides, the successful cueing in sleep, typically manifested by increased recall of novel items, was not observed in Tamminen et al. (2017). Thus, assuming that successful cueing may interfere with integration aspects of novel knowledge, be it cued or non-cued, we would not expect this interference to take place when cueing effect is not observed (Tamminen et al., 2017).

Tamminen et al. (2017) found a relationship between lexical integration and percentage of time spent in REM. Although weak, this correlation implicated a potential role for REM sleep in mediating lexical integration processes. Such correlation was not observed in our study. Firstly, this may be due to the fact that we did not observe significant increases in lexical competition effects from session 1 to session 2 for cued and non-cued items. Thus,

since novel items were not integrated well within the lexicon there was also no changes in REM that would reflect the lexical integration processes taking place. Secondly, the relationship between time spent in REM sleep and lexical competition could be a consequence of a nap paradigm used in the study as opposed to a full night of nocturnal sleep. Two studies reporting REM as a sleep stage important for integration processes (Batterink et al., 2017; Tamminen et al., 2017) used cueing during an afternoon nap. The role of REM in memory consolidation is controversial (Diekelmann & Born, 2010) and it may well be that the sleep stages during naps are governed by different processes than in the full night of sleep. In sum, the role of REM in integration process is yet to be elucidated.

The finding that cueing in sleep enhances verbal recall of newly learned words the next day has potentially a high relevance to every-day learning context, in particular due to the growing need for communication in foreign languages. However, the retrieval of new words was tested only after one night of sleep. Future studies are needed to examine the long-term effect of cueing in sleep after several days or weeks. Additionally, it is also important to determine whether the beneficial influences of TMR in sleep on memory recall are accompanied by any potential detrimental effect on sleep-dependent memory consolidation, for example processes of integration within pre-existing knowledge.

3.4.2 Neuro-correlates of cueing in sleep

The analysis of neural responses to cues presented in sleep showed differential event-related responses to items that reflected a clear behavioural change in recall accuracy, namely gains and losses. Surprisingly, the effect of different cue categories on event-related responses indicated an early negativity (400-600 ms after stimulus onset) that marked changes in performance (i.e., resulting in later memory losses). This finding is different to previous research which has suggested an opposite trend with more pronounced negativity, albeit at a later time (800-1,100 ms), being related to memory gains (Schreiner & Rasch, 2014). The authors interpreted this finding within the literature of wake ERPs. They pointed out the resemblance of the enhanced negativity following reactivations in sleep related to increased performance, to the negativity typically observed during waking encoding for correctly remembered items. However, these wake negative markers are typically observed at an earlier time interval following stimulus presentation (for example, before 800 ms; cf. Guo, Voss, & Paller, 2005) than the one reported in Schreiner and Rasch (2014; after 800 ms post-stimulus). Above all however, it remains an open question whether the neural responses following reactivation effects in sleep are similar to processes underlying encoding and retrieval during waking. An alternative explanation would be that the observed negativity could merely relate to sensory memory.

For example, Ibanez, San Martin, Hurtado, and Lopez (2009) reviewed event-related potentials (ERPs) observed in sleep in response to cognitive processing. The authors pointed out that N300 and N550 components observed in stage 2 and SWS are affected by contextual characteristics of stimuli (Cantero, Escera, & Atienza, 2001), as well as stimulus novelty (Bastien & Campbell, 1992) and probability of appearance (Colrain et al., 1999).

Still, another explanation which relates to the precise timing of cues presentation also exists. Recent unpublished work by van Poppel, Korjoukov and Talamini (2016) showed that only the cues presented exactly at the SO up-state resulted in memory benefits, whilst cues presented at the SO down-state led to higher rates of forgetting. Therefore, it could be that the negativity deflection observed following item loss at the post-test reflects the timing of the reactivations that took place at a point before the SO down-states. As we did not control for the precise timing of the reactivations the question whether these neural responses are indeed a reflection of different SO phases following reactivations requires further examination. Slow oscillations has been shown to play a crucial role in memory consolidation during sleep (Marshall et al., 2006; Ngo, Martinetz, et al., 2013) and they may provide a vital temporal frame for the externally induced reactivations to be successfully used in a process of memory consolidation. Further studies, which take these variables into account, will need to be undertaken.

A possible explanation of different evoked responses to cueing in sleep obtained in this and previous research may be due to the sleep stage when the cues were administered. Schreiner and Rasch (2014) administered their cues in N2 and SWS whereas here the cues were presented during SWS only. This may have caused qualitative changes in observed neural responses. For instance, the active systems consolidation model proposes a vital role for SOs in synchronising hippocampal memory reactivations with thalamo-cortical spindle activity (Bergmann, Mölle, Diedrichs, Born, & Siebner, 2012; Rasch & Born, 2013). Although the authors observed an increased number of post-stimulus SOs in both N2 and SWS, the increased spindle activity (11-13 Hz) was observed when analysis included SWS only but not SWS and N2. This suggests that both SOs as well as spindle activity may reflect successful reactivations taking place in sleep. In fact, spindle activity, slow and fast, has been previously related to memory improvements (Schabus et al., 2004). However, the relationship between occurrence of spindle at the point of external reactivations is far from being clear. Some studies indicated reduced responsiveness of the brain to external stimuli during slow spindles phase and co-occurring SO downstate (Schabus et al., 2012). Here, due to a short epoch duration we were not able to assess the amount of post-stimulus slow oscillations.

The time-frequency analysis revealed an increased fast spindle (14-17 Hz) activity following cues for items that were subsequently remembered at the post-test (gains and hits) as opposed to the items that were not remembered (misses and losses). This augmented fast spindle activity for remembered items was previously reported in a study using TMR paradigm (Groch, Schreiner, et al., 2017). Groch, Schreiner, et al. (2017) investigated the effects of TMR on learning new items with and without reference to existing knowledge. They found that although both fast spindle and theta activity showed increase in response to later remembered stimuli related to prior knowledge but not for stimuli not related to prior knowledge, only fast spindle activity, but not theta, was correlated with a beneficial effect of cueing (Groch, Schreiner, et al., 2017). This is in agreement with our findings. Besides, the role of fast and slow spindles in memory consolidation is quite distinct. For example, slow spindles occur at a different time of the SO cycle than fast spindles with fast spindles being driven by SO up-states and slow-spindles at the down-state. It has been shown that the fast-spindles, and not the slow spindles, play a key role in sleep-dependent memory processing (Mölle et al., 2011). Similarly, since the fate of external cueing may depend on the SO up state this is the fast spindle activity that may accompany the effective cueing.

An increase in the spindle density has been previously reported to accompany successful integration of novel phonological forms into the lexicon (Tamminen et al., 2010). However, we did not observe the integration of novel items despite increased spindle power. This may be due to the fact that the novel items were not encoded at a level sufficient to ensure their successful integration. Secondly, as we observed the increase in the fast spindle power following the presentation of the cue, these fast spindle power increases may differ from a naturally occurring higher number of sleep spindle that accompany lexical integration. Lastly, due to a low number of items and thus a low statistical power, we did not perform an analysis that would allow us to distinguish between integration processes for different item categories such as items remembered and not remembered after sleep. Future investigations could look into how the difference in pre and post-sleep memory and TMR affects the integration processes.

Lastly, we did not observe any evidence of increased theta activity with regards to items that were remembered at the post-test, e g. hits and gains when analysed separately and together. This outcome stands in contrast to previous reports which found increased theta response when successfully cueing items recalled after sleep (Schreiner & Rasch, 2014). There are several possible explanations that could have impacted these results. Firstly, these outcomes may be a consequence of the lack of an adequate power related to a

limited number of electrodes which entered our analysis (4 electrodes). This means that we may not have picked up the signal at the topography where it was present. Secondly, as mentioned earlier the current study replayed the cue sounds only during SWS and not as previous studies reported in SWS as well as stage 2 (N2) sleep. This may have affected theta activity more directly than reactivation in SWS where these two oscillations are co-ordinated by SOs. Indeed, a study by Schreiner and Rasch (2014) reported more pronounced increases in theta activity for gains as compared with losses during stage 2 sleep. Nevertheless, the increased theta power has been implicated as playing an important role in memory improvement in a wake condition (Lisman & Jensen, 2013). It remains to be further clarified whether the theta activity in sleep indeed reflects memory improvement similar to wakefulness and if so, what is its part in successful memory consolidation during sleep following external reactivations.

3.5 Conclusions

Our results demonstrated that cued reactivation of newly learned novel phonological forms during sleep results in enhanced recall of cued items. This process is accompanied by sleep-specific neural spindle activity. Although cueing newly learned words during post-learning sleep is an efficient tool to increase the recall of novel words we did not find any evidence of the beneficial role of cueing on integration of newly learned tokens. We conclude that cueing in sleep may be an effective way to increase performance related to episodic memory traces however its role in a more complex processing and integration of learned material remains unclear. Future studies will need to be carried out to elucidate the role of cueing in sleep for lexical integration of novel words and also the potentially different role of memory reactivation in processes of memory consolidation and memory integration.

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CHAPTER 4
PROBING CONSOLIDATION WITH TDCS IN QUIET WAKEFULNESS

Sleep supports memory via the process of memory consolidation. These sleep benefits for memory can be enhanced using transcranial direct current stimulation (tDCS) techniques (Marshall et al., 2004). Recent evidence suggests that quiet wakeful rest can result in memory increases that are comparable to sleep. However, whether similar consolidation mechanisms operate during sleep and wake is currently unknown. Here, we tested whether applying anodal tDCS to the right occipital-parietal region of the brain during quiet wakefulness will result in better memory for a word list when compared to a sham condition. A recall test was administered immediately following the rest period and after a week delay. We also examined the neural correlates associated with potential memory improvements. We found that applying tDCS to the right occipital-parietal site enhanced memory for a list of words in comparison to a sham condition. This memory enhancement was still present after a week delay. Although the tDCS group showed a trend towards reduced brain activity in the alpha frequency band, we found no significant differences between the two conditions in this oscillatory activity of interest. Our findings suggest that memory consolidation during quiet wakefulness can be manipulated with tDCS. We suggest that the default brain network of the brain at rest (i.e. the default mode network) may participate in this process, however, the exact mechanism remains speculative.

4.1 Introduction

Despite a great amount of learning accomplished every day, the majority of what we learn is forgotten (Spear, 2014). Some memories however, endure in the long-term. It is currently unclear what causes some of the memories to last whilst other to undergo forgetting. From a behavioural perspective, numerous studies have shown that sleep after learning facilitates better retention of memory in comparison to wakefulness. It is widely accepted that sleep benefits in memory are due to a process of memory consolidation (Diekelmann & Born, 2010; Stickgold, 2005). Research indicates that the consolidation process may be due to a neural replay which facilitates spontaneous reactivation of newly learnt information during a stage of deep sleep, called slow-wave sleep (SWS; Gais & Born, 2004).

Thus far, sleep has been considered most suited to facilitate memory consolidation on both a cellular and system level, as it provides a period of reduced interference (time

when there is no new information input). Cellular consolidation involves molecular and cellular processes that stabilise memory traces by strengthening synaptic connections according to the synaptic homeostasis hypothesis (Tononi & Cirelli, 2003). System consolidation on the other hand, refers to a two-stage process whereby new memories would be initially coded in the hippocampus and then followed by their successive reactivation within the hippocampal-cortical networks to allow them to be gradually integrated within neocortical networks (McClelland et al., 1995).

More recently, Mednick, Cai, Shuman, Anagnostaras, and Wixted (2011) proposed a new hypothesis according to which the consolidation of hippocampal-dependent memories happens not only in sleep but in fact whenever the encoding of new information is sufficiently reduced (i.e. the hippocampus is not otherwise occupied by the task of encoding new memories). Indeed, although prior work indicates that the spontaneous neural replay of memories is mostly sleep-specific, some evidence suggests that it can also take place during an awake resting state (Davidson, Kloosterman, & Wilson, 2009; Karlsson & Frank, 2009; Nakashiba, Buhl, McHugh, 2009). Amongst other states of alertness, the quiet wakefulness, a non-sleep resting state with reduced encoding and interference, seems to provide particularly favourable conditions for memory consolidation to take place. This would be due to a limited learning and consequently, a reduced hippocampal plasticity happening during this state, just as during SWS (Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999).

Interestingly, few studies that compared quiet wakefulness with sleep observed similar memory improvements across both conditions (Bohbot et al., 1998; Gottselig et al., 2004). In a study using the hippocampus-dependent visual search task (Greene, 2007), similar learning profiles were observed when comparing nap and quiet wake groups. This was, however, not the case for an active wake group, which instead of resting was asked to play a computer game (Cai, Mednick, Harrison, Kanady, & Mednick, 2009; Dewar et al., 2014). In fact, most studies investigate the effect of sleep on memory and compare it to active wakefulness, which does not control for interference from recently encoding memories.

Additional evidence that quiet wakefulness benefits memory has emerged in recent years. For example, Dewar, Alber, Butler, Cowan, and Della Sala (2012) and Dewar, Alber, Cowan, and Sala (2014) showed that a brief period of quiet resting wake can improve later memory in elderly and younger participants (Craig et al., 2015). Moreover, superior retention was still observed one week after training suggesting that the memory benefits endured over the long-term. Importantly, the researchers also showed that quiet

wakefulness can support the integration of new spatial memories (Craig et al., 2016), a process that has, hitherto, been strongly considered sleep-dependent. The authors hypothesised that the memory improvements following quiet wakefulness are due to a hippocampal replay of novel information taking place during rest.

It was proposed that quiet wakefulness may mimic sleep, and particularly SWS, in facilitating memory consolidation. For example, neuroimaging studies indicate that increased performance after quiet wakefulness has potentially similar underlying neural mechanism to sleep. A fMRI study by Tambini, Ketz, and Davachi (2010) showed that hippocampal-cortical connectivity, as measured by the blood oxygenation level-dependent (BOLD), was enhanced after a period of quiet wakefulness in comparison with the pre-task resting baseline. Furthermore, individual differences in the magnitude of the post-task functional connectivity were predictive of later memory performance (Gottselig et al., 2004). This hippocampal-neocortical cross-talk is in fact a vital part of the sleep-dependent memory consolidation process according to one of the most influential models of memory, the Complementary Learning Systems account (CLS) (Davis & Gaskell, 2009; McClelland et al., 1995). Similarly, the neurophysiological signatures of sleep-dependent memory consolidation in sleep, such as oscillatory pattern of large amplitude activity called sharp wave ripples (SWRs; Sirota & Buzsáki, 2005), can also occur during quiet wakefulness (Headley & Paré, 2017). In sleep, the SWRs have been specified as driving the spontaneous and endogenous reactivation of cortical activity patterns observed during learning and indicate a potentially similar mechanism taking place during quiet resting state. Indeed, neuronal replay has been observed during both sleep and restful waking with reduced interference in rodents (Foster & Wilson, 2006). Furthermore, the low level of acetylcholine, a neurotransmitter indicated important in memory consolidation (Rasch, Born, & Gais, 2006), has been observed during both the quiet wake and deep part of sleep (SWS), in contrast to active wake (Hasselmo, 1995).

However, not all memories undergo wakeful consolidation (Wilhelm et al., 2012). According to Breton and Robertson (2014), some memories may be enhanced during wakefulness while enhancement of others may be delayed until sleep. The authors suggested that this process may be mediated by inhibitory mechanisms that create a processing "bottleneck" in the brain that prevents certain memories from being consolidated during wakefulness. This bottleneck results in the delay of immediate consolidation of one memory over the other (Breton & Robertson, 2014). For example, when a motor skill and a word list are learnt in quick succession, the consolidation of motor skill is prevented. Yet, disruption of the bottleneck using transcranial magnetic stimulation

(TMS), allowed multiple memories to be consolidated simultaneously during wakefulness, suggesting that the bottleneck can be 'overwritten' using brain stimulation techniques (Breton & Robertson, 2014). Still, the question of whether this mechanism operates when learning exclusively declarative material remains unanswered.

There is some suggestion that oscillatory brain activity, and particularly alpha rhythms, may play a role in the inhibitory mechanism of the bottleneck. Meeuwissen, Takashima, Fernández, and Jensen (2011) reported stronger parieto-occipital alpha power during rehearsal of successfully recalled word sequences when compared to unsuccessfully recalled sequences tested after a maintenance interval of approximately 5 minutes. Furthermore, a reduction in alpha oscillatory activity has been observed immediately following encoding, but only for unsuccessfully consolidated items (Breton & Robertson, 2014). Although these findings relate more to the process of encoding new information, alpha rhythms may also play a critical role in the control of memory consolidation during wakefulness following learning.

For example, increased alpha power during quiet wake would offer reduced interference and, consequently, a protection from new input that may disrupt new memory traces during a critical period after acquisition, (e.g. Gottselig & Re, 2004). The exact mechanism underlying reduced interference would relate to the idea of inhibition or disengagement (Cooper et al., 2003; Jensen, 2002; Klimesch, 1997; Klimesch et al., 2000; Tuladhar et al., 2007; Vanni et al., 1997) of the brain regions irrelevant to the task, and where such alpha increases were observed. Such inhibition would prevent the flow of information into brain areas responsible for retaining memories. For example, the inhibition (or disengagement) of occipital-parietal areas could suppress visual input which could disturb the maintenance of working memory in frontal areas. The inhibition hypothesis would allow minimal disruption to on-going consolidation processes and as a results, benefit memory. Previous research has shown that it is possible to reduce the cortical excitability in humans during wake by modulating alpha activity using a tDCS technique (Balconi & Vitaloni, 2012). tDCS is a non-invasive brain neuro-stimulation which uses constant, low direct current delivered via electrodes on the head and has been previously shown to influence cognitive function in healthy volunteers (Antal et al., 2004; Gandiga, Hummel, & Cohen, 2006).

It is worth noting that improvements in memory have been previously observed following external stimulation during sleep, achieved by using both sound stimulation and tDCS (Marshall, Helgadóttir, Mölle, & Born, 2006; Marshall, Kirov, Brade, Mölle, & Born, 2011; Ngo, Martinetz, Born, & Mölle, 2013). For example, transcranial direct current

stimulation of delta activity (<3 Hz) during SWS significantly decreased forgetting in declarative memory but not procedural memory performance (Marshall et al., 2004). This indicate that it is possible to successfully alter memory consolidation by modulating the naturally occurring brain rhythms with tDCS technique.

Following excitatory anodal tDCS during wakeful rest increases in alpha power have been reported across the brain (Spitoni, Cimmino, Bozzacchi, Pizzamiglio, & Di Russo, 2013). For example, Spitoni et al. (2013) investigated modulations of spontaneous alpha activity during rest using a 64-channel EEG following low current tDCS delivered to right posterior parietal cortex. The study compared anodal and cathodal conditions across the rest interval during which participants were instructed to close or open their eyes every 30 seconds. The authors found that anodal tDCS altered the ongoing brain activity specifically in the alpha band, with strongest effects reported at the occipito-parietal and frontal sites at 7.5 minutes post-stimulation for the eyes-closed condition. This effect was not observed following cathodal or sham stimulation.

The effect of anodal tDCS on alpha rhythms has been attributed to two factors. Firstly, anodal tDCS was argued to enhance the endogenous activity of the resting brain during which large alpha waves are most pronounced due to reduced information processing (Pfurtscheller, 2001). Therefore, the increased alpha amplitude reflects enhancement of relaxed wakefulness. Secondly, due to its excitatory effect on inhibitory neurons in parietal cortex, the anodal tDCS led to an inhibition of the parieto-occipital sites and thus an increased alpha activity. However, as pointed out by Spitoni et al. (2013), the opposite (i.e. lower alpha activity) could also be expected—since anodal tDCS is typically associated with greater cortical excitability it could decrease the alpha activity commonly correlated with cortical deactivation or inhibition (Klimesch et al., 2007). Nevertheless, similar alpha increases following anodal tDCS have previously been reported (Mangia, Pirini, & Cappello, 2014). Additionally, the increased alpha activity that expanded over frontal sites, far from the stimulation area, suggested a 'functional coupling of alpha' (Sauseng et al., 2005) when distinct cerebral regions become co-activated and synchronised on a large-scale including fronto-parietal network (Sadaghiani et al., 2012).

Recent studies have also demonstrated that cognitive task performance also correlates with increases of alpha activity in task-irrelevant areas. For example, Fu et al. (2001) showed the increases in posterior alpha activity when participants attended to the auditory stimuli, typically processed by temporal regions. This finding reflected the fact that the parietal regions are not needed to process auditory stimuli, hence become 'disengaged'. Following the argument that alpha activity decreases in engaged regions, while it increases

in disengaged regions, Meeuwissen, Takashima, Fernández, and Jensen (2011) asked their participants to learn a list of words and showed a dramatic increase in alpha activity over occipital regions. Interestingly, the authors were able to predict whether the word list was later remembered based on the alpha activity alone. This suggested that the occipital regions were not required for learning the word lists and thus it was proposed that optimal task performance on this memory task depends on the active inhibition of occipital regions in order to allocate resources to task-relevant areas (Jensen & Mazaheri, 2010).

Similarly, the alpha synchronisation between different brain regions was also examined during the encoding and memorization of spoken word (Schack & Weiss, 2005). The researchers showed co-activation between parietal and more anterior areas during the memorisation of lists of concrete spoken words. The inhibition of task-irrelevant pathways from parietal site coincided with increased activity in other regions, due to alpha synchronisation, assuring optimal memory performance. This association between increased alpha activity in occipital-parietal sites and successful learning and retention of word lists made it a promising task in the context of the research presented here which examined the effects of tDCS applied to parietal regions during quiet rest on memory performance.

In sum, an enhancements in memory have been observed following periods of overnight sleep consolidation (Born, Rasch, & Gais, 2006; Davis, Di Betta, Macdonald, & Gaskell, 2009) and further improvements in memory are observed following external stimulation during sleep (Ngo, Martinetz, Born & Mölle 2013; Marshall, Helgadóttir, Mölle & Born 2006, Marshall, Kirov, Brade, Mölle, & Born, 2011). At the same time, it has also been suggested that brief wakeful rest may also provide favourable conditions for consolidation. A long-term enhancement of memory performance has been observed following wakeful rest, when compared to active wakefulness (Dewar et al., 2012). This suggests that wakeful rest after learning allows memory traces to undergo some form of consolidation leading to a long-term increase in memory retention. Furthermore, recent evidence suggests the relationship between wakeful consolidation and alpha oscillatory activity (Breton & Robertson, 2014).

In order to study the relationship between wakeful consolidation and the role of alpha oscillatory activity, we proposed a study that modulates alpha activity during restful wake using excitatory (anodal) tDCS. Following evidence that learning a list of spoken words is a suitable task for investigation of alpha activity in parietal regions we employed similar task. During an encoding phase participants were asked to learn a list of twenty-five concrete objects. Following encoding they took part in a 30-minute period of wakeful rest

where tDCS or sham stimulation was applied to the right parietal-occipital brain area. Memory performance was then assessed by a free recall task. As previous studies on quiet wake showed a long term effects up to 7 days post encoding (Craig et al., 2016; Dewar et al., 2012, 2014) our participants also completed behavioural tests measuring their memory and recognition of word list during a second session a week later.

The aim of the proposed study was to explore the effects of tDCS on neuro-correlates that underpin wakeful rest, the role of alpha activity in particular, and their relationship with memory consolidation. If the effect of tDCS on memory consolidation was observed, it would be an original and important advance in the area of learning, memory, consolidation and in literature that proposes tDCS as a potential technique for memory and learning rehabilitation. Additionally, an investigation into memory consolidation mechanism utilised in quiet wake would broaden our understanding of how memory processes are regulated and controlled in a situation when sleep is a limited option.

4.2 Materials and Methods

4.2.1 Participants

Right-handed native speakers of English, aged between 18-35 years, were recruited from the campus at the University of York in return for payment reward. Participants were excluded if they had any history of psychological or neurological disorder (including seizures and stroke), past or present drug/alcohol abuse, or if they were taking any medication that could affect attention or memory. All participants were additionally screened for any language and sleep disorders in accordance with typical sleep lab requirements. Thirty-three individuals were deemed eligible and participated in the study. Two participants were excluded for falling asleep during the experiment and one was excluded because of a computer error during data collection. Ultimately, thirty participants (twenty females) were included in the final sample, fifteen in each condition (i.e. tDCS and sham). All research procedures were approved by the Research Ethics committee of the Department of Psychology, University of York, and each participant provided written informed consent. Participants were free to withdraw from the study at any time without giving a reason.

4.2.2 Material and design

50 semantically unrelated common words (see Appendix D), describing objects, were grouped into two list of 25 words (targets and foils). The words were matched for the number of letters, syllables, familiarity, concreteness, imageability and frequency. For each

participant one of the lists was used for training and the other list remained untrained and acted as foils in the recognition memory task. The stimuli lists were counterbalanced across participants.

The study utilised a between-participants' design. Each participant was randomly assigned to and tested in one of the two experimental conditions: a stimulation condition where participants underwent tDCS or a sham condition. Participants, but not the experimenters, remained blind throughout the duration of the experiment regarding the type of condition they participated in. The experiment spanned over two sessions separated by an interval of 1 week. The first session consisted of several phases which involved training on the word list followed by an immediate free recall test (serving as a baseline performance), and a quiet wakeful rest when tDCS or sham was applied. In order to measure any potential impact of tDCS stimulation on memory performance the delay was followed by another free recall test. Additionally, to control for any long-term effects, participants completed a third test which took place a week later.

4.2.3 Procedure

Prior to taking part in the experiment, each participant was sent a brief information about the study which explained study's aims and tDCS stimulation procedure. Additionally, all participants were also asked to complete an eligibility questionnaire before their participation including a safety screening form and a risk assessment form. At the beginning of the first session, participants were again fully briefed about the use of polysomnography (PSG) and tDCS and possible side effects and written consent was obtained. The experiment took place in the Sleep, Language and Memory Laboratory at the University of York.

The first session began with the application of the electrodes for PSG, including: electroencephalography (EEG, 12 channels: 10 scalp channels and 2 mastoids) and horizontal electrooculography (EOG). This was followed by the application of tDCS electrodes to the right parietal site (anodal) and left shoulder (cathodal). Once EEG and tDCS equipment was set up, participants were seated in a comfortable position in a high back reclining chair where they remained for the duration of the study.

To investigate any potential impact of tDCS stimulation on memory retention, the experimental session was split into five separate phases.

Phase one. The first phase consisted of the training during which participants were aurally presented with the 25 target words over high-quality earphones. They were asked to keep their eyes closed during this phase. During the presentation of the word list

participants' EEG brain activity was continuously recorded in order to supply 2 minutes of tDCS stimulation-free interval for later comparisons of oscillatory activity levels (see Figure 4.1; pre-stimulation interval is marked in red). The words were presented at the rate of 1 word per second with a 2-second interval between words. The volume threshold was kept at a comfortable level and adjusted individually on participant's request. Participants were informed that they would hear a list of words which they would be asked to recall immediately, before they would be allowed to rest. However, participants were not informed about the surprise second recall test that took place after the quiet rest interval to minimise possibility of active rehearsal. Participants were also not informed about the third recall test and a recognition test that took place after a 7-day delay. They were instead asked to return to the lab for session 2 to complete the tDCS evaluation form.

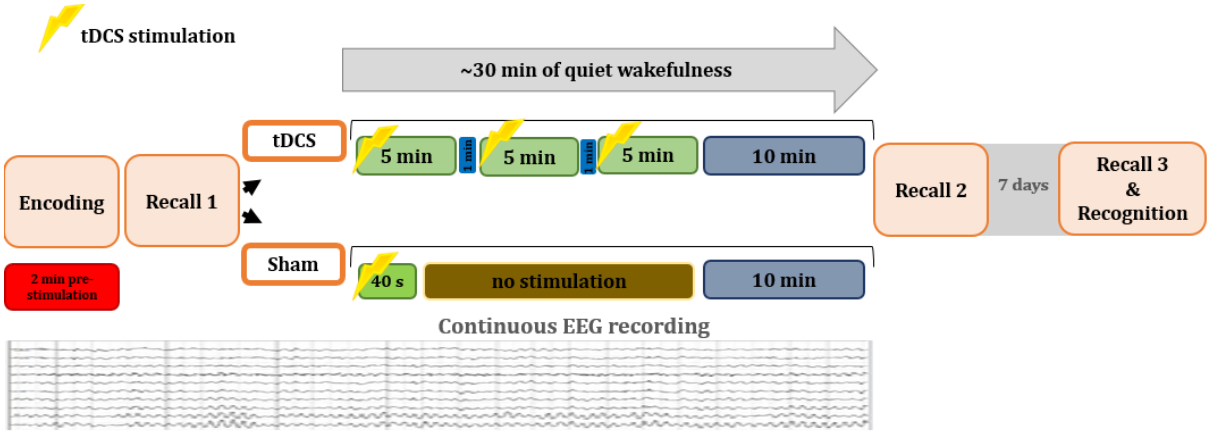

Figure 4.1. Experimental procedure in the tDCS study. Participants completed the encoding phase which was followed by the first recall test. Participants then underwent a quiet wake delay where they were instructed to rest with their eyes closed. The surprise second recall test was implemented after the quiet rest delay was finished. Participants returned to the lab a week later to complete another surprise recall test and a recognition test. During the experiment participants' EEG was continuously recorded. A 2-minute-long pre-stimulation interval is marked in red whereas a 10-minute-long post-stimulation interval is in blue.

Phase two. Following encoding, in the second phase of the session, participants completed an immediate free recall test where they were asked to orally recall as many of the 25 words as possible, in any order. They were then asked to relax in a darkened room with their eyes closed for approximately half an hour.

Phase three. During the quiet wakefulness, eye movements were constantly monitored online by experimenter to ensure that participants kept their eyes closed throughout the experiment. Participants were informed that the tDCS would be applied during this time and asked to avoid any movements or speaking unless they find the stimulation uncomfortable or if they felt they were close to falling asleep. During the first

18 minutes of the quiet rest either the tDCS or sham stimulation was applied. In the tDCS condition, three 5-min periods of stimulation, interleaved with 1-min stimulation-free intervals, took place. In the sham condition, the tDCS current was applied for the first 40 seconds of the rest delay in order for participants to feel initial stimulation. As the experimenter and tDCS amplifier were located behind a screen wall and silent, the participants could not see or hear the experimenter switching the equipment. To allow for any residual effects of tDCS to dissipate (Spitoni et al. 2013) additional 10 minutes were added following the tDCS/sham stimulation and before the second surprise free recall test (see Figure 4.1).

Phase four. Following the quiet wake delay, participants were asked to complete a surprise free recall test. After this final memory test, the EEG and tDCS equipment was removed and participants were free to take a shower. Additionally, upon completion of the experiment, all participants were asked to complete a debriefing questionnaire regarding any tDCS sensations experienced during the stimulation time (adapted from Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010).

Phase five. For the second session of the study, participants were asked to return to the lab 7 days later to complete an additional post-study questionnaire. However, before participants completed a study evaluation form, they were asked to complete a surprise free-recall test. During this session, participants were also asked to complete a recognition task based on Hu, Stylos-Allan, and Walker (2006). In this task they were presented with 50 words (25 target words and 25 foils). Each trial began with a fixation crosshair (1,000ms), which was followed by a sound stimulus (a word) and then a response screen (3,000 ms). However, the next trial did not begin until participants made a key-press response indicating that they (a) consciously recollected hearing the specific word from the prior study session (well-remembered judgment, *WR*), (b) knew that the word was presented in the prior study session but could not recall any contextual information about its previous occurrence (familiar judgment, *F*), or (c) thought the word was new (new judgment, *N*). Instructions on the WR/F/N distinction were presented before the task and on each response screen to clarify these examples and the correct buttons. Recognition trials were classified according to whether WR, F, or N judgments were correct or incorrect. Data points with no response were removed from analysis. Following Hu et al. (2006), we compared not only the accuracy of memory recognition between the tDCS and sham groups, but also the memory bias (selection criterion) of recognition judgments.

All instructions given to participants were presented aurally and recorded by a native speaker of British English in the sound-proof booth. The task presentation was

controlled by E-Prime version 2.0 (Psychology Software Tools, Inc.) with an automated script. The EEG recordings were collected using an Embla N7000 PSG system with RemLogic version 3.4 software. The triggers which marked the beginning and the end of each tDCS stimulation period (or sham) were recorded as a series of square waves at the respective time points sent from the PC that controlled the experimental task to the Embla amplifier using Arduino device. The first session took approximately 2 hours to complete and the second session took 15 minutes to complete. Upon completion of the final session participants were again debriefed about the aim of the study and reimbursed for their participation.

4.2.4 EEG and tDCS set up

EEG signal was continuously recorded from 10 channels: F7, F3, Fz, Fpz, F4, F8, C3, Cz, P3, and O1 (see Figure 4.2). The channels were initially referenced to the ipsilateral mastoids (M1 or M2; the Fz, Fpz, Cz electrodes were referenced to averaged left and right mastoids). Horizontal eye movements were monitored by recording from the electrode at the corner of the right eyelid. Blinks and vertical eye movements were recorded by the electrode under the left eye. However, participants were instructed to keep their eyes closed throughout the experiment, hence the eye movements were kept to minimum. EEG scalp electrodes were attached according to the international 10-20 system and monitored with the Embla N7000 PSG system (with RemLogic version 3.4 software). After the scalp was cleaned with NuPrep exfoliating agent (Weave and Company), the electrodes were attached using EC2 electrode cream (Grass Technologies). The ground electrode was positioned on the forehead at Fpz. Each electrode had a connection impedance of < 5 kΩ and all signals were digitally sampled at 200 Hz. Of a strategic value was recording taken at two time points: during encoding (in order to get a baseline measure of brain activity and to monitor for potentially elevated theta activity during memory task) and during a 10-minute delay following tDCS (10 minutes). This enabled to quantify the effect of tDCS on brain activity within the frequency bands of interest.

The tDCS stimulation was applied using a Magstim DC+ simulator with a pair of saline-soaked sponge electrodes. The anode (7 x 5cm) was placed over P4 of the 10-20 system for EEG electrode placement. The cathode was placed on the left shoulder (7 x 5cm). In the anodal tDCS condition a constant current of 1.5mA intensity was applied on the skin intermittently over the 18-minute quiet wake period. During this time there were three 5-min periods of stimulation (fade in 15s, fade out 10s) followed by 1-min stimulation-free intervals, which allowed us to record the clear EEG signal. In the sham condition, a sham stimulation was performed exactly in the same way as tDCS, however it was applied only

once at the beginning of quiet rest. More specifically, the stimulator was ramped up to 1.5mA current over 15s, then delivered for a following 15s, before being faded out over 10s. Thus, the stimulation in sham condition lasted no longer than 40 seconds and after that time no stimulation was applied. This sham protocol ensured that participants felt the same initial sensations of tDCS, but prevented any modulation of cortical excitability, making participants blind to the tDCS or sham condition. By taking care that all participants in the sham condition had a chance to experience initial tDCS sensation we improved on the previous tDCS studies which rarely used the actual stimulation during sham condition (cf. Marshall, Mölle, Hallschmid, & Born, 2004).

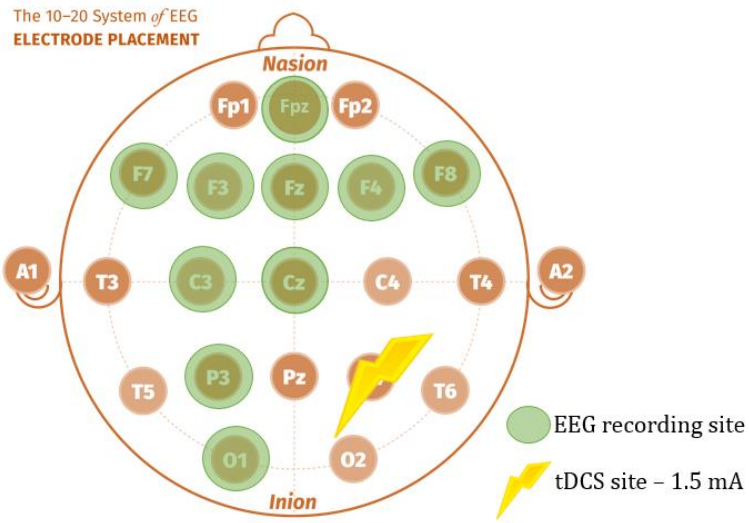

Figure 4.2. The electrode placement and site of tDCS application.

4.2.5 EEG pre-processing and analysis

All EEG data pre-processing and analysis was done using custom-made MATLAB scripts and Fieldtrip toolbox (Oostenveld et al., 2011). The EEG signal was first re-referenced offline to the averaged left and right mastoids and the DC offset was removed from recordings. The recordings were filtered at 2-50 Hz (following Spitoni et al., 2013). The filtered continuous data sets were then epoched into arbitrary one-second windows for ease of data segment rejection prior to independent components analysis (ICA). At this stage, any noisy channels were rejected to facilitate artefact detection and improve the ICA results. The epoched (segmented) data was then subjected to an artefact detection procedure for non-stereotyped artefacts only, such as non-ocular muscle activity or static

noise, using visual inspection. After these epochs were rejected, the remaining epochs were subjected to an ICA (Makeig, Jung, Bell, Ghahremani, & Sejnowski, 1997). The independent components reflecting any stereotyped (e.g. potential vertical eye blinks) noise sources were rejected. Identification of artefactual independent components was based on the topography and frequency spectrum of the component, as well as the qualitative characteristics of the amplitude over time (Groppe, Makeig, & Kutas, 2009). In the next step, the channels removed prior to ICA were spherically interpolated. The resulting ICA weights were then copied into the continuous data sets which were subsequently epoched into two segments corresponding to the two phases of the experiment: the encoding period (2 mins) and a 10-minute interval of quiet rest following the tDCS stimulation. Finally, another artefact detection procedure was applied to the ICA-cleaned continuous segments using a visual inspection.

4.2.6 Statistical analyses

Behavioural data analysis. Statistical analyses used an ANCOVA with stimulation (tDCS and Sham) as a between-groups factor. To control for a baseline performance in the pre-delay free recall test the scores from this test were entered as a covariate. A p value <.05 was considered significant. Independent t-test was used for comparison of recognition scores.

EEG analysis. For EEG analysis, four subjects were excluded in the tDCS condition and three subjects in the sham condition due to either a high number of artefacts in the data (~40% of all trials), which resulted in a too few artefacts-free epochs in these dataset for the analysis stage (4 subjects), or an equipment error which impeded the identification of tDCS-free segments in the datasets (3 subjects). Consequently, data from 11 participants in tDCS condition and 12 participants in Sham condition entered EEG analyses.

All EEG data analysis was performed using Fieldtrip toolbox (Oostenveld et al., 2011). EEG continuous segments, that were free of artefacts, were accepted for the fast Fourier transformation (FFT). Data was segmented into 2.5 seconds long trials and the power spectrum for each trial was computed by applying the multitaper frequency transformation with a Hanning window of 10% of the length. The results were expressed in power values (μV^2). The frequencies of interest were selected based on the previous research and limited to the alpha (8-12 Hz) and theta (4-8 Hz) frequency bands (Jensen & Mazaheri, 2010; Kawasaki et al., 2010; Klimesch, 2012; Osipova et al., 2006). The averaged power of these two frequency bands was calculated for each participant (for all 10 EEG channels) separately and then the grand averages across all participants for each condition were computed. These grand averages were then used for statistical analysis of 3 areas of

interest, based on the scalp topography, over frontal (F3, F4, F7, F8, Fpz) and midline (C3, Cz, Fz) electrodes and over left occipito-parietal (P3, O1) site where the alpha activity is typically most prominent.

To examine changes in the effects of tDCS, we compared two segments of the data: taken pre and post stimulation. Specifically, we compared the 2-min stimulation-free intervals before the tDCS/sham stimulation and a 10-minute interval after all tDCS/sham stimulations has finished for any elevated alpha or theta activity (see Figure 4.1; the 10-minute interval is marked in blue). The first two minutes from the 10-min post-stimulation segment were discarded to avoid the tDCS carry-on effect. Thus the post-stimulation segment was measured three minutes after stimulation until the end of the post-stimulation rest, leaving a total post-stimulation time of 8 minutes. Since the tDCS effects were expected to dissipate over time and the alpha and theta level to return to its baseline by the end of the 10-minutes post-stimulation delay, we analysed the effects of tDCS stimulation over time, following Spitoni et al. (2013). We divided the remaining 8 minutes of the post-stimulation interval into 4 epochs of 2 minutes each. In order to account for any possible differences between the groups in the pre-stimulation oscillatory activity, we subtracted the pre-stimulation alpha/theta power from the post-stimulation alpha/theta power, for each of the 4 post-stimulation epochs. The data were analysed using mixed design repeated measures ANOVA with Time (4 levels) and Region of Interest (ROI, 3 levels) as within and Stimulation as between-subject factors. The levels of the factor Time were the 4 two-minute long epochs obtained post-stimulation whereas the ROI factor included frontal, midline and occipital-parietal sites. The between subject factor was the type of the Stimulation (tDCS and Sham).

4.3 Results

4.3.1 Behavioural tests

Analyses focused on comparison of memory performance between the tDCS and sham conditions.

4.3.1.1 Free recall

Pre-delay recall was comparable between tDCS and sham conditions ($t(28)=.53$, $p=.599$; see Table 4.1). ANCOVA with pre-delay recall entered as a covariate revealed that accuracy on recall test after 30-minute delay of quiet rest was significantly higher following tDCS condition ($F(1,27)=4.78$, $p=.038$, $\eta_p^2=.151$; see Figure 4.3). This effect was long-lasting

with significantly better memory recall in tDCS group in comparison to sham group after a 7-day delay ($F(1,27)=4.30$, $p=.048$, $\eta_p^2=.138$).

Table 4.1
Mean percentage (%) of Words Recalled in the Free Recall Test Immediately after Encoding (Recall 1), after 30 Minutes of Quiet Wakefulness (Recall 2) and after a 7-Day Delay (Recall 3).

Condition	Recall 1	Recall 2	Recall 3
tDCS	45.6 (20.0)	47.2 (18.9)	29.9 (15.7)
Sham	42.1 (15.4)	38.4 (15.9)	21.1 (9.9)

Note: Standard deviations are given in parentheses.

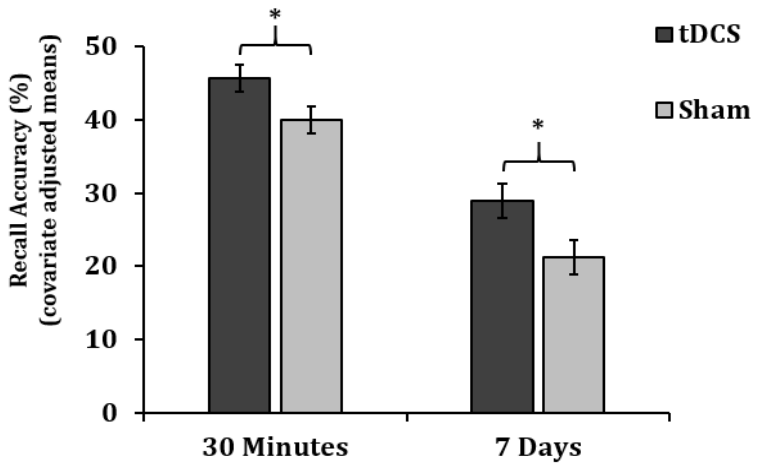

Figure 4.3. Recall accuracy in the tDCS experiment. Plots show performance in the free recall task after anodal tDCS and sham stimulation demonstrating an effect of tDCS-induced memory improvement. Participants remembered more items after tDCS as compared to sham after 30-minute of quiet rest. The memory for item list was significantly better in tDCS condition as compared to sham following a 7-day delay, revealing a long-lasting effect of memory improvement. Asterisks indicate statistical significance ($p<.05$).

4.3.1.2 Recognition test

After a 7-day delay participants performed a free recall and recognition task. Data points where no answer was provided were removed from analyses (~1% of all data points). Recognition trials were classified according to whether WR (well-remembered), F (familiar), or N (new) judgments were correct or incorrect. From these classifications, we calculated both recognition accuracy (d'—a measure of discriminability) and memory bias (C—an index of conservative vs. liberal response tendency), according to a signal detection

theory (Macmillan & Creelman, 1991). Here, the 'yes' response to items that participants heard in the previous session, both familiar and well-remembered, was classed as a *hit* (correct 'yes' response) whereas the same response to new items was classed as *false alarm* (incorrect 'yes' response). At this point one participant from tDCS condition had to be excluded from analysis due to an equipment malfunction. Table 4.2 presents a summary of the responses in the tDCS and sham condition.

Recognition Accuracy (d')

In order to calculate recognition accuracy, hits and false alarms between items recognised as familiar and well-remembered were collapsed. Although mean recognition accuracy was better following the tDCS than sham (*d'*=1.11 vs. 0.67; see Figure 4.4), this difference was not significant ($t(27)=1.49$, $p=.148$).

Table 4.2
Mean Number of Hits, False Alarms, Correct Rejections, and Misses in the tDCS and Sham Conditions.

Condition	Hits		False alarms		Correct Rejections	Misses
	F	WR	F	WR		
tDCS	12.1 (3.5)	6.4 (2.1)	1.7 (2.2)	7.4 (2.9)	15.5 (4.5)	6.8 (3.0)
Sham	9.3 (4.3)	7.7 (2.7)	1.4 (1.7)	9.7 (2.6)	13.7 (3.6)	7.8 (3.4)

Note: Hits and false alarms are broken down into familiar (F) and well-remembered (WR) judgments. Standard deviations are given in parentheses.

We also analysed well-remembered (WR) and familiar (F) judgments separately. *d'* measure for WR and F judgements were calculated as specified above: items learnt in the previous session and recognised as WR or F were scored as *hits*. Conversely, if the new items were classed as F or WR they were scored as *false alarm*s, separately for each category. From these measures a recognition discriminability (*d'*) was calculated separately for WR and F judgments. WR judgments as well as F judgments showed a higher mean *d'* score following tDCS condition in comparison to sham (d'_{WR} =-.12 for tDCS vs. -.23 for sham; d'_{F} =1.79 for tDCS vs. 1.31 for sham). These differences were again non-significant (d'_{WR}: $t(27)= .99$, $p=.333$; d'_{F}: $t(27).62$, $p=.538$; see Figure 4.4). These results demonstrate no significant influence of tDCS on recognition memory measured 7 days later.

However, as our participants completed the recognition test only in the second session, we could not control for the potential differences in recognition memory before the 7-day delay. In order to account for this potential differences in baseline memory performance, we ran an ANCOVA on *d'* scores with the accuracy score in the pre-delay free recall test entered as a co-variate. The results revealed no significant difference between the two groups when *d'* scores for familiar and well-remembered judgments were collapsed ($F(1,26)=3.86$, $p=.060$, $\eta_p^2=.129$) or analysed separately ($F_{WR}(1,26)=.90$, $p=.351$, $\eta_p^2=.033$; $F_F(1,26)=.36$, $p=.555$, $\eta_p^2=.014$).

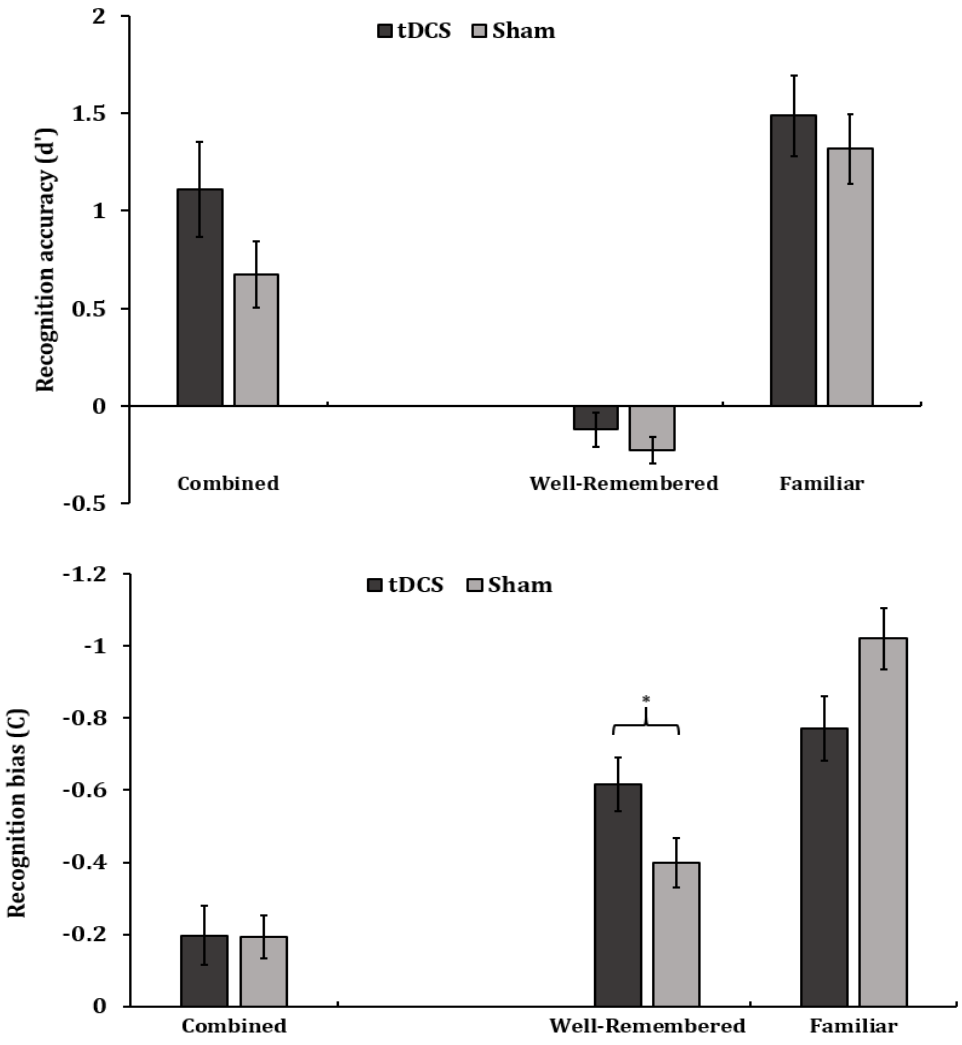

Figure 4.4 Recognition accuracy (d') and recognition bias (C) for the tDCS and sham group. Well-remembered and familiar judgments are presented combined and separately. Error bars indicate standard errors of the means. Significance of the differences between conditions is indicated, $p < .05$.

Memory Bias (C)

We also investigated changes in the modulation of memory bias. With the WR and F judgments combined, no significant differences in recognition bias emerged ($t(27)=-.045$, $p=.964$). However, the assessment of memory bias for WR items between the two groups showed a significantly higher bias scores (more conservative responding) for sham condition in comparison to tDCS condition ($t(27)=-2.15$, $p=.040$). The difference between groups in memory bias for F items showed an opposite trend and was only marginally significant ($t(27)=2.02$, $p=.054$). In sum, although taken together WR and F items showed no recognition bias differences between the two groups, the memory bias was significantly different between the two conditions for WR judgements, with sham group responding more conservatively than tDCS group (see Figure 4.4).

Reaction Times

Reaction times (RTs) were analysed only for correct responses (hits and correct rejections). A t-test showed no difference between tDCS and sham conditions for hits and correct rejections combined ($t(27)=-.60$, $p=.556$; see Table 4.3 for mean RTs). RTs for WR and F judgments (hits) analysed separately also showed no significant differences between tDCS and sham conditions ($t_{WR}(27)=.13$, $p=.900$; $t_{F}(27)=-1.49$, $p=.148$). Similarly, RTs for correctly rejected items did not differ between the conditions ($t(27)=.43$, $p=.669$).

Table 4.3
Mean RTs (in ms) on the Recognition Test in the tDCS and Sham Conditions.

Condition	Hits		False alarms		Correct Rejections	Misses
	F	WR	F	WR		
tDCS	1,311 (502)	1,691 (683)	1,771 (805)	1,733 (643)	1,512 (557)	1,478 (553)
Sham	1,435 (537)	1,760 (608)	1,600 (481)	1,673 (688)	1,474 (448)	1,534 (504)

Note: Hits and false alarms are broken down into familiar (F) and well-remembered (WR) judgments. Standard deviations are given in parentheses.

4.3.2 Debriefing questionnaire

Upon completion of the experiment each participant completed a debriefing questionnaire including the tDCS post-stimulation assessment form (adapted from Fertonani et al., 2010). The questionnaire was intended to assess the extent to which participants were aware of tDCS stimulation during the experiment. Participants were asked whether or not they felt the tDCS sensation during the quiet rest interval and were required to respond yes or no. We also assessed self-reported sensations of itchiness, discomfort, burning, heat, pinching and fatigue associated with the stimulation. Participants who had indicated that they had felt some sensation were asked to rate each of the sensations they felt with a number (0 indicating no sensation, 1 - mild, 2 - moderate, 3 - considerate and 4 - strong sensation).

The assessment of responses revealed that all participants in tDCS condition reported feeling the tDCS sensation (100%) whereas 10 out of 15 participants (67%) reported feeling the sensation in the sham condition. The association between the type of stimulation (tDCS or sham) and whether or not participants felt anything was significant ($\chi^2(1)=6.00$, $p=.014$). In the next step, we compared ratings for different types of sensation between the groups. The ratings for participants who reported feeling no sensation associated with tDCS were entered as zeros. There were no significant differences between the two groups on the reported level of itchiness ($M_{tDCS}=1.00$, $M_{Sham}=1.00$, $t(28)=.00$, $p=1.00$), discomfort ($M_{tDCS}=.40$, $M_{Sham}=.20$, $t(28)=-.84$, $p=.410$), burning ($M_{tDCS}=.40$, $M_{Sham}=.40$, $t(28)=.00$, $p=1.00$), pinching ($M_{tDCS}=.47$, $M_{Sham}=.33$, $t(28)=-.54$, $p=.597$), heat ($M_{tDCS}=.53$, $M_{Sham}=.86$, $t(28)=1.16$, $p=.258$) and fatigue ($M_{tDCS}=.60$, $M_{Sham}=.53$, $t(28)=-.21$, $p=.836$). In addition, participants reported whether they thought the sensation they felt could affect their performance on the recall tests. There was no association between the type of stimulation (tDCS or sham) and whether or not participants thought the sensation affected their performance $\chi^2(1)=.83$, $p=.361$).

To evaluate the contribution of the differences in tDCS sensation reported by the tDCS and sham group to the performance on the recall tests, we calculated the overall tDCS sensation score by taking the average of all the ratings for tDCS-associated sensations. We then re-ran analyses of accuracy in recall tests using both the overall tDCS sensation score and pre-delay recall test score as covariates. The ANCOVA results revealed that the benefit of tDCS stimulation on the recall test remained significant after a 30-min delay ($F= 4.79$, $p=.038$, $\eta p^2=.156$). The results of these analyses also confirmed that benefits of tDCS extended to a longer, 7-day delay ($F= 4.24$, $p=.0497$, $\eta_p^2=.140$).

Additionally, we asked participants who had reported that they had felt some sensation to indicate when they felt the tDCS sensation and how long it lasted. These results are reported in Table 4.4. The majority of participants in both groups indicated that the tDCS sensation occurred at the beginning of the wakeful rest interval and stopped soon after it started.

Table 4.4
Timing and Length of tDCS Sensation.

Condition	Timing			Length		
	At the beginning	In the middle	At the end	Stopped soon	Some minutes	Up to the end
tDCS	11	3	1	10	4	1
Sham	9	1	0	7	3	0

Note: Numbers indicate the number of participants.

In sum, the tDCS and sham group differed significantly in the number of participants who experienced tDCS sensation. We attempted to account for this difference by including tDCS-related sensation ratings in our analyses which confirmed the effect of tDCS stimulation on recall test following both a 30-min rest and a 7-day delay. Nevertheless, the possibility that the difference in sensation experienced by the tDCS and sham group contributed to the outcome of behavioural tests cannot be ruled out. For example, the observed difference in memory tests performance between groups could be attributed to the placebo effect. This will be discussed further in the next section.

4.3.3 EEG results

4.3.3.1 Alpha activity

There was no significant difference between the groups in the level of pre-stimulation alpha power in frontal ($t(21)=-1.20$, $p=.245$), midline: $t(21)= -1.43$, $p=.168$) and occipital-parietal region ($t(21)= -1.60$, $p=.124$).

As we were most interested in alpha power increases following tDCS/sham stimulation, which were expected to dissipate over time, we examined the tDCS stimulation effects over the course of the post-stimulation quiet rest interval. The post-stimulation recording was divided into 4 epochs of approximately 2 minutes each (starting from 3 minutes' post stimulation). As mentioned before, to account for potential differences in alpha power

between the groups in pre-stimulation interval we subtracted the pre-stimulation alpha power from the post-stimulation alpha power measured at the four time points. The remaining values of alpha power, which reflected a difference score of alpha power fluctuation in response to stimulation/sham between groups, were entered into a mixed-design repeated measures ANOVA with within-subject factors Time (4 levels) and ROI (3 levels) and a between-subject factor Stimulation (tDCS and sham).

The ANOVA did not reveal a main effect of time ($F(3,63)=.56$, $p=.641$, $\eta_p^2=.026$), suggesting that the alpha power values did not change significantly as the post-stimulation time unfolded. There was no main effect of ROI ($F(2,42)=.21$, $p=.812$, $\eta_p^2=.010$), which suggested that the alpha power did not differ significantly between different brain regions. Although we observed a reduced alpha power following tDCS as compared to sham, particularly in the occipital-parietal site, the interactions: ROI x Stimulation, Time x Stimulation, ROI x Time and ROI x Time x Stimulation were non-significant ($F(2,42)=.12$, $p=.884$, $\eta_p^2=.006$; $F(3,63)=.33$, $p=.805$, $\eta_p^2=.015$; $F(6,126)=.66$, $p=.679$, $\eta_p^2=.031$, $F(6,126)=1.66$, $p=.136$, $\eta_p^2=.073$, respectively), indicating that both groups did not show significantly different alpha power in different brain regions over the 4 time epochs following stimulation. Although the sham condition appeared to show more alpha power overall (sham M=4.97, $SE=.725$; tDCS M=2.46, $SE=.758$), the between subject factor Stimulation was not significant ($F(1,21)=.33$, $p=.575$, $\eta_p^2=.015$).

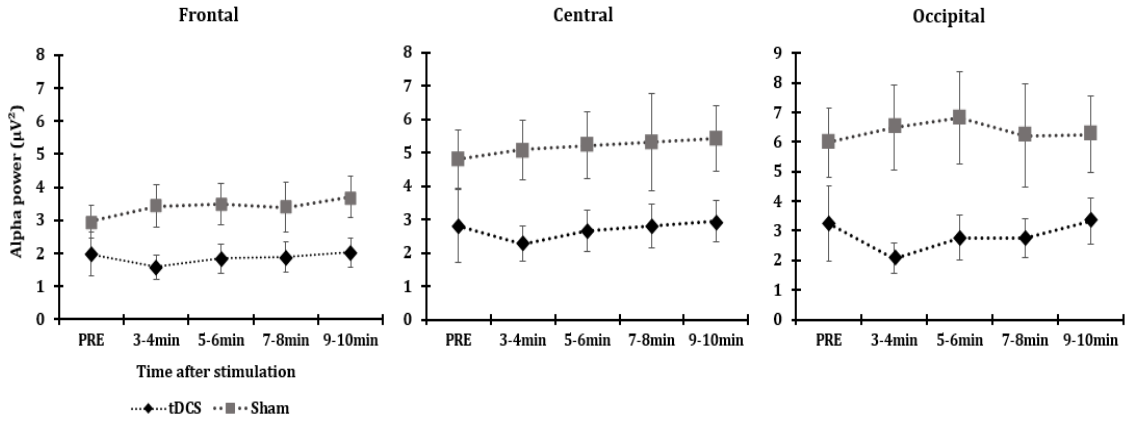

Figure 4.5. Alpha power across pre and post-stimulation time interval in the three regions of interest: frontal, central and occipital-parietal. The error bars illustrate the standard error of the means.

4.3.3.2 Theta activity

There was no significant difference between the groups in the level of pre-stimulation theta power in frontal ($t(21)=.11$, $p=.913$), midline: $t(21)= -.05$, $p=.964$) and occipito-parietal region ($t(21)= -.22$, $p=.832$).

As with the alpha power, we examined the tDCS/sham stimulation effects on theta power fluctuations over the course of the post-stimulation quiet rest interval. The post-stimulation recording was again divided into 4 epochs of approximately 2 minutes each (starting from 3 minutes' post stimulation). To account for potential differences in theta power between the groups in pre-stimulation interval we subtracted the pre-stimulation theta power from the post-stimulation theta power measured at the four time points. The remaining values of theta power, which reflected a difference score of theta power fluctuation in response to stimulation/sham between groups, were entered into a mixed-design repeated measures ANOVA with within-subject factors Time (4 levels) and region of interest (ROI, 3 levels) and a between-subject factor Stimulation (tDCS and sham).

The ANOVA did not show a main effect of time ($F(3,63)=.81$, $p=.491$, $\eta_p^2=.037$), meaning that the theta power values did not change significantly overall as the post-stimulation time unfolded. There was a main effect of ROI ($F(2,42)=3.51$, $p=.039$, $\eta_p^2=.143$), which suggested that the theta power did differ significantly between different brain regions. The pairwise comparisons revealed that this effect was driven by overall more change in power in central region as compared to frontal region ($p=.003$). The interactions: ROI x Stimulation, Time x Stimulation, ROI x Time and ROI x Time x Stimulation were non-significant ($F(2,42)=1.19$, $p=.314$, $\eta_p^2=.054$; $F(3,63)=.38$, $p=.767$, $\eta_p^2=.018$; $F(6,126)=.74$, $p=.622$, $\eta_p^2=.034$, $F(6,126)=.78$, $p=.587$, $\eta_p^2=.036$, respectively), indicating that the groups did not show significantly different theta power in different brain regions over the 4 time epochs following stimulation (see Figure 4.6). The between subject factor Stimulation was also not significant ($F(1,21)=1.29$, $p=.270$, $\eta_p^2=.058$). These results indicated that the two groups did not show different profiles of theta power fluctuations across the quiet rest interval.

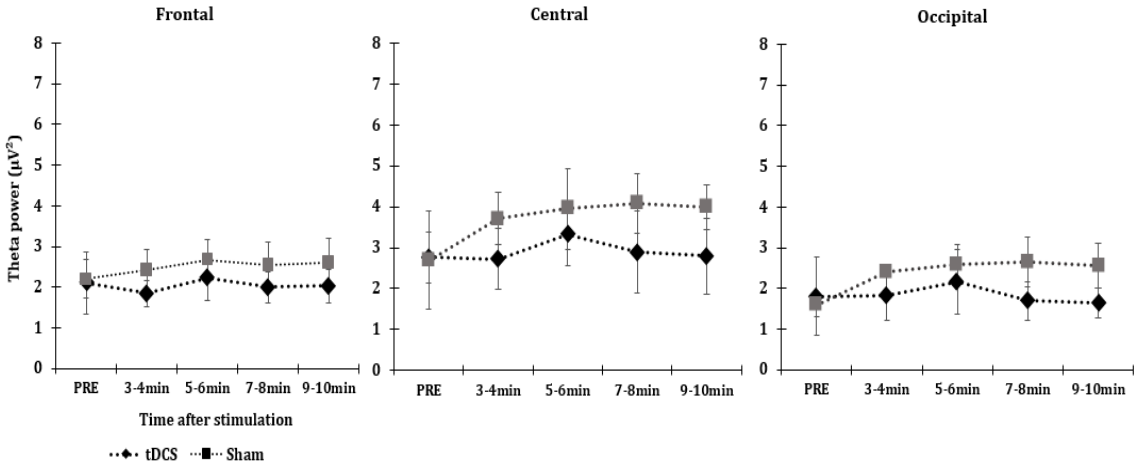

Figure 4.6. Theta power across the stimulation interval in three regions of interest: frontal, central and occipital. The error bars illustrate the standard error of the means.

4.4 Discussion

We investigated memory processing of a word list following a 30-minute quiet rest delay with and without anodal tDCS. The study also examined potential differences in memory recall and recognition following tDCS stimulation relative to sham stimulation after a longer, 7-day delay. To our knowledge, the findings reported here are the first to demonstrate that: a) applying anodal tDCS to the right parietal area during period of quiet wakefulness results in a better memory performance on the free recall test, as compared to a sham condition; b) the beneficial effects of stimulation on memory recall lasts up to 7 days' post training, and c) following a 7-day delay these effects were only reflected in the free recall scores, but not in the recognition scores. The tDCS-effects observed here stand in agreement with recent studies demonstrating tDCS-related modulation of higher cognitive functions (Balconi & Vitaloni, 2012; Mangia et al., 2014).

The reported observations are consistent with our hypothesis that anodal tDCS applied to the right parietal area during quiet wakefulness can boost memory performance. Based on the previous work (Spitoni et al., 2013) however, we predicted an increase in alpha oscillatory rhythm following tDCS. Against our hypothesis, the alpha power level observed in our experiment did not differ between the two conditions. If anything, the alpha power showed a trend in the opposite direction, i.e. the group that underwent tDCS showed an attenuated alpha in comparison to the sham group. Thus, if memory benefits following the stimulation are at all related to alpha power, they would be associated with a reduced alpha level. With regards to theta oscillatory activity, in contrast to previous research

(Jacobson, Ezra, Berger, & Lavidor, 2012) there was no significant difference between the tDCS and sham group in the level of theta at any four points of the post-stimulation interval and we did not observe any significant fluctuation of theta activity following tDCS.

Our data show that applying tDCS in quiet wakefulness has the potential to enhance memory consolidation processes naturally occurring during this state, although the exact mechanism is still unclear. This is broadly consistent with theoretical accounts that propose that memory systems take opportunity of any down-time in order to consolidate newly acquired memories (Dewar, Cowan, & Della Sala, 2007; Mednick et al., 2011). However, few caveats related to the design utilised in this experiment must be noted. Firstly, it could be argued that in order to state for sure that declarative memory improvement observed in our study are due to quiet rest, and furthermore tDCS, a comparison to a busy condition (i.e. where participants actively attend to a task) following learning is needed. Nevertheless, the lack of the busy control group in our design was motivated by the fact that several previous studies reported a superior memory recall following quiet resting in comparison to a condition when participants attended to a distractor task (i.e. busy condition; Brokaw et al., 2016; Craig et al., 2015; Dewar et al., 2012, 2014).

Secondly, a more precise account for the type of consolidation processes taking place in quiet wakefulness could be offered by contrasting it with memory retention following sleep. For example, some studies suggested that both sleep and quiet resting offer qualitatively similar memory consolidation mechanisms which are driven by the endogenous reactivation of memories in the hippocampus and their transfer into the neocortical networks (Tambini et al., 2010). However, whilst targeted reactivation of memories in sleep resulted in memory being strengthened, similar attempts to externally target such reactivation in quiet wakefulness resulted not in stronger but in fact more labile memory representations (Diekelmann et al., 2011). This indicates that sleep and quiet wakefulness may actually support memory consolidation in different ways. As the exact character of memory consolidation taking place in quiet wakefulness remains unclear further studies, which take both sleep and quiet rest conditions into account, will need to be undertaken.

Dewar et al. (2014) proposed that wakeful resting allows for superior memory consolidation resulting in stronger representations of experienced events as detected via tests of free recall and recognition. This was the main motivation for using these tests in our experiment. However, it could be argued that the improvement observed in the free recall task following tDCS as compared to sham may be due to the retrieval guided memory as several free recall tests were used. However, as the tDCS and sham group did not differ in

their performance on the recall test before stimulation. Thus, if the active memory retrieval influenced later memory improvements, we would expect such improvements for both groups, which was not the case in our experiment.

In contrast to free recall we did not observe any enhancing effects of tDCS on performance in the recognition test. Previous reports (Craig et al., 2015, 2016, Dewar et al., 2012, 2014) have shown an increase in recognition accuracy following quiet wake, hence our results may reflect a ceiling effect in both groups as both groups underwent quiet resting. However, as we did not include the busy condition in our experiment, we cannot state that for sure. The recognition test scores stand in contrast to free recall test results which indicated that undergoing tDCS has potential to boost memory for list of words. This may indicate that memory recall and memory recognition are governed by different underlying memory processes. Secondly, it may reflect the fact that it is a memory recall and its underlying mechanisms, as oppose to recognition, that are susceptible to modulations of oscillatory brain activity. Thirdly, it is also possible that a longer time delay of 7 days may had reversed any possible effects of stimulation on recognition memory which would otherwise be observed if tested immediately after stimulation. As we did not test memory recognition after the 30-minute stimulation delay this cannot be determined. Further work is necessary to establish whether recognition memory is affected by tDCS in the short-term.

We also calculated memory bias during memory recognition to examine whether tDCS may affect the confidence of memory judgments. The results showed that both groups differed in memory bias for well-remembered (WR) items. More specifically, the tDCS stimulation shifted the response criterion, leading to more liberal responses (lower C scores) relative to the sham condition. These findings suggest that, at least for WR judgments, a lack of stimulation produced less indiscriminate responding, potentially by strengthening confidence judgments for well-remembered stimuli. Despite this more conservative responding (reduced tendency to respond ‘‘old’’) in the sham condition, memory accuracy (d’) was comparably good in both the tDCS and sham conditions.

However, the question of how tDCS could modulate decisions towards more liberal ones remains open. One rather speculative explanation is related to the altered level of acetylcholine following tDCS. For example, previous research (Hasselmo, 1995) reported a lower level of acetylcholine observed during both quiet wake and deep part of sleep (SWS), in contrast to active wake. In fact, a lower level of this neurotransmitter has been shown to promote reactivation and strengthening of associations encoded within the hippocampus (Headley & Paré, 2017). This suggests that at the neuronal level comparable mechanisms may be taking place during quiet wake and sleep. If tDCS did enhance the natural

consolidation mechanisms during quiet resting, it could be reflected in a reduced level of acetylcholine and hence manifest itself in the more liberal memory bias exhibited by participants from tDCS condition. For example, some diseases (e.g., Alzheimer's disease) that display low levels of cortical acetylcholine are associated with abnormally liberal recognition bias (Fuld, Katzman, Davies, & Terry, 1982). Vice versa, the sham group which did not undergo the tDCS during quiet resting would manifest a stronger level of confidence judgment upon recognition with this greater confidence reflected in more discriminate (conservative) responding. If that was the case it would suggest that the process of memory bias can be neurochemically mediated. Although interesting this explanation remains speculative and further testing would be required to establish the link between tDCS, memory consolidation and level of acetylcholine.

As mentioned before, in line with our prediction we observed an enhancing effect of tDCS on memory following quiet rest in comparison to sham. Based on the previous reports (Brunoni et al., 2012; Mangia et al., 2014; Spitoni et al., 2013) we hypothesised that the application of anodal tDCS to the right parietal region should result in an elevated alpha activity. However, the analysis of the oscillatory activity associated with this enhancement showed that there was no difference in the alpha power level between the tDCS and sham group. If anything, the alpha power level showed a reverse trend to the one predicted. These discrepant results may be due to the differences in study designs implemented here and in the experiment which we based our prediction on (Spitoni et al., 2013). One possible explanation of the non-significant effect of tDCS on alpha rhythm observed in our study, which is contrast to and in Spitoni et al. (2013), may relate to the measurement of alpha activity. More specifically, Spitoni et al. (2013) measured alpha activity precisely at the area of the stimulation. This was not the case in our study, as we did not place the EEG sensors at the site where tDCS was applied. Therefore, it could be that the alpha activity, captured by sensors placed on the other (left) hemisphere failed to reflect the actual alpha level present in the right parietal area following tDCS. Another factor that could potentially affect the oscillatory activity of the brain was the presence of the cognitive task and instructions relating to the quiet rest employed in our experiment. Here, we used a memory task before the wakeful delay and our participants were explicitly informed about the wakeful rest that would follow. This was in divergence to the protocol utilised by Spitoni et al. (2013) where participants remained in constant communication with the experimenter and were repeatedly asked to open and close their eyes, therefore preventing any quiet wakefulness state.

Another explanation is that the experiment reported by Spitoni et al. (2013) compared anodal and cathodal tDCS stimulation rather than anodal and no stimulation at all. This could account for possible differences in the alpha power modulations observed here and in Spitoni et al. (2013). In fact, previous research observed a significant decrease in oscillatory power in the alpha band following cathodal tDCS over the parietal cortex as compared to anodal tDCS (Heimrath, Sandmann, Becke, Müller, & Zaehle, 2012). Therefore, it could be that the observed alpha power following anodal tDCS was interpreted as an increase relative to further reduction of this power band following cathodal stimulation (cf. Heinen et al., 2016). Future studies could help to provide more clarity of the oscillatory power modulations induced by cathodal and anodal tDCS in comparison to sham.

Although against our hypothesis, a trend towards reduced alpha power following tDCS and an increased performance in behavioural test following wakeful rest are in fact consistent with recent research investigating neurocorrelates of resting state (Brokaw et al., 2016). Brokaw et al. (2016) showed that it was a reduced alpha activity, together with an increase in slow oscillatory activity (<1Hz), that accompanied an increased memory performance following resting wake state. Moreover, Brokaw et al. (2016) found that reduced alpha during wakeful rest, and improved behavioural performance was associated with elaborated mind-wandering during the wakeful delay. The authors also suggested that mind-wandering may mark time when the brain enters an offline state required for consolidation. Indeed, the low alertness during mind wandering has been recently associated with reduction in alpha power reflecting diminished sensory processing during this state (Braboszcz & Delorme, 2011).

Previous investigations demonstrated that mind-wandering is associated with activity in a default-mode network (Mason et al., 2007). Default-mode network (DMN), in other words the "baseline" state of the brain, has been shown to be highly dependent on fluctuation in the balance of cortical inhibition/excitation represented by respective increases/decreases in the power of the EEG alpha oscillation (Mayhew, Ostwald, Porcaro, & Bagshaw, 2013). This resting state network is defined by synchronous oscillations across different brain regions (with synchronisation and spectral power reflecting different measures). Studies showed that the DMN subunits may be coordinated specifically by alpha rhythm (Jann et al., 2009). Thus, the synchronisation/desynchronisation of alpha activity between different brain regions, could offer more insight into the memory consolidation processes in quiet wakefulness.

Interesting, the parietal region, and the angular gyrus specifically, has been indicated a vital part of the DMN (Mason et al., 2007). It is worth noting that tDCS applied in

our study covered precisely these areas of the brain. Consequently, if the DMN is indeed necessary to support consolidation during quiet wake, then we would observe an enhancement in memory following stimulation of this site. These memory benefits could be potentially mitigated by alpha power decrease in this regions during the retention interval when the network is successfully engaged. Indeed, since alpha activity is found to decrease in engaged regions and increase in disengaged regions (Haegens et al., 2010; Mathewson et al., 2011), the trend towards attenuated alpha power following tDCS in the occipital-parietal area would indicate an active role of this region in memory strengthening during quiet wake. As indicated above, the measurements of alpha power were taken at different location (left occipital and parietal region) to the actual tDCS stimulation site (right parietal region), and this could account for less pronounced and non-significant differences between tDCS and sham group. For example, other studies successfully showed the selective targeting and modulation of alpha power by parietal anodal tDCS (Brunoni et al., 2012; Capotosto et al., 2016; Mangia et al., 2014). It is worth noting that parietal alpha-band power is considered to reflect a greater task involvement and increased attention to the environment (Klimesch, 1999) which may suggest that in our experiment the sham group, who exhibited higher alpha power, did not "switched off" as effectively as the tDCS group during the quiet rest delay which may account for memory benefits.

Alpha rhythms are one of the most prominent signatures of human wake EEG and have been previously indicated as important for cognitive processing such as working memory performance (Klimesch et al., 2005). For example, low occipital alpha power has been associated with higher performance in verbal short-term memory (VSTM) tasks following anodal tDCS to right posterior parietal cortex (Hsu et al., 2014). Although in contrast with previous studies which show that successful memory maintenance correlates positively with higher alpha level (Jensen et al., 2002; Palva & Palva, 2007; Scheeringa et al., 2008; Tuladhar et al., 2007), Hsu et al. (2014) interpreted their findings within the hypothesis of inhibition or disengagement (Jensen et al., 2002; Jensen & Mazaheri, 2010). This hypothesis postulates that information is gated through the brain by functional inhibition of task-irrelevant areas. Furthermore, this functional inhibition is reflected by oscillatory activity in the alpha band. The alpha-driven inhibition may be interpreted in two ways: firstly, while task-relevant information may be more efficiently processed due to alpha power being further decreased, task-irrelevant information may be less well suppressed. Following from this, a low alpha power in the task-irrelevant regions would facilitate potential communication between different brain areas whereas a strong alpha power would prevent it. In that way, by enabling the communication of distant neural areas observed in the DMN it would be the reduced, rather than increased alpha level that would

facilitate memory consolidation. Importantly, the resting state network is a state that naturally occurs during quiet wakefulness. In consequence, the reduced alpha rhythm may augment the connectivity within the resting state network and consequently enhance memory.

Finally, the debriefing questionnaire implemented in our study indicated that 66% of the sham group experienced the tDCS sensation (as compared to 100% in the tDCS group). Therefore, we cannot rule out that the beneficial effect of tDCS on memory observed in our study was a consequence of the tDCS sensation differences between the groups, and not the properties of the stimulation itself. In that way, the memory enhancement following tDCS could be either attributed to the placebo effect and the brain response to the treatment context (Ashar, Chang, & Wager, 2017) or a higher level of alertness in tDCS group induced by tDCS sensation. We attempted to account for this difference by including the sensation ratings as a covariate in our analyses, which confirmed the benefit of tDCS on recall tests. However, the sensation rating measure used provided only a rough estimate of tDCS experience as it was limited to a few options only (i.e. for itchiness, discomfort, heat, fatigue, pinching and burning). Thus it may have lacked the sensitivity that would otherwise allow us to capture the actual variability in tDCS sensation experienced by the groups. A detailed interview following tDCS and sham could offer a more sensitive measure. Although special care was taken to ensure both tDCS and sham groups experienced the initial sensations (which is an improvement from previous studies in which the sham condition did not produce any sensation; Marshall et al., 2004), future research could further address this issue by minimising the variability in physical experience of tDCS and sham stimulation. Furthermore, as the experiment was not double-blinded and the experimenters were aware of the condition which each participant was assigned to, we cannot rule out the possibility that the experimenter gave unconscious cues to participants with regards to the condition type.

4.5 Conclusions

In this study, we observed successful enhancement of memory for declarative material following tDCS. These memory benefits could be interpreted within the opportunistic consolidation hypothesis according to which the memory consolidation unfolds during hippocampal down-time present during quiet rest. However, the exact mechanisms underlying these memory improvements are unclear. One possible explanation points to the trend of reduced alpha level in the tDCS groups, as compared to sham, although this difference was not significant. The reduced alpha level could be

associated with the default mode network and mind-wandering which may play a role in facilitating memory consolidation during quiet wakefulness. Alternatively, the difference in the tDCS sensation experienced by the tDCS and sham group could account for behavioural results due to the placebo effect or higher level of alertness induced by tDCS sensation. Taken together, the results suggest that hippocampal-based memory consolidation may utilise optimal brain states to process prior learning, and is not specific to sleep *per se* (Mednick et al., 2011). However, whether processes governing memory consolidation are qualitatively similar in wake and sleep (i.e. including neural replay) is currently not known. These results can be considered an important step towards a better understanding of the mechanisms involved in tDCS-induced modulations of cognitive processing. Notwithstanding, further work is required to establish the precise mechanism of memory consolidation during quiet wakefulness.

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CHAPTER 5
GENERAL DISCUSSION

This final chapter summarises the main findings within this thesis. I will review the main conclusions of each chapter and discuss how employing different experimental methods complemented the investigations into mechanisms of memory consolidation. I will show that memory consolidation is a dynamic process that goes beyond a single state of the brain i.e. sleep. I will also discuss different factors that influence how we remember and how we can manipulate our memory using new techniques such as TMR or tDCS. The theoretical implications of the findings will be discussed in the context of the key research questions outlined in the introduction. Following on from these discussions, I will assess what the data revealed and what still remains to be discovered. Potential future research will also be suggested.

5.1 Summary of Findings

The experiments reported in this thesis were designed to test and explore mechanisms of memory consolidation and aimed to shed light on their neural underpinnings. The view derived from the experiments reported here, as well as from the literature of the subject, indicates that memory consolidation is not a uniform process and many factors come into play to determine how and when we consolidate. In order to capture this diverse nature of consolidation process, this thesis explored in three ways how our memories become stabilised in the long-term.

In **Chapter 2**, I asked what factors influence memory consolidation in the domain of word learning. As stimuli, novel words are particularly suited to explore consolidation processes—several reports have shown that offline consolidation of lexical representations results in their integration into the mental lexicon (Dumay & Gaskell, 2007; Tamminen & Gaskell, 2013). The behavioural evidence of the successful lexical integration can be measured by examining the interaction between newly learnt and existing words in a process of lexical competition (Bakker et al., 2014; Dumay & Gaskell, 2007; Gaskell & Dumay, 2003b). In Chapter 2, I tracked the time-course of novel word integration with two different training procedures: the relatively implicit Hebb repetition task and the phoneme monitoring—an explicit task typically used in word learning studies. Here, I tested the proposal that the Hebb-style learning offers a consolidation of novel tokens that is less associated with sleep in comparison to more explicit tasks (Szmalec et al., 2012). The results

reported in Chapter 2 stand against this proposal and show that the Hebb task not only does not offer a swifter integration of novel phonological knowledge but in fact results in poorer lexical representations of novel words in comparison to the explicit training. Based on these results, I suggested that it is the material to be learnt and its properties, such as a degree of the overlap with existing knowledge, that impacts the trajectory of novel word learning and their consolidation. Novel words that closely overlap with already known words may become integrated within the lexicon shortly after exposure whereas unfamiliar novel forms that are more distinct neighbours require longer, and typically sleep-associated, consolidation. Due to their novel nature, the formation of non-episodic representations of distinct novel words requires support of the hippocampal mediation and consequently, an off-line consolidation offered by sleep.

Chapter 3 elaborated on findings described in Chapter 2 by looking at the sleep-mediated consolidation of novel words in more detail. Here, I employed a TMR paradigm to explore the underpinnings of memory consolidation in sleep such as neural replay (i.e. the endogenous reactivation of memories learnt during preceding wakefulness). TMR capitalises on this natural mechanism, believed to take place during SWS, in order to selectively reinforce memories (Rasch et al., 2007). Additionally, Chapter 3 looked at the neuro-correlates that accompany successful TMR in sleep in order to provide a more fine-grain measure of this method. The results presented in Chapter 3 demonstrated that although the TMR method allows chosen memories to become strengthened it may not offer their better integration within existing knowledge. This calls for future investigations which will help to clarify the advantage of TMR for some but not other consolidation processes. It also highlights a potential need to stipulate the difference between memory enhancement, consolidation and integration. Furthermore, the study revealed that the memory reactivation in sleep is accompanied by increased activity in fast sleep spindle frequency range, whereas other frequencies play a more elusive role in this process.

Chapter 4 offered a newer view on consolidation from the perspective of awake state. The consolidation during wake appears to bring similar enhancing benefits to consolidation during sleep (Craig et al., 2015; Dewar et al., 2014). Furthermore, recent research indicated that consolidation during wakefulness may affect consolidation in sleep (Schapiro, Mcdevitt, Rogers, Mednick, & Norman, 2017), thus it may be a crucial part of memory consolidation processes in general.

In Chapter 4, I explored the hypothesis which suggests that memories are in fact consolidated whenever there is no new information input (Mednick et al., 2011). I test this using a quiet wakeful rest—an awake state that has been previously indicated to be

beneficial for memory in a similar way to sleep (Dewar et al., 2014). In parallel to the previous chapter, which used TMR to boost the naturally occurring consolidation processes in sleep, here I used tDCS technique to prompt the possible underlying mechanisms of consolidation in quiet wakefulness. The results presented in this chapter suggest that it is possible to enhance the memory consolidation processes naturally occurring during the resting state with tDCS. Although the underlying mechanism of such memory improvement is currently unclear, the results hint towards the DMN of the brain potentially being mediated by attenuated alpha power. In Chapter 4, I speculated that the ongoing oscillatory activity supporting consolidation during quiet wake, reflects the default mode network of the brain and associated with this state mind-wandering, an internally-directed state of mind. The default mode network and mind-wandering may be of crucial importance for memory consolidation during wakefulness as naturally providing limited input from the external environment.

5.2 Elucidating the Mechanisms of Memory Consolidation in Sleep and Wake

This section discusses the implications of the findings reported in this thesis within the context of research questions regarding memory consolidation and integration and the role of sleep, or wake, in these processes. These questions are:

1) Are the consolidation (and integration) processes exclusively sleep-dependent? And if not:

2) What are the factors that influence memory consolidation in sleep and wake and how do they mediate the consolidation process?

3) Is it possible to externally enhance the consolidation (and integration) processes during sleep and wake?

The experiments reported in Chapters 2, 3 and 4 aimed to investigate different aspects of the mechanisms underpinning memory consolidation. Despite the fact that each chapter elucidated different aspects of memory consolidation they share an investigative commonality. Hence, when discussing the implications of the findings I will use cross-referencing to highlight the shared aims of each study.

5.2.1 Underpinnings of memory consolidation

5.2.1.1 The role of the hippocampus

According to the Complementary Learning Systems (CLS), new information is initially bound by the hippocampus in the form of episodic representation, in order to avoid catastrophic interference with the neocortical-based mental networks (Davis & Gaskell, 2009; McClelland et al., 1995). This view is not only supported by a broad number of studies on word learning in adults and children (Gaskell & Dumay, 2003b; Henderson et al., 2012) but also neuropsychological data from studies on amnesia (Bayley et al., 2008; Nadel & Moscovitch, 1997). An additional argument for systems consolidation is provided by imagining studies which emphasised the activation of the hippocampus during the initial phase of learning, for example novel words (Breitenstein et al., 2005; Davis et al., 2009).

However, the contribution of the hippocampus to encoding may be determined in part by the relation between novel input and existing knowledge (McClelland, 2013). Under some circumstances, the hippocampal mediation may not be necessary. For example, when encoding information is highly overlapping or consistent with pre-existing knowledge, we may observe a rapid incorporation of new material into the neocortical representational areas, by-passing the hippocampus. Chapter 2 discusses such possibility in the realm of word learning. Novel words are stimuli particularly suited for such investigation due to the richness of mental lexicon and the possibility of tracking the time-course of novel word integration within lexicon using behavioural tests. Moreover, the contemporary ongoing need to learn novel terms from first, or second, language makes novel word learning an ecologically valid area of research.

The rapid neocortical integration of new information, as opposed to slower hippocampally-mediated consolidation, mimics the idea of memory schema proposed by Bartlett (1932). Schema theory maintains that schema-consistent information can be rapidly integrated into the neocortical memory network and does not rely on the hippocampus to the same degree as schema-inconsistent representations. This was shown to be the case when learning consistent and inconsistent with the native language rules of grammar (Mirković & Gaskell, 2016). Thus, the fit of a novel word within neocortical networks may be a vital factor that mediates the time course of its integration. Moreover, this fit may not be all or nothing. It may in fact be represented on a spectrum of overlap with neocortical networks and as such provide a graded and varied need for hippocampal mediation and, consequently, time needed for consolidation. For example, an immediate integration may be expected when specific training conditions are used such as a training that interleaves novel and known words (Lindsay & Gaskell, 2009) or an encoding task

which requires simultaneous processing of novel and existing concepts as in fast mapping paradigm (Coutanche & Thompson-Schill, 2014). Completely new information would require the most optimal conditions in order to become consolidated and this would be provided in sleep. The findings in Chapter 2 corroborated the overlap hypothesis—the distinct novel neighbours entered the lexical competition process, a sign of their successful lexical integration, only after the optimal consolidation conditions were fulfilled- after a time delay that consisted of sleep.

In sum, Chapter 2 tests whether using a specific training procedure (i.e. implicit versus explicit) may diminish the need for hippocampal mediation when learning novel words. Interestingly, the conclusions drawn in Chapter 2 show that a degree of overlap of new words with existing lexicon is what matters and mediate how we learn novel words. For example, Chapter 2 proposes that learning novel distinct neighbours, as opposed to learning words more similar to already known ones, requires more extensive training and optimal conditions such as sleep-associated consolidation. Thus, Chapter 2 sets the scene for investigation undertaken in Chapter 3, which aimed directly to elucidate the mechanism behind learning and integration of novel words that cannot be easily incorporated into the lexicon and require off-line consolidation provided by sleep.

5.2.1.2 The sleep-associated mechanisms of memory consolidation

Having established the need for hippocampal mediation and sleep in learning and lexical integration of distinct phonological tokens, we used this learning paradigm in Chapter 3. Here, we utilised the TMR method to externally manipulate the process of hippocampal reactivation of memories in sleep and hence elucidate some aspects of it. In agreement with a growing body of evidence we found that TMR selectively strengthens the episodic representations of novel linguistic items, i.e. items reactivated during sleep were recalled better in the morning than the ones that were not reactivated. However, this experiment did not detect any evidence that TMR also supports lexical integration of strengthened items. In fact, no lexical integration was observed following sleep for both reactivated and non-reactivated items. This finding suggests a dissociation between strengthening and integration of new lexical knowledge. Moreover, it may reflect the fact that TMR mediates the consolidation and integration of novel items in a different way depending on the level of encoding. For example, a low number of exposures to novel items (13 exposures) allowed the memory traces to become strengthened in the course of TMR but did not promote their integration.

Nevertheless, the low number of exposures employed in Chapter 3 was specifically chosen to boost any TMR effects on recall and novel items' integration as previous reports

showed that TMR is most effective for items that are weakly encoded (Cairney et al., 2016; Creery et al., 2015). Also, the fact that TMR boosted some but not other aspects of novel word learning (i.e. their recall but not lexical integration), something that has not been investigated separately before, suggests that alternative explanation may be plausible. Based on assumptions that TMR paradigm is designed to mimic and utilise the naturally occurring memory reactivation in sleep, I speculate that this offline memory replay strengthens memory traces yet different consolidation process is required to integrate them. This is in line with newer evidence indicating that other, heavily sleep-dependent processes such as generalisation and abstraction, may not be supported by TMR and may even be impeded by it (Hennies et al., 2017). This would indicate the dual character of reactivation-dependent consolidation process which channels the strength of episodic representations but may require an additional support from, for example other sleep stages (i.e. REM; Batterink, Westerberg, & Paller, 2017; Tamminen, Lambon Ralph, & Lewis, 2017). The observed enhancement of episodic representations without their integration calls for a re-definition of the processes of consolidation.

Furthermore, another important finding reported in Chapter 3 was that event-related brain responses in sleep have potential to reflect the on-going consolidation processes. For example, we found that forgetting items overnight was marked by significantly more negative brain responses in comparison to memory improvements (i.e. behavioural gains when items were remembered after but not before sleep). These results differed from the previous reports. For example, Schreiner and Rasch (2014), in a similar TMR study on word learning, showed an opposite brain response to memory losses and gains. Interestingly, the comparison of stimuli used in Schreiner and Rasch (2014) and in this study may shed some light on the reason for those different brain responses. Specifically, Chapter 3 investigated the effects of TMR when learning distinct lexical neighbours, whereas Schreiner and Rasch (2014) used items of high phonological and semantic overlap with the native language of their participants. This overlap between newly learnt items and existing lexicon was discussed in Chapter 2 where I concluded it to be an important factor when learning novel phonological forms. Similarly, the augmented theta oscillatory activity that accompanied learning of novel words in Schreiner and Rasch (2014) was not observed in our study. Interestingly, theta activity has been indicated to reflect the successful integration of novel words in wakefulness (Bakker et al., 2015a), suggesting that more overlapping neighbours may have undergone the integration process in Schreiner and Rasch (2014) but learning was insufficient in our study to induce similar oscillatory signature. Also in contrast to Schreiner and Rasch (2014), Chapter 3 showed an increased fast spindle activity that accompanied learning of distinct lexical neighbours—something

that has previously been shown in a study using similar tokens (Tamminen et al., 2010). Spindle activity was indicated to play an important role in synaptic plasticity and memory formation (Ulrich, 2016). Therefore, the different brain responses to TMR in sleep observed in this and previous studies (Schreiner & Rasch, 2014) may reflect the overlap of new information with the neocortical networks.

Interestingly, some research suggested that the hippocampus itself consists of separate memory systems. Using simulation of potential hippocampal pathways, it was shown that the hippocampus is able to acquire both the episodic information and the regularities by using separate anatomical pathways within itself (Schapiro, Turk-Browne, Botvinick, & Norman, 2016). In more details, the pathway connecting entorhinal cortex directly to hippocampal region CA1 supported statistical learning whereas the pathways that involved the dentate gyrus and hippocampal region CA3 aided learning of individual episodes. This suggests that the hippocampus may provide different learning systems that can help to coordinate between different types of memory through separate pathways. This may help to explain the partial effect achieved with the TMR method on consolidation of new linguistic tokens (i.e. memory enhancement without their integration).

5.2.1.3 Consolidation of memories in context of quiet wake: when, what and how we consolidate without sleep

Although hippocampal replay has been shown to take place mostly during sleep, newer research have indicated that memory consolidation may also happen during wake. According to this opportunistic consolidation hypothesis (Mednick et al., 2011), the hippocampus takes the opportunity of any down-time in order to consolidate new memories. However, whether the memory consolidation in wake resembles the one in sleep and what are the mediating factors is currently unknown. Chapter 4 explores the consolidation mechanism in quiet wakefulness using transcranial direct current stimulation (tDCS)—a technique that has been previously shown to alter the ongoing brain activity in sleep (Marshall et al., 2004) and wake (Flöel, Rösser, Michka, Knecht, & Breitenstein, 2008; Spitoni et al., 2013). Here, I examined a specific wake state that may provide favourable conditions for consolidation when sleep is not an option — a quiet wakeful rest.

Studies have shown that benefits of quiet wakeful rest for memory consolidation are most pronounced when accompanied by such activities as mind-wandering or daydreaming (Brokaw et al., 2016). These 'states of mind' are most commonly shown to be active when a person is not focused on the outside world and the brain is at wakeful rest, in other words in its default mode state (Buckner, Andrews-Hanna, & Schacter, 2008). The brain enters this default mode network (DMN) when it is not otherwise occupied with other goal-oriented

tasks, thus providing beneficial conditions for consolidation in agreement with the opportunistic consolidation hypothesis.

Based on the previous findings (Brokaw et al., 2016; Craig et al., 2016; Dewar et al., 2012, 2014), Chapter 4 proposes that quiet wakefulness can support consolidation of new material similarly to sleep. Importantly, Chapter 4 provides first evidence that this consolidation may be cued with tDCS method. In this way Chapter 4 follows on from Chapter 3 which used TMR method to prompt consolidation in sleep. Here, I showed that similar memory enhancements can be achieved during quiet wakefulness when targeting oscillatory activity that accompany this state with tDCS; however, the exact mechanism is still to be discovered. Below, I discuss a possible consolidation mechanism which may have contributed to memory improvement in wake.

The DMN consists of interacting brain regions known to have activity highly correlated with each (Graner, Oakes, French, & Riedy, 2013). It has also been indicated that the hippocampus appears to play a prominent role in the default-mode network (Greicius et al., 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Greicius, Srivastava, Reiss, & Menon, 2004). For example, when comparing normally aging adults and adults showing signs of Alzheimer, a co-activation of the DMN and the hippocampus was shown, suggesting that the default-mode network is closely involved with episodic memory processing (Greicius et al., 2004). Additionally, the default state of the brain exhibited a high inter-region connectivity which allows separate brain regions to communicate. The studies showed that the same is true for the hippocampus; the hippocampus can only support episodic memories if it interacts closely with other brain regions (Moscovitch et al., 2016); therefore the increased connectivity with other brain areas during the default mode state would promote the hippocampal involvement in memory processes.

According to Moscovitch et al. (2016) and the component process model they proposed, the interaction between distant regions of the brain may be turned off and on rapidly by brain oscillations. Amongst all brain oscillations, the alpha activity seems to be the most likely candidate to operate this gating mechanism in quiet wakefulness. For example, Sadaghiani et al. (2012) demonstrated that phase-synchronization of alpha-oscillations across distant cortical regions could regulate integration of information and communication between fronto-parietal networks. The alpha oscillations were also important in regulating attention and alertness, both of which are reduced during the quiet wakefulness state. Thus, it is possible that the reduced alpha activity reflects an increased connectivity between different brain regions within the default mode network. In that way, the DFM could provide beneficial conditions for memory consolidation during wake not

only by limiting the interference from the environment but also by actively supporting the information flow and processing between hippocampus and other parts of the network. Nevertheless, the alpha level between the tDCS and sham groups in our study did not differ significantly, hence the role of alpha in the DMN is yet to be established. It is possible that it is a different aspect of alpha activity, for example alpha synchronisation between brain regions, and not the alpha power that was looked at, that is important for memory processes during wake.

Additionally, some evidence that the neural network connectivity in resting state may underlie episodic memory consolidation in wake comes from the resting-state fMRI study (Kukolja, Göreci, Onur, Riedl, & Fink, 2016). This study implicated that, during post-encoding rest, the connectivity changes between different brain regions predicted memory performance post-rest. Therefore, if a reduced alpha activity did increase the flow of information between brain areas, we would observe a better performance in the group that showed lower alpha power.

Nevertheless, whether the underlying mechanisms of consolidation in sleep and wake are comparable remains unknown. A note of caution is due here as the proposed interpretations above are speculative and thus must be considered with care. A more controlled study could help to verify the actual engagement of the default mode network and the exact role of alpha oscillations in quiet wake.

5.2.2 Factors mediating memory consolidation in sleep and wake- the bottleneck of memory consolidation

Apart from the degree of information overlap discussed in the previous section, there are many elements that come into play during encoding and consolidation. These factors may have direct impact on how new information is learnt and consolidated. Below, I will list and discuss some of the most important factors that have been the focus of attention throughout this thesis.

Type of memory has been shown to be an important factor that has potential to affect the time-course of consolidation. For example, associative memory had been indicated to be more sleep-dependent than non-associative memory. In fact, Breitenstein et al. (2005) found the hippocampal involvement in particularly supports the formation of associative memories. At the same time the performance in non-associative recognition tasks was shown to depend more on the initial encoding strength. Interestingly, the effects obtained in Chapters 3 and 4, where external manipulations were used, were only found in the recall tasks (a cued recall in Chapter 3 and a free recall in Chapter 4) but not the

recognition tasks. Although an overall improvement was observed overnight, or over a week delay, the recognition tasks remained insensitive to the TMR or tDCS effects. Interestingly, similar dissociable findings for recall and recognition memory were previously reported by other studies using the TMR paradigm (Ashton et al., 2017; Schreiner & Rasch, 2014; Tamminen et al., 2017). This suggests that only some aspects of memory, formed at the encoding, remain susceptible to external manipulations.

One plausible explanation of selective benefits gained from sleep-related consolidation has been attributed to memory strength. Previous studies showed that TMR-induced strengthening applies only to weakly learnt but not nearly perfectly-memorised information (Creery et al., 2015). In the same way, the recognition memory, due to its more durable and robust nature in comparison to more retrieval-based recall tests (Standing, 1973), may remain insensitive to subtle benefits induced by TMR or tDCS methods. Furthermore, recent research (Schapiro et al., 2017) has demonstrated that memories that were weakly encoded are replayed more during wakefulness and that the amount of this replay can in fact predict memory improvement measured after a night of sleep. This points to the inter-dependence of memory replay that occurs in wake and sleep and that, although qualitatively different, the memory consolidation processes utilised during both these states are not fully independent from each other. The data obtained in Chapter 4 confirms that memory strengthening in wake and in sleep are not completely independent. For example, memory representations which were strengthened under the tDCS condition during wake, remained still stronger in comparison to the sham condition after a week long delay. This finding implies that subsequent nights of sleep taking place prior to the final test, had not abolished the tDCS-induced memory benefits gained during the wakeful rest.

Chapter 2 and Chapter 3 capitalised on the fact that memory strength at encoding may affect its later consolidation. Chapter 2 demonstrated that the number of exposures when learning distinct novel words, and hence the strength of their representations, matters. For example, the consolidation and lexical integration of these items was not observed before or after sleep following only 12 exposures. However, clear lexical integration effects were obtained after sleep when the number of exposures was increased to 36. This suggests that optimal conditions for integration of novel phonological tokens include a good level of encoding and delay with sleep. Previous research has shown that a mass exposure to novel words, resulting in nearly perfect representations, may even further reduce the need for overnight consolidation (Lindsay & Gaskell, 2012). In comparison, learning new words that show more phonological overlap with existing lexicon may not require such robust encoding and/or offline consolidation (Sobczak & Gaskell, submitted).

Chapter 3 deliberately employed the low number of exposures to novel words which Chapter 2 showed to be insufficient in inducing lexical integration effects. This was motivated by the previous findings that weakly encoded memories benefit most from the TMR in sleep (Creery et al., 2015). The results were two-fold: firstly, the memory for novel words reactivated in sleep was better than for the non-reactivated ones, however no evidence of lexical integration across novel items was observed. Although the findings cannot definitely explain the reason for these dissociable effects, they offer some speculative interpretations. Firstly, the level of exposure could affect the lexical integration process. On the one hand, too weak encoding would be insufficient for any lexical integration effects to emerge, despite a clear cueing effect in the recall test, which may have been the case in our study. On the other hand, too robust encoding would result in lexical integration of all items and no effect of cueing in the recall test (cf. Tamminen et al., 2017). An alternative explanation however, points to separate processes that may govern memory strengthening and integration. This twofold way in which the memory consolidation works has indeed been shown by recent investigations for such processes as generalisation (Hennies et al., 2017) or rule abstraction (Batterink et al., 2017), thus far considered to be heavily sleep-dependent. This lack of clarity could be addressed by future studies by fine-tuning the level of exposure to novel words in order to shed more light on the role of offline replay in strengthening and integration of novel memories.

5.2.3 Hide and seek – the game of manipulating memory consolidation

The idea of manipulating and enhancing our memory has a longstanding history. Recent technical innovations allowed us to alter the ongoing brain activity with more or less invasive techniques described in the introduction. This thesis takes advantage of such techniques in Chapter 3 and 4 where it employs the TMR method, to selectively probe memory consolidation in sleep, and tDCS method to investigate the consolidation process taking place during quiet wakefulness.

A growing body of research provides support for the TMR technique as a way to enhance sleep-associated memory. New research have helped to discover novel applications but also limitations of this method. These in turn helped to fine-tune some of the method's properties in order to cease the spontaneous processes of memory replay in sleep. Chapter 3 makes use of this advance in order to prompt consolidation of material that is novel to participants and has little overlap with existing concepts or knowledge, i.e. distinct novel words. As indicated in the previous section, Chapter 3 showed that TMR may be useful for some but not other processes engaged in memory consolidation. Additionally, as I discussed in Chapter 3, the precise mechanism of memory reactivation is still unknown.

The investigations into the neuro-correlates of cueing in sleep undertaken in Chapter 3, suggested that the precise timing of reactivation is crucial. Indeed, recent evidence implied that the phase of slow oscillations in sleep is vital when cueing memories in sleep. Göldi, van Poppel, Rasch, and Schreiner (2017) demonstrated the slow oscillatory up-states represent privileged time windows for memory reactivation. The authors also showed that the interplay of slow oscillations, theta and sleep spindle activity promotes successful memory consolidation during sleep. Although an increased spindle activity was observed in the study reported in Chapter 3, no such increases were seen in theta frequency range. One possible explanation points to the missing element- the absence of integration of novel memories which may have manifested itself in the lack of theta increases. Future studies could elaborate on these findings by employing a more precise timing of reactivation to examine possible effects on memory consolidation.

Previous research have shown that tDCS technique can successfully augment consolidation in sleep and wake (Fogel & Smith, 2011; Marshall et al., 2006). At the same time, growing evidence suggests that quiet wakefulness provides favourable conditions for memory consolidation, comparable to sleep. Chapter 4 investigates those claims further by looking specifically at whether applying tDCS during quiet wake would affect later recall of an object list learnt prior to quiet resting. The results showed that it is possible to enhance memory consolidation during quiet wake with tDCS. Although the precise mechanism is unclear, evidence suggests that the memory increases may be due to mind-wandering and the DMN naturally occurring during quiet wakefulness. The mind wondering and default state network would promote memory improvement in two ways: firstly by allowing different brain regions to successfully communicate with each other (Greicius et al., 2004) and secondly, by preventing new information input and hence interference from the environment. Nonetheless, although a fascinating proposal, the precise mechanism which stands behind memory consolidation during mind-wandering is not known. Further work is required to establish the viability of the relationship between the DMN and memory consolidation. Moreover, Chapter 4 looked specifically at the alpha power in response to the parietal tDCS- this may be an insufficient measure as previous reports have indicated that it may be the synchronisation of alpha oscillation between different brain regions, and not its power (Palva & Palva, 2007). A further study with more focus on phase-locking of alpha oscillations between cortical areas involved in the DMN is therefore suggested.

Furthermore, as sleep and wake have both been implicated as contributors to memory consolidation separately but also interdependently, future direction could target this relationship by employing wake and sleep conditions together.

5.3 Conclusions

Investigating memory consolidation in the light of current neurocognitive models and the newest experimental advances allowed us to provide some insights regarding the mechanisms of this essential human ability. In this thesis, I argued that memory consolidation mechanisms are varied in nature. I put forward the claim that wake and sleep are both crucial in stabilising our memories. The approach taken in this thesis, to look at the memory consolidation processes from the perspective of sleep and wake, provided an empirical basis that the offline consolidation processes change our memory representations during both states. The findings of these investigations complement those of earlier studies. Moreover, this thesis provides evidence that it is possible to enhance memory benefits externally, be it in sleep or quiet wake. By employing the TMR in the paradigm of novel word learning, I pushed the method into untested ground and successfully showed its application for completely novel material. Similarly, just as in sleep, I also demonstrated that the memory benefits in quiet wakefulness may depend on the ongoing brain activity which is susceptible to change. This work has contributed to our understanding of consolidation and integration of novel information by showing that the integration process may be dependent on the type of material to be learnt and its fit with our pre-existing knowledge. It was also shown that the level of encoding may impact how we consolidate what has been learnt.

A key strength of the experiment reported was drawing on results and methods from different domains of memory. This allows us to illustrate the complexity of our adaptive behaviour such as learning and remembering. The memory consolidation is a phenomenon itself that escapes single theory or model however; it shows strong biological underlying mechanisms. In that way it provides a testing field for general models of memory and effectiveness of various innovative techniques. It also offers a promise of important clinical applications in such problems as Alzheimer's or amnesia.

On the basis of the presented findings, this thesis provides insight into mechanisms of memory consolidation at the behavioural and neural level. It shows the importance of offline consolidation in both sleep and wake. Furthermore, the research outlined here shows the need to shift the emphasis from the 'all or nothing' to a more graded picture of memory consolidation. Memory consolidation is a multifaceted, dynamic and gradual process which may take place during actual sleep as well as during merely daydreaming.

APPENDICES

Appendix A

List of stimuli used in all three experiment reported in Chapter 1.

List	English Base Word	Novel Word	Foil
List 1	celery	celedo	celemi
	finale	finato	finady
	recipe	recino	reciby
	bikini	bikiso	bikita
	colony	colopy	colofo
	sesame	sesana	sesara
	salary	salamo	salaky
	libido	libima	libiny
	cinema	cinedy	cinero
	casino	casira	casibu
	kimono	kimota	kimore
	pagoda	pagory	pagono
List 2	tomato	tomany	tomare
	bakery	bakeva	bakemo
	rosary	rosano	rosava
	karate	karano	karaby
	saliva	saliro	salika
	banana	banary	banamo
	safari	safano	safany
	melody	meloro	melova
	sonata	sonary	sonake
	corona	corode	coroso
	canary	canato	canafy
	mimosa	mimoly	mimora

Note. The pronunciation of the novel words and foils matched the base words on the first two syllables in terms of phonemic overlap and stress pattern.

Appendix B

Listening Task

In order to investigate the neural correlates of lexical integration of novel words after a period of an offline consolidation, we employed a passive EEG listening task taking place after sleep. Here, the EEG responses were recorded while participants passively listened to the trained novel and existing words, as well as untrained novel words.

Previous studies demonstrated that the change in the lexical status of newly learnt novel words has distinct electrophysiological signatures. For example, Bakker, Takashima, van Hell, Janzen, and McQueen (2015a) showed that novel words which underwent a 24-hr consolidation period elicited more word-like oscillatory responses than novel words learned immediately before testing. The theta oscillatory activity (4-8 Hz) was in particular indicated to reflect lexical access with unfamiliar words eliciting lower power in this frequency band than familiar words (Bakker et al., 2015a; Bastiaansen & Hagoort, 2006; Bastiaansen et al., 2005). Similarly, Bakker, Takashima, van Hell, Janzen, and McQueen (2015b) showed neural markers of the lexical consolidation with distinct event-related potentials (ERPs) such as N400 and a later positive component (LPC). For example, the authors showed that the N400 and LPC components' amplitudes between novel and existing words decreased significantly after a 24-h consolidation period, providing additional support for the hypothesis that offline consolidation aids lexicalisation.

In order to further assess whether the lexical status of novel words learned in our experiment changed with offline consolidation, and what impact the cueing in sleep had on this process, we measured the EEG responses to different categories of linguistic tokens. To mimic Bakker et al. (2015a), the stimuli included in the listening task comprised of the newly learnt novel words, familiar English words and never heard, unfamiliar novel words. Here, based on the previous reports which tracked brain signatures of successful integration of novel words we expected to see: 1) different event-related potential (ERP) responses to known and new words as a measure of task effectiveness, 2) different ERP responses to newly learned and consolidated words as opposed to novel but never heard ones and 3) comparable responses to known and newly learned but consolidated words. Consequently, the supplementary purpose of this task was to assess the extent to which the cueing in sleep impacts novel word integration at a neural level as measured during following wakefulness. If TMR facilitates better integration of newly learned material within pre-existing memory networks, then we would expect to see different brain responses to cued and non-cued items during this task.

EEG Task

During the listening task the participants were asked to lie down on the bed with their eyes closed and listen to a set of words, played through earphones. The word sets comprised of five categories of stimuli: 1) novel spoken words learned in the previous evening and reactivated during sleep (20), 2) novel spoken words learned in the previous evening and not reactivated during sleep (20), untrained novel spoken words that participants did not hear in the experiment (20), existing English words (20) and 5) catch trials (15). With the exception of the catch trials, each item was replayed five times (400 trials in total). The existing English words used in this task were taken from the pause detection task fillers' sets to avoid the effect of the first exposure to these words (Bakker et al., 2015a). In the catch trials, participants heard a word and were asked to provide a verbal response whether they heard this word previously or not whilst their responses were recorded. Two thirds of these trials were completely new novel words that participants had never heard in the experiment and the rest of the trials were randomly drawn from the pool of words that participants had already heard in the task. The main aim of the catch trials was to maintain participants' attention on the task and thus they were later discarded from analyses. The inclusion of the existing items was to provide a "response baseline" to which the lexical status of novel trained items could be compared (Bakker et al., 2015a). The inter-stimulus interval, measuring from word onset, was 2,600 ms. The listening task took approximately 25 minutes to complete.

EEG acquisition and pre-processing

Continuous EEG was recorded from 13 channels (F3, F4, C3, C4, O1, O2, Fpz, F7, F8, T3, T4) plus from mastoids used for a referencing purpose (2 channels). EEG scalp electrodes were attached according to the international 10-20 system and monitored with the Embla N7000 PSG system (with RemLogic version 3.4 software). Additionally, we recorded the electromyography (EMG, 3 channels) and electrooculography (EOG, 2 channels) activity to control for eye movements and muscle artefacts. Impedances were kept below 10 kΩ.

All EEG data pre-processing was done using EEGLAB toolbox (Delorme & Makeig, 2004). Data was first re-sampled to 200 Hz. The EEG signal was then re-referenced offline to the averaged left and right mastoids and filtered at 1-30 Hz. Epochs were extracted from continuous data with 400 ms pre-stimulus and 1,700ms post-stimulus interval. Trials containing muscle or hardware noise as well as eye blinks were rejected. The noisy channels were interpolated using the average signal from neighbouring channels. Each dataset was

baseline corrected and further processed into separate sets for each event type in order to perform the ERPs analyses; the catch trials were removed from further analyses leaving 4 categories of event type: 1- novel words learnt reactivated; 2- novel words learnt not-reactivated; 3-unfamiliar new words; 4- known English words.

EEG analysis

Event Related Potentials (ERPs) analysis

The statistical analyses of ERPs were performed in Mass Univariate ERP Toolbox (OpenWetWare, 2017) using the non-parametric permutation method that was described previously in the Chapter 3. This allowed for an exploratory investigation into a longer time window. The parameters of the non-parametric permutation method followed the ones from sleep event-related response analysis.

Time-frequency analysis

The previously pre-processed data were analysed for power changes in response to the stimulus presentation in the listening task. The analysis of power changes was performed using FieldTrip toolbox (Oostenveld et al., 2011). For frequencies in the 4–30 Hz range, time–frequency representations (TFRs) were computed for each trial by using 3-cycle Morlet wavelet decomposition. In order to avoid edge effects, the trials entering the wavelet transform were segmented from −400 to 1,700 s with respect to stimulus presentation. Data was analysed between 400 ms pre-stimulus and 1,700 mc post-stimulus, in steps of 10 ms and 0.5 Hz. An interval of 200 ms at the beginning and the end of the trials was discarded afterward. The average signal across all conditions was baselined corrected using a 200–100 mc pre-stimulus interval. We analysed the time window from -120 ms pre and 900 ms post stimulus onset, based on a time where significant effects were reported in the literature (Bakker et al., 2015a). Statistical analyses of the EEG data were performed with a nonparametric randomization test using cluster correction as implemented in FieldTrip. The cluster alpha was set to 0.05 and 1000 randomizations were conducted for all tests. Clusters were considered significant at $p< 0.05$ (two-sided).

Results

Event Related Potentials (ERPs)

We first investigated the difference between known words (e.g., *carrot*) and new items (novel words that participants never heard before, e.g., *drabon*). The assumption here was that if we observed a difference between these two item categories, it would reinforce

the reliability of the novel passive listening task in investigating the lexical status of newly learnt phonological forms.

The results showed that the new items differed from the old items at two time windows: an early positive component, from 200 to 355 ms after stimulus onset, with fronto-central and temporal distribution (significant electrodes: C3, C4, F3, F4, T3, T4, Fpz, F7), and at a later negative component, from 675 to 710 ms post stimulus onset (significant electrodes: C3, F4, F3, C4, Fpz), with bilateral fronto-central distribution (see Figure B1a). Critical t-score(s) values were set at $t(34)=+/-4.52$; all $p<.048$, corrected for multiple comparisons.

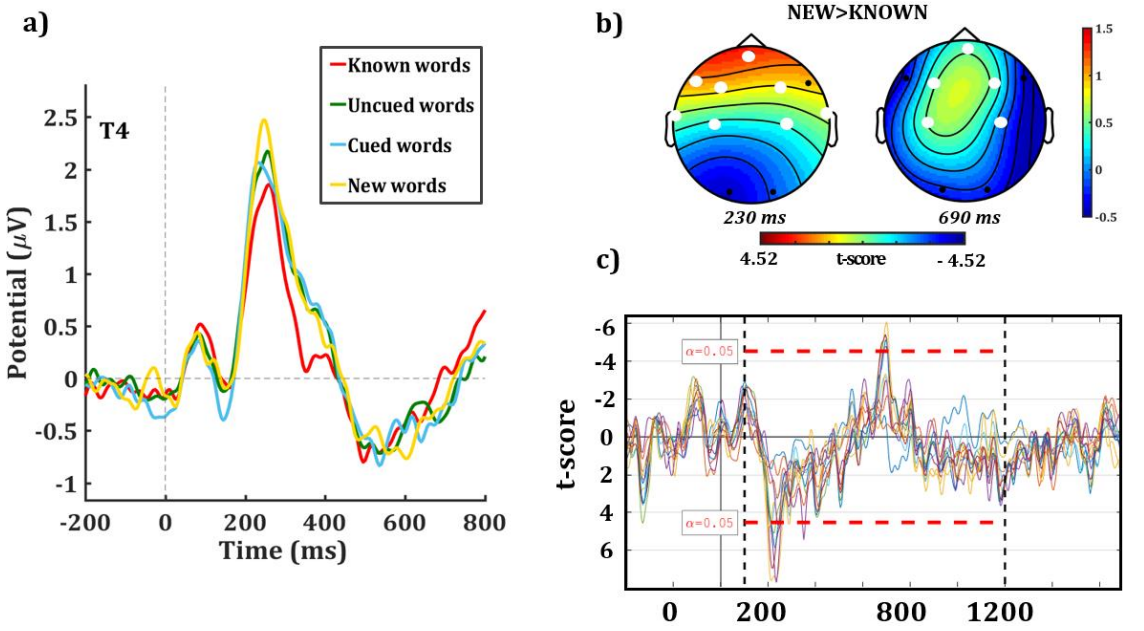

Figure B1. ERP results. a) Electrophysiological results illustrating the ERPs to different stimuli type at a representative electrode T4. b) Scalp maps representing the topographical distribution for the difference in response to the new and known words at two time points representing the biggest difference. c) The t-scores of a comparison between brain responses to new and known words plotted for all 15 electrodes (the red dotted line shows significant difference between two categories below 0.05 cut-off point) showing two components: an earlier positive component (higher amplitude to new items in comparison to known items) and a later negative component (lower amplitude to new items in comparison to known items).

With regard to the cued and non-cued items we did not observe any significant differences (all $p>.05$). We compared the cued and non-cued items to known items to quantify whether the two categories show similar neural signatures. Previous studies have shown that new items, which had a chance to undergo sleep-related consolidation

processes, and thus became integrated within neocortical lexicon, elicited brain responses undistinguishable from known items (Bakker et al., 2015b). Here, we observed that the non-cued items showed the same difference from known items as completely new items, with an early component (200-350 ms time window) and a later component (from 670 to 700 ms time window; the following electrodes were significant: Fpz, F4, F8, T4, C3, C4, F3; $t(34)$=+/- 4.52, all p<.05). Similarly, the cued items also differed from the known items at the earlier time window in the same way as new items did (200-350 ms; the following electrodes were significant: Fpz, T4, F8, F3, F4, C3; $t(34)$=+/-4.56, all p<.05). The grand average ERP responses to four conditions are illustrated in Figure B2.

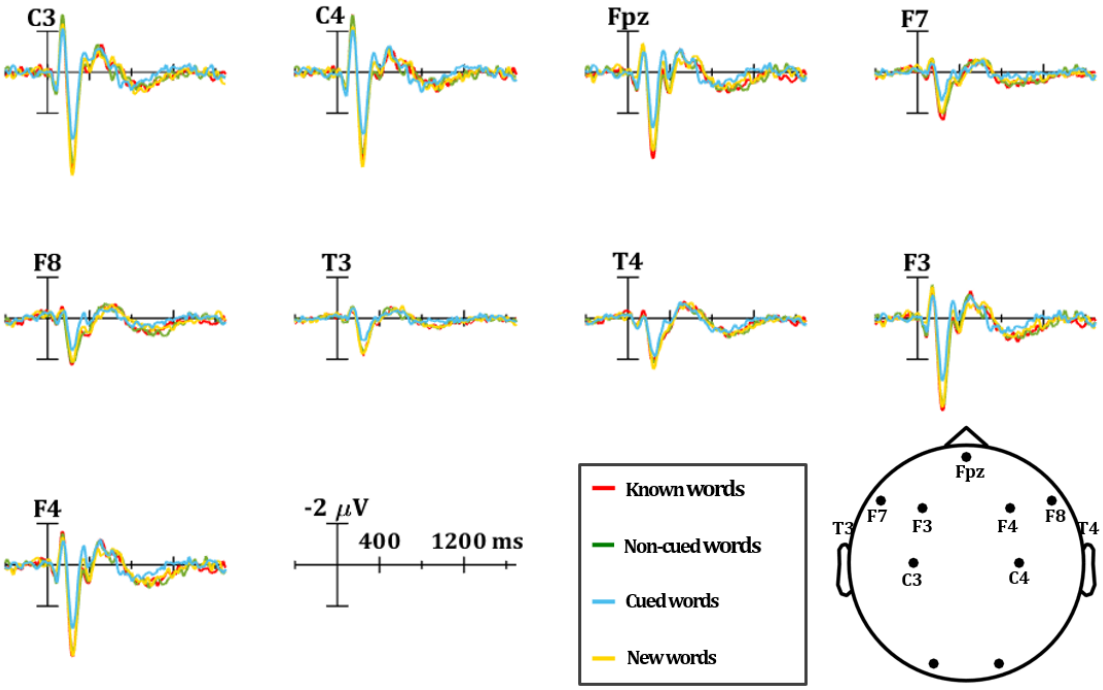

Figure B2. Grand average ERPs (N=35) to four word types: known items, learned items (cued and non-cued) and new items and a topographical map of all electrodes.

Time-frequency

Although we did not observe the lexical integration of novel items at a behavioural level, the neurophysiological measures may sometimes offer more insight as to the ongoing cognitive processes without their behavioural manifestation. Previously, it has been reported that lexical access is reflected by the power in theta frequency band with unfamiliar novel words eliciting less power in theta than existing words (Bakker et al., 2015a). For example, the novel words learnt 24 hours before a test, and therefore having an

opportunity to undergo the sleep-related consolidation processes, mimicked the responses to the real words in theta frequency band in the left hemisphere from 400 ms to 600 ms following word presentation. Therefore, in order to investigate whether the known, newly learnt (cued and non-cued) and new items induced a different neural response in theta band we also analysed the brain correlates of these four word types in the time-frequency space. The results showed that the known words elicited more theta power than the new words (see Figure B3a) at the investigated time interval from 200 to 400 ms after word presentation, at the right central site (positive time cluster; p<.01). Similarly, the words learned before sleep showed a similar pattern; both, the cued and non-cued words elicited significantly less theta power than known words (both p<0.05; See Figure B3b). The newly learnt cued and non-cued words also did not differ in theta frequency band between each other and in comparison to new items (all p>.05). These results suggest that the newly learnt novel words were processed more like the never heard new pseudo-words and not like the known and integrated lexical items. These results are consistent with the behavioural measures which also showed lack of a robust lexical integration of the learnt novel words.

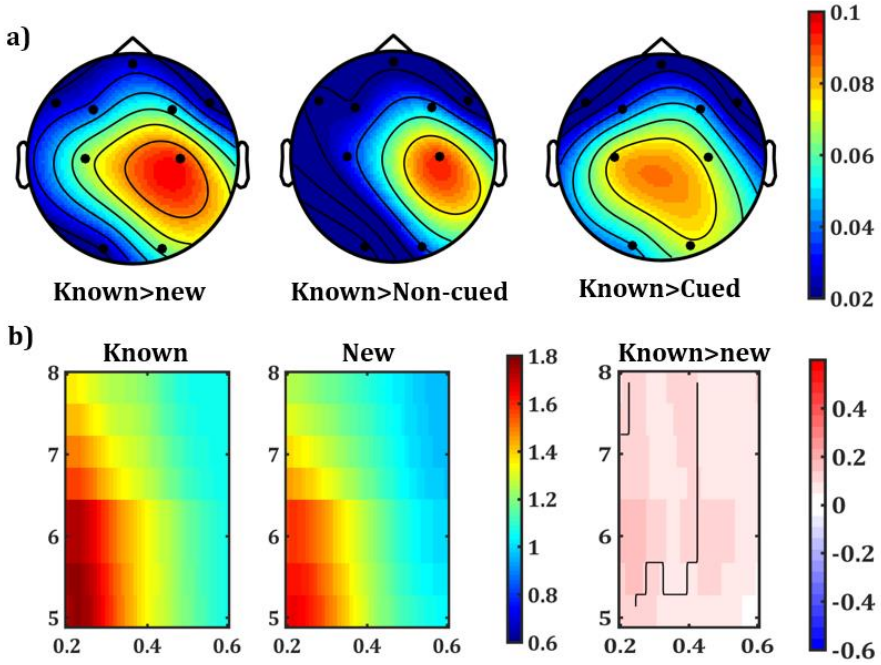

Figure B3. Time-frequency results. Electrophysiological results a) Topoplots illustrate a similar pattern of averaged difference in theta frequency band (5-8 Hz) at the time interval from 200 to 600 ms after word presentation between known words and new words, known words and cued words as well as non-cued words. Red indicates higher power in theta for known words. The difference in the theta power exhibited central distribution (significant electrode C4). b) Time- frequency plots illustrate the theta power for known and new items. The difference (Known>new) plot outlines the area of significant differences between the two conditions.

Discussion

In order to assess the neural correlates of lexical integration of novel words and the influence of TMR on this process, we employed a passive listening task taking place after sleep. The listening task examined neural markers of the lexical integration of novel words in the morning after an opportunity for the overnight consolidation. We hypothesised that if the lexical consolidation entails a fundamental change in the nature of novel word representations, the neural responses to the learnt items should exhibit a more word-like neural pattern after a consolidation period of sleep. We found no evidence that novel words, learnt prior to sleep, behaved like existing words. In fact, the brain responses to words learnt in our experiment, both cued and non-cued in sleep, resembled more closely the response pattern elicited by completely new and never learnt items. This outcome is in contrary with previous studies which indicated that novel words which underwent a 24-hour consolidation delay become integrated within lexicon and are processed alike the existing words (Bakker et al., 2015a, 2015b). As these findings are consistent with our behavioural results, which did not show evidence of successful lexical integration of new items, it suggests that the lexicalisation process in our study was not yet completed after a delay of sleep.

We expected different brain responses to familiar and new items as a measure of task efficacy. Here, according to our predictions, the results showed that the familiar English words and the never encountered new items induced differential neural responses. This finding confirmed that the passive listening task used in our study offers a potentially effective tool to examine the neural correlates of lexical integration.

The examination of the differences in neural responses to the known English words versus the new pseudo-words and newly learnt novel words indicated two time points of such differences. An early positive peak at approximately 300 ms post-stimulus and a later negative peak at 600 ms post-stimulus. The earlier component identified in our data, which has a positive-going maximum amplitude over frontal/central electrode sites and a peak latency in the range of 250-350 ms post stimulus onset, may indicate the P3a component, or novelty P3. The P3a has been associated with brain activity related to the engagement of attention (especially the orienting, involuntary shifts to changes in the environment), and processing of novelty. Thus, the early component may reflect different attention demands when listening to known and new words with a higher amplitude reflecting a larger novelty effect when listening to the new words.

The late negative component, with a peak latency at about 700 ms post stimulus onset, has been previously indicated in the literature as elicited in response to concrete words and suggested to index imagery (Gullick, Mitra, & Coch, 2013). It is plausible that the later component observed in our data may reflect a late positive component (LPC), previously showed to be elicited in response to known words (Borovsky, Kutas, & Elman, 2010) and typically observed between a 500-700ms post word onset. As a part of the LPC the literature indicates a late P600 component which has been shown to reliably differentiate between skilled and poor readers. For example, high-skilled readers show stronger familiarity effects for learnt words, whereas less-skilled readers do not distinguish between the learnt words, familiar words, and unlearnt words. The P600 component is a positive going waveform with central and parietal electrode distribution on the scalp that appears around 500–800 ms after the onset of a word. It has been often referred to as the old/new ERP recognition memory component (P600) that distinguishes between recently presented items and new items. It is characterized by a more positive amplitude for 'old' items than for 'new' items (Curran, 2000; Rugg & Curran, 2007). The P600 old/new effect has also been directly observed in word learning studies. For example, Perfetti, Landi, and Oakhill (2005) exposed learners to the form and meaning of rare unknown words. They reported a positive component that peaked at around 500 ms (i.e., P600) after the presentation of a word, and showed larger amplitudes after the presentation of a learnt word than unpresented rare or familiar words. Thus, they concluded that the P600 may be a marker for a recently learnt word.

In sum, the passive listening task showed differential EEG responses to the well-known English words and never heard pseudo-words confirming the task efficacy. We observed similar differences in response to known words and novel words (cued and non-cued in sleep) that were learnt on the previous day. This indicates that the neural lexical representations of newly learnt words resembled the unconsolidated pseudo-words and not, as expected, the well-known English words. These results may be due to the fact that the low level of exposure (13 exposures) to novel items was not sufficient for the lexical integration effects to emerge. Future studies could include a semantic element when learning novel words in order to strengthen their semantic and lexical processing.

Appendix C

Stimuli used in the TMR experiment reported in Chapter 3

Base word	Novel word	Foil	Sound Description
slogan	slowgi	slowgith	key
cartridge	cartroce	cartrole	turkey
bramble	brambooce	bramboof	hammer
shrapnel	shrapnidge	shrapnit	accordion
molecule	moleky@n	moleky@k	applause
skeleton	skeletobe	skeletope	money
pyramid	pyramon	pyramotch	train
anecdote	anecd@l	anecd@n	dog
parachute	parah@ff	parah@n	cards shuffle
badminton	badmintel	badmintet	cat
artichoke	artich@d	artich@n	car
hyacinth	hia@l	hia@d	elephant
fellow	fellowks	fellowkt	piano
sorrow	sorrowkt	sorrowft	copy
veto	vetolt	vetont	walk
elbow	elbowNk	elbowlk	bomb
shadow	shadowks	shadowkt	heart
jelly	jellylk	jellyk	spring
pity	pitylv	pitylm	toothbrush
movie	movient	moviet	toilet
napkin	napk@m	napkas	rooter
squirrel	squirrome	squirrope	gong
dungeon	dungeill	dungeic	glass breaking
tulip	tulode	tulome	bowling
alcohol	alcohin	alcohid	camera
caravan	caravoth	caravol	match
ornament	ornameat	ornameab	lightening
pelican	pelikiyve	pelikibe	chain saw
daffodil	daffadAt	daffadAn	popcorn
hurricane	hurricarb	hurricarth	sneezing
apricot	aprickel	apricken	vacuum
bayonet	bayonis	bayonil	tea pouring
orgy	orgykt	orgyft	ball bouncing
kilo	kilolf	kilolp	crying
beauty	beautynd	beautyns	dolphin
jury	jurynts	jurylt	monkey
willow	willowlb	willowlv	cough
banjo	banjolp	banjolk	electricity
fairy	fairynd	fairynt	saxophone
laundry	laundrysk	laundrylk	coocoo clock

blossom	blossail	blossain	tennis
lantern	lantobe	lantoke	drum
culprit	culpr@n	culpr@d	drill
parsnip	parns@g	parsn@s	snore
cathedral	cathedruke	cathedruce	saw cutting
specimen	specimAl	specimAv	cow
porcelain	porcelote	porcelole	violin
assassin	assassool	assassood	yawn
cardigan	cardigite	cardigile	telephone
utensil	utenont	utenop	harmonica
clarinet	clarinern	clarinerl	gun
gelatine	gelatord	gelatorl	bell
body	bodyft	bodykt	harp
duty	dutylm	dutyld	chime
story	storymp	storylp	city
brandy	brandyst	brandyft	whip
pantry	pantryld	pantrylv	kiss
glory	gloryls	glorylf	deck of card
boogie	boogiens	boogiend	chirping
quarry	quarrysp	quarrymp	water

Appendix D

Stimuli lists used in the tDCS experiment reported in Chapter 4.

List 1	List 2
actress	beach
bacon	beard
bell	belly
cash	bullet
chalk	chest
clock	coach
cloud	corn
coin	crowd
desk	dirt
gate	dust
grass	film
gravel	jacket
guitar	jockey
lounge	knife
mask	leaf
note	milk
nurse	parcel
parade	pipe
pine	rock
plate	sail
pump	sausage
quarry	scrap
stream	throne
wagon	tongue
wheel	tooth

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