The Role of Sleep in the Formation of Semantic Memory

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Medical and Human Sciences

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Contents

List of Figures 6
List of Tables 7
List of Abbreviations 8
Abstract 9
Declaration 10
Copyright Statement 10
Acknowledgements 11
Chapter 1 Introduction: Semantic Memory, Sleep and Consolidation 13
  1.1 Overview ................................................................. 13
  1.2 Semantic memory ..................................................... 14
    1.2.1 Semantic memory representations: The hub-and-spoke model ..... 15
    1.2.2 Formation of new conceptual knowledge ....................... 18
  1.3 Memory consolidation ............................................... 22
    1.3.1 Standard model for systems memory consolidation .............. 22
    1.3.2 Semanticisation as a product of memory reorganisation ....... 24
    1.3.3 Schema theory .................................................. 26
    1.3.4 Schema assimilation model .................................... 27
    1.3.5 Relationship between semantic memory and schemas .......... 28
  1.4 Sleep physiology ................................................... 29
    1.4.1 Sleep stages .................................................... 29
    1.4.2 Synchrony of sleep-related rhythms .......................... 32
    1.4.3 Synaptic plasticity during sleep ............................. 33
  1.5 The role of sleep in systems memory consolidation and semanticisation ... 34
    1.5.1 Active systems consolidation model ............................ 34
    1.5.2 Evidence that memories are processed during sleep .......... 35
    1.5.3 Evidence that sleep supports systems memory consolidation 38
  1.6 Summary ............................................................... 42
  1.7 Research objectives .................................................. 42
# Chapter 2  Time- but not sleep-dependent memory consolidation promotes the emergence of conceptual knowledge

2.1 Abstract ................................................................. 46
2.2 Introduction ........................................................... 46
2.3 Methods .................................................................
   2.3.1 Participants ...................................................... 48
   2.3.2 Stimuli and stimulus generation .............................. 48
   2.3.3 Experimental tasks ............................................ 49
   2.3.4 Procedure ........................................................ 52
   2.3.5 Statistical analysis ............................................ 52
2.4 Results .................................................................
   2.4.1 Experiment A ..................................................... 53
   2.4.2 Experiment B ..................................................... 55
2.5 Discussion ............................................................. 57

# Chapter 3  Cued memory reactivation during SWS abolishes the beneficial effect of sleep on abstraction

3.1 Abstract ................................................................. 62
3.2 Introduction ........................................................... 62
3.3 Methods .................................................................
   3.3.1 Participants ...................................................... 64
   3.3.2 Stimuli ............................................................ 64
   3.3.3 Experimental task and design ............................... 66
   3.3.4 Equipment ........................................................ 68
   3.3.5 Behavioural data analysis .................................... 68
   3.3.6 PSG data acquisition and analysis .......................... 69
3.4 Results .................................................................
   3.4.1 Auditory recall task ............................................ 70
   3.4.2 Visual recall task ............................................... 70
   3.4.3 Alertness and response times ................................. 71
   3.4.4 N-back task ...................................................... 71
   3.4.5 Association between overnight performance change and SWS  ... 72
   3.4.6 Differences between groups in sleep structure ............ 73
   3.4.7 Differences between groups in sleep quality ............... 74
3.5 Discussion ............................................................. 75

# Chapter 4  Sleep spindles mark hippocampal to neocortical consolidation of schema-related memories

4.1 Abstract ................................................................. 80
4.2 Introduction ........................................................... 80
4.3 Results ................................................................. 82
4.4 Discussion ............................................................. 88
4.5 Methods .................................................................
   4.5.1 Participants ...................................................... 90
4.5.2 Stimuli .............................................. 90
4.5.3 Procedure ........................................... 91
4.5.4 PSG data acquisition and analysis ......................... 91
4.5.5 Statistical analyses ................................... 92
4.5.6 fMRI data acquisition and analysis ....................... 93
4.6 Supplemental material .................................... 95

Chapter 5 A weak schema link is sufficient to trigger the schema benefit and the association with sleep spindles 109
5.1 Abstract .................................................. 110
5.2 Introduction ............................................. 110
5.3 Methods ................................................... 111
5.3.1 Participants .......................................... 111
5.3.2 Stimuli ................................................. 112
5.3.3 Pilot study .............................................. 113
5.3.4 Procedure .............................................. 113
5.3.5 Equipment ............................................. 118
5.3.6 PSG data acquisition and analysis ....................... 118
5.3.7 Statistical analyses ................................... 119
5.4 Results .................................................... 119
5.4.1 Subjective ratings ..................................... 119
5.4.2 Behavioural memory performance ....................... 119
5.4.3 Reaction time results .................................. 120
5.4.4 Polysomnography results .............................. 121
5.5 Discussion ................................................ 124

Chapter 6 General Discussion 127
6.1 The impact of sleep on processes of abstraction and integration .......... 127
6.1.1 Summary of findings (Chapters 2 and 3) ................... 127
6.1.2 Relation to semantic memory ................................ 128
6.1.3 Benefit of consolidation on the formation of semantic memory ........ 129
6.1.4 What determines which memories are processed during sleep? .......... 130
6.1.5 What determines how memories are processed during sleep? .......... 131
6.1.6 Underlying mechanisms of memory reorganisation during sleep .......... 133
6.1.7 Function of sleep versus wakefulness ........................ 135
6.2 Sleep and the integration of new information with semantic memory ....... 136
6.2.1 Summary of findings (Chapters 4 & 5) ..................... 136
6.2.2 Schema benefit on memory ................................ 137
6.2.3 Association between sleep and the schema benefit .................... 137
6.2.4 Schema-related differences during memory acquisition .................. 139
6.3 Future directions .......................................... 139
6.4 Conclusions ............................................... 140

Word count: 55,966
## List of Figures

1.1 Models of conceptualisation ............................................. 17  
1.2 Standard model for systems memory consolidation ...................... 24  
1.3 Schema assimilation model ............................................... 28  
1.4 Sleep physiology .......................................................... 30  
1.5 Active systems consolidation model .................................... 35  
2.1 Category structure and CMCL-task trial structure ...................... 50  
2.2 Schematic illustration of the experimental procedures .................. 53  
2.3 Reaction time results for Experiment A and Experiment B ......... 54  
3.1 Generation of structured and unstructured sequences .................. 65  
3.2 Experimental design ..................................................... 67  
3.3 Behavioural results ....................................................... 71  
3.4 Relationship between SWS and behavioural performance ............. 73  
4.1 Experimental design ..................................................... 82  
4.2 Behavioural results ....................................................... 83  
4.3 Overnight change in hippocampal activity ............................. 84  
4.4 Spindle-modulated hippocampal activity for the interaction ....... 86  
4.5 SM: Illustration of the schema structure ................................ 95  
4.6 SM: Spindle-related hippocampal activity ............................ 105  
5.1 Schema structure .......................................................... 113  
5.2 Experimental design ..................................................... 114  
5.3 Encoding and recall trials ............................................... 117  
5.4 Response accuracy ........................................................ 121  
5.5 Reaction time results ..................................................... 122  
5.6 Spindle density predicts the overnight change in the schema effect . 123
# List of Tables

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Parameters for the stimulus generation</td>
</tr>
<tr>
<td>2.2</td>
<td>Results of the explicit memory tasks of Experiment A</td>
</tr>
<tr>
<td>2.3</td>
<td>Results of the explicit memory tasks of Experiment B</td>
</tr>
<tr>
<td>3.1</td>
<td>Polysomnography results</td>
</tr>
<tr>
<td>3.2</td>
<td>Power spectral density during slow wave sleep</td>
</tr>
<tr>
<td>3.3</td>
<td>Overall sleep quality</td>
</tr>
<tr>
<td>3.4</td>
<td>Sleep quality of slow wave sleep</td>
</tr>
<tr>
<td>4.1</td>
<td>SM: Examples of schema-related facts</td>
</tr>
<tr>
<td>4.2</td>
<td>SM: Schema-learning procedure</td>
</tr>
<tr>
<td>4.3</td>
<td>SM: Polysomnography results</td>
</tr>
<tr>
<td>4.4</td>
<td>SM: Activation clusters for the contrast recent &gt; remote</td>
</tr>
<tr>
<td>4.5</td>
<td>SM: Activation clusters for the interaction contrast</td>
</tr>
<tr>
<td>4.6</td>
<td>SM: Activation clusters for the interaction contrast modulated by spindle density</td>
</tr>
<tr>
<td>4.7</td>
<td>SM: Activation cluster for the overnight change of schema-related facts, modulated by spindle density</td>
</tr>
<tr>
<td>4.8</td>
<td>SM: Polysomnography results of the control group</td>
</tr>
<tr>
<td>4.9</td>
<td>SM: Activation clusters for the interaction contrast modulated by the SWS spindle density</td>
</tr>
<tr>
<td>5.1</td>
<td>Examples of schema-related facts</td>
</tr>
<tr>
<td>5.2</td>
<td>Procedure and tasks involved in the schema-learning</td>
</tr>
<tr>
<td>5.3</td>
<td>Polysomnography results</td>
</tr>
</tbody>
</table>
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>BBSRC</td>
<td>Biological Sciences Research Council</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
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<td>KSS</td>
<td>Karolinska Sleepiness Scale</td>
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<tr>
<td>M</td>
<td>Mean</td>
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<tr>
<td>MNI</td>
<td>Montreal Neurological Institute</td>
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<tr>
<td>mPFC</td>
<td>Medial prefrontal cortex</td>
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<td>MTL</td>
<td>Medial temporal lobe</td>
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<tr>
<td>nonREM</td>
<td>non-rapid eye movement</td>
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<tr>
<td>PSG</td>
<td>Polysomnography</td>
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<td>REM</td>
<td>Rapid eye movement</td>
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<td>RT</td>
<td>Reaction time</td>
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<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SE</td>
<td>Standard error</td>
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<tr>
<td>SHY</td>
<td>Synaptic homeostasis hypothesis</td>
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<td>SM</td>
<td>Supplemental material</td>
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<td>SWA</td>
<td>Slow wave activity</td>
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<td>SWR</td>
<td>Sharp wave ripples</td>
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<td>SWS</td>
<td>Slow wave sleep</td>
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<td>TC</td>
<td>Thalamo-cortical</td>
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<td>TE</td>
<td>Time echo</td>
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<tr>
<td>TR</td>
<td>Time repetition</td>
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<tr>
<td>TRN</td>
<td>Thalamic reticular nucleus</td>
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</table>
Abstract

The role of sleep in the formation of semantic memory

Nora Hennies, The University of Manchester

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Semantic memory represents our general knowledge about the world. The formation of semantic representations requires three key computational challenges: i) integrating information in a time- and modality-invariant fashion, ii) abstracting statistical regularities, and iii) assimilating new information into existing semantic networks. All three processes have been suggested to benefit from sleep-dependent memory consolidation. During sleep, memories are repeatedly reactivated, which is assumed to cause a reorganisation, such that memories are integrated into long-term memory and qualitatively altered to become decontextualised, schema-like representations. Although memory processing during sleep and the mechanisms involved in the formation of semantic memory are obviously related, this relationship has hardly been considered in research so far. The work described in this thesis utilised polysomnography (PSG), behavioural memory testing, and functional magnetic resonance imaging (fMRI) to investigate sleep-related memory reorganisation with regard to the three computational processes that are thought to be involved in the formation of semantic memory.

In Chapter 2 we assessed whether time- and sleep-dependent consolidation facilitates cross-modal category learning. We found that offline consolidation had a beneficial effect on category learning, but surprisingly this benefit was specific to consolidation across wake, but not sleep. These results suggest that the integration of information from different sensory modalities may preferentially occur during wakefulness. Together with other findings in the literature our results emphasise the question of what determines whether memories are processed during sleep. In Chapter 3 we explored whether the beneficial effect of sleep on the extraction of statistical regularities could be enhanced by cued memory reactivation. Interestingly, our manipulation interfered with the abstraction of the underlying pattern. These findings raise important questions about the underlying mechanisms of statistical abstraction during sleep. Lastly, Chapters 4 and 5 addressed whether sleep plays a role in the assimilation of newly learned information into pre-existing semantic networks. In Chapter 4 sleep-dependent differences in the consolidation of information that either related to prior knowledge or was completely unrelated were investigated. Our findings suggest that sleep spindle density marks the process of assimilating new information into long-term memory, reflected in enhanced memory retention and decreased hippocampal engagement. In Chapter 5 we replicated the association between sleep spindle density and the development of the schema effect across time and showed that a weak link to pre-existing knowledge was sufficient in triggering the schema benefit.

In conclusion, our results provide new insights to the role of sleep in memory reorganisation. We have provided evidence that cued reactivation during sleep can influence the extraction of statistical regularities and that sleep spindles are associated with the assimilation of new information into semantic networks.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Chapter 1

General Introduction:
Semantic Memory, Sleep and Consolidation

1.1 Overview

This thesis investigates the role of sleep in the formation of semantic memory and addresses some of the unanswered questions surrounding memory reorganisation during sleep. Anecdotal reports on scientific discoveries suggest that sleep actively promotes alterations to memories. For example, Dimitri Mendelejew saw in his sleep how chemical elements fell into place to form the period system; the discovery of the circular structure of benzene owe we to dancing molecules in a dream of August Kekule, and also Otto Loewi reported that the idea for his key experiment on neurotransmission came to him in his sleep. Research over the last three decades has led to considerable advances in our understanding of how sleep contributes to a mental restructuring that can lead to insights or the emergence of regularities as described in these famous cases. Memory reorganisation during sleep is thought to result from repeated memory reactivation, which gradually induces a shift in the brain circuits that support memory from the hippocampus to the neocortex (Rasch & Born, 2013). This change in the underlying neural substrates seems to be tied to a transformation in the memory quality from detail-rich, context-bound memories to more abstract and generalisable representations (McClelland et al., 1995; Inostroza & Born, 2013). Specifically, sleep has been shown to facilitate a range of different processes, including the integration of distinct elements into unified concepts, the extraction of statistical regularities, and the assimilation of new information into existing knowledge networks (Stickgold & Walker, 2013). Importantly, research on semantic memory suggests that these processes that seem to be facilitated by sleep play a crucial role in the formation of semantic representations (Lambon Ralph et al., 2010; Rogers et al., 2004). Semantic memory represents our general knowledge about the world, extracted from regularities and repeated occurrences in our experience. Current research suggests that there are various routes towards creating semantic memory. However, they all seem to rely on
the same key computational challenges, which include the extraction of regularities, and the integration of information in a time- and modality-invariant fashion (Lambon Ralph et al., 2010; Rogers & McClelland, 2004). Although memory processing during sleep and the mechanisms involved in the formation of semantic memory are obviously related, this relationship has hardly been considered in research so far. The goal of this thesis was to investigate memory reorganisation during sleep with a focus on the processes that are thought to be involved in the formation of semantic memory.

This thesis has been submitted in the alternative thesis format. As such Chapters 2 to 5 were prepared for submission to scientific journals and are at various stages of publication. The author was the primary investigator for all work presented in this thesis. Contributions from co-authors included supervisor guidance, sleep scoring (where scoring by two experimenters was a requirement), assistance with data collection (Chapter 4) and paradigm development (Chapter 2). All Chapters address different aspects of memory reorganisation during sleep. Chapters 2 and 3 investigate the impact of sleep on basic computational mechanisms, including the integration of information from different sensory modalities and the extraction of regularities, that are thought to play a role in the formation of abstract semantic representations. The role of sleep in the integration of newly learned information into existing semantic networks is investigated in Chapters 4 and 5. Chapter 6 provides a general discussion of the results and attempts to integrate our findings within current theoretical models of sleep-dependent memory consolidation. This chapter continues with an introduction to the background literature, divided into four themes: semantic memory, memory consolidation, sleep physiology, and memory processing during sleep. The introduction aims to give a brief overview of each theme with a focus on the relationship between sleep-dependent memory reorganisation and the formation of semantic memory. It starts with a brief introduction to semantic memory, which covers the organisation of well-established knowledge and the formation of new semantic representations. It then moves on to describe the concept of memory consolidation and how this relates to the formation of semantic memory. In section three sleep physiology is summarised with a focus on the components that seem to be involved in memory processing. In section four the role of sleep in systems memory consolidation is described. Here, ideas from the research on semantic memory, consolidation and sleep are related and an influential theoretical framework, the Active Systems Consolidation model (ASC), that proposes a mechanism, by which sleep may facilitate memory reorganisation, is introduced. Lastly, the aims of the thesis are stated and it is outlined how these aims are addressed in the Chapters 2 to 5.

1.2 Semantic memory

Semantic memory (also sometimes referred to as 'conceptual knowledge') as an individual memory type goes back to Tulving, who introduced the distinction of declarative memory between episodic and semantic (Tulving, 1972). Semantic memory refers to general knowledge about facts, objects, people and relations, which enables us to bring meaning to the
1.2.1 Semantic memory representations: The hub-and-spoke model

More than 100 years ago, Wernicke and Meynert proposed that conceptual representations result from the conjoint activation of cortical areas that store modality-specific representations (engrams) of sensory, motor, and verbal information (see Eggert 1977). This view that semantic memory is formed through a dense network of direct interconnections between modality-specific regions, sometimes referred to as distributed-only models (Patterson et al., 2007), prevailed for many years and still forms the basis of contemporary theories (Martin, 2007; Patterson et al., 2007). Evidence that the organisation of semantic memory is based on sensory and motor association regions comes from neuroimaging studies, which showed that these areas are activated when participants access conceptual knowledge (Chao et al., 1999; Goldberg et al., 2006; Hauk et al., 2004; Martin, 2007; Pulvermüller, 2005). The distributed-only view, however, was challenged by the neurodegenerative condition known as semantic dementia in which semantic memory is selectively impaired and atrophy is centred on the anterior temporal region. Semantic dementia is the temporal lobe variant of frontotemporal dementia, characterised by a modality-independent breakdown of conceptual knowledge across all verbal and non-verbal domains including visual, auditory and tactile perception as well as taste and olfaction (Bozeat et al., 2000; Hodges et al., 1992; Lambon Ralph et al., 1999, 2001; Luzzi et al., 2007; Piwnica-Worms et al., 2010; Warrington, 1975). While damage to modality-specific stores causes selective impairment of the related sensory information (Gainotti et al., 1995), global semantic impairment as observed in semantic dementia (Hodges et al., 1992; Nestor et al., 2006; Desgranges et al., 2007) cannot be explained by the distributed-only model without positing damage throughout the entire brain (Patterson et al., 2007; Lambon Ralph & Patterson, 2008). An influential alternative to the distributed-only view is the so-called 'hub-and-spoke' model (see Figure 1.1), which was inspired by studies of semantic dementia patients (Lambon Ralph et al., 2010; Patterson et al., 2007; Rogers et al., 2004). The hub-and-spoke (or distributed-plus-hub) model forms an extension to the distributed-only view by proposing the existence of a transmodal hub, which draws together our sensory, motor and verbal experience (Lambon Ralph et al., 2010; Lambon Ralph, 2014; McClelland & Rogers, 2003; Patterson et al., 2007; Rogers et al., 2004; Rogers & McClelland, 2004). The spokes represent the information that arises in modality-specific association cortices and interact via the hub. Semantic memory is characterised by the critical function of relating concepts into meaningful groups, which allow semantic computations and generalisation beyond that solely based on surface similarity alone (Lambon Ralph et al., 2010; Murphy & Medin, 1985; McClelland & Rogers, 2003; Rogers et al., 2004). Here is an example. While an orange and a ball share visual features but are conceptually not related, an orange and a pineapple are visually very different but fall into the same concept `<fruit>`, which allows us to generalise our knowledge about fruits in general to the orange and pineapple but not over-extend this knowledge to the ball and other
superficially-similar items. While direct connections between modality-specific areas are considered insufficient to explain such higher-order generalisation (Rogers & McClelland, 2004), the hub-and-spoke model offers a mechanism by which multi-modal experience can be brought together to form 'coherent' and generalizable representations (Lambon Ralph et al., 2010; Patterson et al., 2007). The semantic hub is thought to carry out a range of computational challenges to fulfil this function (Rogers et al., 2004; Lambon Ralph et al., 2010; Lambon Ralph, 2014), which are summarised below:

1. **Integration of information across different modalities and experiences**
   Semantic representations are comprised of information that arises across different experiences, involving different sensory modalities. The hub is thought to draw this information together in a time- and modality-invariant fashion, allowing the flexible use of conceptual knowledge.

2. **Encoding the deep statistical structure of conceptual relationships**
   Often we encounter new exemplars of an object that can vary across all possible dimensions, such as the different cars we see on our way to work. Even though we have not experienced these specific exemplars before, we automatically generalise our knowledge, which allows us to easily identify new exemplars as members of a specific category. To allow for this function semantic representations need to capture statistical regularities and variation across different exemplars and experiences. The hub is assumed to encode the deep statistical structure of concepts.

3. **Enabling higher-order generalisation**
   The statistical structure of concepts goes beyond surface similarities and also represents complex sets of non-linear and conceptual relationships between objects that do not necessarily have similar specific attributes. The hub has been shown to be crucial to allow for such higher order generalisation (Lambon Ralph et al., 2010).

That a transmodal hub, which performs these computational challenges, can account for a range of semantic tasks was demonstrated in a computational model by McClelland and Rogers who used a parallel distributed processing approach for the implementation of the hub-and-spoke theory (McClelland & Rogers, 2003; Rogers et al., 2004; Rogers & McClelland, 2004). The aim of this study was to investigate how modality-specific information can be combined to form coherent semantic representations. Their model demonstrated that modality-specific brain regions are necessary but not sufficient to perform cross-modal mappings and generalisation via statistical learning mechanisms. An additional layer of representational units (the hub), which allowed the encoding of conceptual relationships, was necessary to simulate core features of semantic memory. Importantly, increasingly severe simulated lesions to this layer also provided a good match to the semantic impairment that is observed in patients with semantic dementia (Rogers et al., 2004; Rogers & McClelland, 2004).

Based on studies with semantic dementia patients, the hub-and-spoke model further proposes that the hub is located within the anterior temporal lobe (ATL). The specific breakdown of conceptual knowledge in semantic dementia is accompanied by atrophy (Brambati
Chapter 1. General introduction

Figure 1.1: Models of conceptualisation: the Wernicke-Meynert model and the Hub-and-spoke model. In the traditional view, first proposed by Wernicke and Meynert, conceptualisation arises through a conjoint activation of cortical areas that store modality-specific representations of sensory, motor, and verbal information. The hub-and-spoke model extends this traditional account by incorporating a transmodal hub, which draws together sensory, motor and verbal experiences and thereby allows for higher order generalisation. Figure adapted from Lambon Ralph et al. (2010).

et al., 2009; Hodges et al., 1992; Mion et al., 2010; Mummery et al., 2000, 1999) and hypometabolism (Nestor et al., 2006; Desgranges et al., 2007) in the ATL, bilaterally. A positive correlation between the degree of damage and the severity of the semantic impairment has been shown, suggesting that conceptual knowledge is localised in these regions (Mummery et al., 2000; Nestor et al., 2006). The ATL also provides the necessary neuroanatomical connectivity to function as a hub, as it is highly interconnected with many primary sensory, primary motor and association cortices (Gainotti et al., 1995; Gloor, 1997; Grey & Bannister, 1995). Its proximity to the medial temporal lobe (MTL), the limbic system and orbitofrontal cortex, regions associated with episodic memory and reward, might provide an ideal location for its integrative function (Patterson et al., 2007). Further evidence for the hub-and-spoke model and the ATL as a transmodal convergence zone comes from neuroimaging studies in healthy individuals. In addition to activation in modality-specific association cortices, these neuroimaging investigations have reported activation of the ATL during semantic tasks across all sensory domains (Patterson et al., 2007; Visser...
et al., 2010). While functional magnetic resonance imaging (fMRI) studies rarely show activation in the ATL during semantic processing, due to a variety of technical issues including a very low signal-to-noise ratio in this region (Binder et al., 2005; Devlin et al., 2000; Tsukiura et al., 2006; Visser et al., 2010), positron emission tomography (PET) and magnetoencephalography (MEG) studies as well as fMRI studies using distortion correction methods (Binney et al., 2010), revealed more consistent results (Binney et al., 2012, 2010; Devlin et al., 2000; Marinkovic et al., 2003; Mummery et al., 1996; Rogers et al., 2006; Visser et al., 2010, 2012). Other support for the hub-and-spoke model comes from neurostimulation. Recent studies using repetitive transcranial magnetic stimulation of the left and right ATL showed that reaction times were selectively slowed for semantic judgements, abstract word comprehension, picture naming and matching non-verbal stimuli (Lambon Ralph et al., 2009; Pobric et al., 2007, 2009, 2010), further suggesting that the ATL plays a causal role in semantic cognition. Overall, there is substantial evidence for the hub-and-spoke model and that semantic representations emerge as a product of statistical learning mechanisms in a cortical region that is suited to performing cross-modal mappings.

1.2.2 Formation of new conceptual knowledge

Concepts are defined as the knowledge or the mental representation about a category (Barsalou et al., 2003; Grossman et al., 2002; Medin & Rips, 2005). What happens when this knowledge breaks down becomes drastically clear in patients with semantic dementia, who suffer from a gradual dissolving of categories boundaries, resulting in over- and under-generalisation (Lambon Ralph et al., 2007, 2010; Patterson & Hodges, 2000). This means, semantic dementia patients are more likely to classify atypical items (low perceptual similarity) as non-members of a category (under-generalisation) while perceptual similar, however conceptually different items are ranked as category members (over-generalisation) (Lambon Ralph & Patterson, 2008; Mayberry et al., 2010; Patterson & Hodges, 2000).

The previous section has introduced the nature of established conceptual knowledge and the hub-and-spoke model as one potential framework for coding this type of knowledge. The following section considers the mechanisms behind the formation of new concepts and category representations.

1.2.2.1 Category learning systems

Semantic memory is thought to arise from regularities and repetitions in our experience. How our brain detects similarity and learns to assign new stimuli into meaningful groups has been extensively studied in category learning experiments. While early category-learning theories proposed a single category-learning system for humans (Ashby et al., 1998; Smith et al., 1998), the majority of contemporary theories assume that there are multiple, qualitatively distinct neural systems that support category learning (Ashby et al., 1998; Erickson & Kruschke, 1998; Johansen & Palmeri, 2002; Milton et al., 2009; Nomura et al., 2007; Smith & Grossman, 2008). They can be broadly divided into two main systems: a verbalisable, rule-based system and a non-verbalisable, complex system (Ashby
et al., 1998; Knowlton & Squire, 1993; Nosofsky & Johansen, 2000). The idea of a rule-based categorisation system is supported by numerous studies demonstrating the use of simple rules in classification and sorting tasks (Ashby & Spiering, 2004; Ashby & Maddox, 2005). In this system categorisation is carried out on the basis of a single dimension and underlies explicit reasoning (Ashby et al., 1998; Lassaline & Murphy, 1996; Medin et al., 1987). But humans are also able to deal with much more complex, non-verbalisable category structures, which require the integration of multiple dimensions (Ashby & Waldron, 1999; Reber, 1967). There is, however, strong disagreement in the literature about the nature of the implicit system and several theories exist. Two main hypotheses can be distinguished: i) decision-function (procedural) models and ii) similarity based-models (Ashby & Waldron, 1999). The decision-function theory proposes a division of the stimulus space into particular response regions and is based on the assumption that stimulus dimensions are definite. Each stimulus dimension represents an axis in a coordinate system and the category samples are specified by their coordinates in the multidimensional space. The response regions are separated by so called decision bounds, which can be linear or non-linear. Categorisation of unfamiliar items occurs by applying the decision bound or by determining in which response region the particular items falls. Decision function models have been shown to explain a broad range of natural categorisation phenomena (Ashby & Gott, 1988; Ashby & Maddox, 2005; Maddox & Ashby, 2004). An alternative or addition to the decision bound theory is constituted by similarity-based models, such as family resemblance or prototype models. Accordingly to this view, categories are formed by grouping multi-dimensional stimuli according to their overall similarity. Category members share several properties, but no single dimension is sufficient for classification (Rosch & Mervis, 1975; Smith et al., 1998). The prototype theory further assumes that the overall category similarity is represented in a prototype and unfamiliar stimuli are categorised by their overall similarity to this prototype (Ashby & Maddox, 2005; Medin & Rips, 2005; Palmeri & Flanery, 1999; Posner & Keele, 1968; Reed, 1972; Smith, 2001; Smith & Minda, 2002; Tunney & Fernie, 2012). A third group of theories propose that categorisation is based on episodic memories of individual exemplars and might therefore be at least partially explicit (Smith et al., 1998; Tunney & Fernie, 2012). Exemplar-based models also referred to as episodic models (Tunney & Fernie, 2012) assume that category knowledge is composed of a set of previously encountered category exemplars. When an unfamiliar stimulus is presented, activation of experience specific episodic memory traces enables categorisation due to individual comparisons. Due to its strong dependence on the episodic memory system, the exemplar-based model contradicts the category learning ability of medial temporal lobe damaged patients (Knowlton & Squire, 1993; Smith & Grossman, 2008; Squire & Knowlton, 1995) and therefore cannot exclusively explain complex category learning. But it still accounts for several problems in category learning and could successfully be applied to many findings of classification tasks (Erickson & Kruschke, 1998; Hintzman, 1986; Nosofsky, 1986; Nosofsky & Johansen, 2000; Tunney & Fernie, 2012).

Evidence for the existence of distinct categorisation system comes from behavioural, neuroimaging and patient studies. Several behavioural studies showed dissociation in the
classification of particular items according to a rule-based and a similarity-based system, depending on the instruction given before the classification task (Allen & Brooks, 1991; Koenig et al., 2005; Waldron & Ashby, 2001). Imaging results of category learning studies using fMRI and PET revealed distinct activation patterns for implicit and explicit categorisation. Rule-based categorisation, which requires working memory functions such as attention, temporary storage of a rule as well as hypothesis testing, is predominantly associated with increased activation in the (pre-) frontal cortex (Grossman et al., 2002; Koenig et al., 2005; Rao et al., 1997; Smith et al., 1998; Seger & Cincotta, 2002), the hippocampus (Nomura et al., 2007) and the striatum (Rao et al., 1997; Seger & Cincotta, 2002). Complex, non-verbalisable categorisation may operate completely implicitly and, in specific tasks, categorisation might even occur in an automated, procedural way (Ashby et al., 2003; Maddox & Ashby, 2004; Smith, 2008). Implicit or probabilistic categorisation, which is promoted by incidental learning conditions or the presentation of many exemplars in a short time frame, has been associated with activation in the striatum, which is known to play a key role in procedural memory (Aizenstein et al., 2000; Cincotta & Seger, 2007; Foerde et al., 2006; Nomura et al., 2007; Seger & Cincotta, 2002; Seger et al., 2010). Complex categorisation that involves only few exemplars has been shown to depend on the MTL (Nosofsky, 1989). Further evidence for distinct categorisation systems comes from patient studies. Patients with Alzheimer’s disease or frontotemporal dementia show a selective impairment for rule-based categorisation, while more complex, implicit categorisation seems to be relatively preserved (Ashby & Spiering, 2004; Grossman et al., 2003; Koenig et al., 2008). Medial temporal lobe amnesic patients perform as well as healthy controls in rule-based and implicit categorisation tasks (Filoteo et al., 2001; Janowsky et al., 1989; Knowlton & Squire, 1993) but all three patient groups show some impairment in complex, explicit categorisation (Ashby & Spiering, 2004; Grossman et al., 2003; Koenig et al., 2008). Another group of patients, who are characterised by a dysfunction specific to the basal ganglia, such as Parkinson’s or Huntington’s disease patients as well as patients with cortico-basal degeneration, show a strong impairment in implicit and rule-based categorisation (Ashby et al., 2003; Filoteo et al., 2001; Maddox & Filoteo, 2001), while categorisation tasks based on overall similarity seem to be preserved (Ashby & Spiering, 2004; Reber & Squire, 1999). All these results support the existence of separate category learning systems: i) a rule-based system, predominantly mediated by frontal-striatal circuits, ii) a complex category learning system based on multidimensional information-integration, which is supported by an implicit system, mediated by the striatum and iii) a complex, explicit system, which mainly relies on the MTL. Although different hypotheses about the relationship between the proposed memory systems exist, one general theme is that the categorisation systems (rule-based and complex) compete for the production of the response. Depending on the task one memory system might be favoured, but there also seems to be an interactive effect, which in some cases promotes or inhibits correct categorisation (Allen & Brooks, 1991; Ashby et al., 1998; Couchman et al., 2010; Erickson & Kruschke, 1998; Koenig et al., 2008).
1.2.2.2 Semanticisation

Though there may be various routes towards creating semantic representations as described above, one seems to involve episodic memory and a process referred to as semanticisation (Battaglia et al., 2011; Cermak, 1984; McClelland et al., 1995; Moscovitch et al., 2005; Meeter & Murre, 2004; Rosenbaum et al., 2001; Stickgold, 2009; Sweegers & Talamini, 2014; Westmacott et al., 2004). In this view semantic memory can arise from the gradual extraction of statistical regularities across different exemplars and experiences that are stored in episodic memory (McClelland & Rumelhart, 1985; McClelland et al., 1995). Here is an example. Assuming we see an object like a car for the first time in our life, we will form an episodic memory of this experience. In another situation we might encounter a different car, which shares certain features with the first car we saw (e.g. it has 4 wheels) but also differs in some attributes (e.g. colour). We will also store this experience in an episodic memory. Semanticisation describes a process in which overlapping features of these two episodic memories are gradually extracted to form a semantic representation of a car. Evidence for semanticisation comes primarily from computational modelling (Battaglia et al., 2011; McClelland et al., 1995), while experimental support is still relatively sparse. Some evidence was provided by developmental and learning research (Conway et al., 1997; Conway, 2009; Nelson, 1974). In line with the idea that the acquisition of conceptual knowledge can rely on a gradual abstraction from episodic memory, Nelson et al. (1974) reported that the learning of novel words in infants is associated with particular events (Nelson, 1974). This means each word is initially bound to an episodic memory before it becomes related to a concept and takes on a meaning that is independent of a specific context. Other support comes from Conway et al. (1997) who demonstrated that the performance of students in a test immediately after a lecture depended on remember responses while the performance after a retention interval, during which additional learning took place, mainly depended on knowledge responses (Conway et al., 1997). This remember-to-knowledge shift, which seems to reflect a shift from the reliance of episodic to semantic memory, was explained by a loss of specific episodic information and increased availability of semantic knowledge. Similar findings were reported by Dewhurst et al. (2009). The theory of semanticisation is apparent in several consolidation theories, which are discussed in the following section of this introduction.

In summary, this section gave a brief overview of how well-established semantic memory is represented in the brain, focused on the hub and spoke model, and concerned the question of how new semantic representations are formed. For well-established semantic memory the hub is thought to code the higher-order statistical structure and allows the formation of modality-invariant multi-dimensional representations. How our brain forms similarity structures of new concepts and learns to relate exemplars of new concepts into meaningful groups has been studied in category learning experiments in great detail. Multiple category learning systems have been identified that are thought to capture different similarity structures. How the representation of well-established concepts relates to the mechanisms involved in formation of new concepts remains largely unknown. One important component in the formation of real-world concepts, which has been largely ignored in
category learning studies so far, is the underlying time frame. While semantic memory is thought to form gradually over time for example through the semanticisation of episodic memory, the vast majority of category learning experiments exclusively focused on online training. In Chapter 2 we address this issue and explore the impact of offline consolidation on cross-modal category learning. The relationship between memory consolidation and the formation of semantic memory is covered in the next section.

1.3 Memory consolidation

In this section the standard model for systems memory consolidation is introduced. During systems consolidation hippocampal-dependent memories are gradually reorganised and integrated into the long-term memory store, the neocortex. This process is assumed to be tied to the semanticisation of memories and seems to provide a main route towards the formation of semantic memory.

Changes in synaptic connections underlie the formation of individual memory traces (Hebb, 1949). Memory traces can be very short-living and fragile or they can turn into a long-term and stable form. This process of memory stabilisation, which occurs post-encoding and makes initially labile memories resistant to disruption and interference, is known as memory consolidation (Dudai, 2004; Frankland & Bontempi, 2005). Two types of memory consolidation are usually distinguished: cellular (or synaptic) consolidation and systems consolidation (Dudai, 2004). Cellular consolidation refers to the stabilisation of changes in synaptic efficiency via long-term potentiation (LTP) and long-term depression (LTD, Frankland & Bontempi, 2005). This process requires protein synthesis and involves for example the modulation of pre-synaptic transmitter release and changes in the density of post-synaptic receptors (Abel & Lattal, 2001; Alberini et al., 2008; Davis & Squire, 1984; Dudai, 2004; Lynch et al., 2004; Takeuchi et al., 2014). Cellular consolidation is accomplished within hours after training (Dudai, 2004). However, memories are not fully processed after this initial phase of cellular stabilisation, but they can be subject to rearrangements on the level of brain networks, known as systems memory consolidation.

1.3.1 Standard model for systems memory consolidation

Systems memory consolidation refers to a gradual reorganisation of the brain circuits that support memory (Dudai, 2004; Frankland & Bontempi, 2005). While memory acquisition usually relies on hippocampal integrity (Squire & Zola-Morgan, 1991; Holdstock et al., 2002; Manns et al., 2003), over time memories can become independent of the hippocampus (Squire & Alvarez, 1995). This hypothesis of a time-dependent shift in the neural substrates that support memory has its origin in the observation that lesions in the medial temporal lobe (MTL) cause a temporally graded retrograde amnesia (Ribot, 1882; Scoville & Milner, 1957). The most prominent case is the one of patient H.M, reported by Scoville and Milner in 1957. After surgical bilateral removal of large parts of the medial temporal lobe H.M.’s retrieval of remote memories was intact while his retrieval of recent memories, which were encoded shortly before the lesion occurred, was impaired (Scoville
& Milner, 1957). This pattern of an increase in severity with a decrease in the remoteness of the memory has been observed in a range of hippocampal lesion studies (Bayley et al., 2006; Kapur & Brooks, 1999; Kirwan et al., 2008; Manns et al., 2003; Rempel-Clower et al., 1996; Squire & Alvarez, 1995; Squire et al., 2010; Zola-Morgan et al., 1986) and forms the basis for the standard model for systems memory consolidation (Marr, 1970; Squire & Alvarez, 1995; Frankland & Bontempi, 2005). McClelland and colleagues implemented this model in 1995 and it is known since then as the Complementary Learning Systems theory (CLS) (McClelland et al., 1995), which is still widely accepted (Diekelmann & Born, 2010; Dudai, 2004, 2012; Frankland & Bontempi, 2005; McClelland, 2013; O’Reilly & Rudy, 2000; Squire & Bayley, 2007; Squire & Wixted, 2011; Tayler & Wiltgen, 2013; Takeuchi et al., 2014; van Kesteren et al., 2012). The CLS posits a two-stage model of memory consolidation, which consists of a fast-learning memory store, the hippocampus, and a slow-learning memory store, the neocortex. During memory acquisition information is thought to be encoded in parallel in both memory stores. The hippocampus is assumed to bind together relevant neocortical regions that store representations of different event features (see Figure 1.2). With time a gradual re-distribution of the memory traces seems to occur. The CLS proposes that through repeated reactivation of this hippocampal-neocortical network cortical-cortical connections are strengthening and memories become integrated into distributed neocortical networks. While the hippocampus seems to have a time-limited function in memory storage and retrieval, the neocortex is thought to represent the long-term memory store. Crucial to the model are the complementary functions that are fulfilled by these two memories systems. In the hippocampus representations are thought to be linked to individual experiences. This separation prevents interference when new memories are acquired and allows very rapid encoding. The neocortex on the other side is thought to store context-independent, structured (semantic) memory representations, which are assumed to be acquired through the extraction of general statistical patterns across different experiences. These complementary systems provide a mechanism to balance plasticity and stability, which allows the storage of new memories without interfering with existing memories (McClelland et al., 1995). Supporting evidence for the two-stage consolidation model comes from a broad range of human neuroimaging and animal studies. The time-limited role of the hippocampus for memory function has for example been demonstrated in studies with rodents, which showed that inactivation of the hippocampus impaired retrieval of recently, but not remotely (weeks or months earlier) encoded memory (Alvares et al., 2012; Anagnostaras et al., 1999; Clark et al., 2002; Kim & Fanselow, 1992; Ross & Eichenbaum, 2006; Takehara et al., 2003; Tse et al., 2007, 2011; Wiltgen et al., 2010). Support for the hypothesis that long-term memory is stored in the neocortex comes from studies which showed that long-term memory was impaired after neocortical inactivation (Maviel et al., 2004; Takehara et al., 2003; Tse et al., 2011; Wang et al., 2013). Increased expression of immediate early genes after consolidation in relevant neocortical regions (Ross & Eichenbaum, 2006; Tayler et al., 2013) and the observation that neocortical plasticity is required for memory consolidation (Lesburguères et al., 2011; Takehara-Nishiuchi et al., 2006; Vetere et al., 2011) also support the CLS. The complementary roles of the hippocampus and the neocortex for recent and remote...
memory were nicely demonstrated by Takashima et al. (2006) who mapped using fMRI in humans memory-related brain activation in the hippocampus and PFC over the course of three months. In line with CLS the results showed decreasing hippocampal and increasing neocortical engagement over time.

While the standard model for systems memory consolidation only refers to declarative memory, non-declarative memories can also show a time-dependent reorganisation at a systems level, which often involves a reorganisation from the hippocampal to the striatal memory system (Jenkins JG, 1924; Karni et al., 1994; Maquet et al., 2003; Pennartz et al., 2004; Robertson et al., 2004; Shadmehr & Holcomb, 1997; Stickgold et al., 2000b; Walker et al., 2003b).

![Figure 1.2: Standard model for systems memory consolidation. This model assumes two distinct memory stores, a fast-learning temporary memory store, the hippocampus, and a slow-learning long-term store the neocortex. Initial information encoding occurs parallel in both stores. The hippocampus is assumed to link together modality-specific neocortical representations to a uniform memory trace. With consolidation a gradual reorganisation and strengthening of cortico-cortical connections occurs, eventually resulting in hippocampal independent representations. Figure adapted from Frankland & Bontempi (2005).](image)

### 1.3.2 Semanticisation as a product of memory reorganisation

Some dispute exists regarding the role of the hippocampus for remote memory. Nadel and Moscovitch introduced in 1997 the Multiple Trace Theory (MTT) as an alternative to standard consolidation models, which was extended in 2010 by Winocur et al. (2010) to the transformation theory. These models propose that the hippocampus is always required for rich contextual or spatial detail and that a second 'semantic' version of the original memory is created in the neocortex. Supporting evidence comes from studies, which show that the hippocampus is sometimes required in the retrieval of remote context memory (Clark et al., 2005; Goshen et al., 2011; Lehmann et al., 2007; Moscovitch et al., 2005; Piolino et al., 2004, 2009; Sutherland et al., 2010; Tayler & Wiltgen, 2013; Winocur et al., 2013; Wiltgen et al., 2010; Wiltgen & Tanaka, 2013). Even though CLS and MTT differ in terms of the proposed role for the hippocampus in remote memory, both models agree that
hippocampal-dependent and hippocampal-independent memories are qualitatively different. The neocortex is thought to store memories in a highly structured, decontextualised way, which allows flexible retrieval and the incorporation of new information. In contrast, the hippocampus seems to codes context-rich experience-dependent memory, indexed by time and space. This dichotomy parallels the contrast between episodic and semantic memory (Battaglia et al., 2011; McClelland et al., 1995; Nadel & Moscovitch, 1997; O’Reilly & Rudy, 2000; Tulving, 1972; Winocur et al., 2010). While episodic memory requires rapid encoding at the time the event occurs, and is characterised by very detailed, specific information content (O’Reilly & Rudy, 2000), semantic memory can generalise and requires the extraction of invariant repeating features from new memories (O’Reilly & Rudy, 2000; Rogers et al., 2004; Rogers & McClelland, 2004). The CLS implies a qualitative memory change from episodic to semantic with memory consolidation due to the different properties of hippocampus and neocortex (McClelland et al., 1995; Meeter & Murre, 2004).

The MTT and the transformation theory propose a more active semanticisation process in which with time and experience, a schematic version of the original episodic memory is created, which retains the gist but few of its contextual detail (Winocur et al., 2010). Both model propose that semantic memory is formed gradually in the neocortex from episodic memories via semanticisation. The observation that descriptions of autobiographical events by patients with amnesia or hippocampal lesions often appear less vivid and flexible but more like a story of general knowledge (Kinsbourne & Wood, 1975), supports this hypothesis (Cermak, 1984; Cermak et al., 1985). More recent evidence for the idea that semanticisation is tied to systems memory consolidation comes from hippocampal lesion studies in rodents, which showed that memories that became independent of the hippocampus lost context detail (Wiltgen et al., 2010; Winocur et al., 2009). Comparable findings in humans, which showed that decreasing hippocampal dependence was associated with the de-contextualisation of event memories, were provided by Talamini & Gorree (2012). Sweegers et al. (2014) reported that consolidation-related semanticisation can also involve the emergence of regularities and increased generalisability of information.

In summary, systems memory consolidation describes a process in which initially labile, hippocampal-dependent memories are gradually integrated into the long-term memory store, which is represented in distributed neocortical networks. Systems memory consolidation is thought to be tied to a process of semanticisation, in which time- and modality-invariant abstract semantic representations are gradually extracted from context-bound episodic memory. Overall, these findings suggest that one route towards creating semantic memories involves offline memory consolidation. While the CLS proposed that memory consolidation is a slow and gradual process, recent research suggests that memory consolidation and the assimilation of new information into semantic networks can be accelerated when the information fits well into existing knowledge structures or so called ‘schemas’. In the following sections schema theory is introduced and evidence for the schema assimilation model is summarised.
1.3.3 Schema theory

Schema theorists assume that our general knowledge is represented in higher order structures such as schemas (Bartlett, 1932; Brewer & Nakamura, 1984; Norman, 1972; Rumelhart, 1980; Spiro, 1977), frames (Barsalou, 1992; Minsky, 1974), scripts (Abelson, 1981; Schank & Abelson, 1975) or plans (Abelson, 1981), which allow us to rapidly comprehend and process stimuli in our environment and generalise our knowledge to new situations. While differing from one another in important ways concerning complexity, organisation and mechanisms all theories propose that unconscious mental structures and processes underlie the molar aspects of human knowledge and skill (Brewer & Nakamura, 1984; Ghosh & Gilboa, 2014). The term schema was introduced by Bartlett in the early 1930s and laid the foundation for later schema theory (Bartlett, 1932). While Bartlett only offered a very loose definition for schemas, as complex, interacting knowledge structures, a more detailed description was provided by Minsky (1975), who used the term frame for the same phenomenon. Minsky defined a schema (or frame) as data-structure with fixed structural relationships between attributes for representing stereotyped situations, like a restaurant. In this view, which has been adopted in many schema theories (see Brewer 1984) a schema is seen as a high-level conceptual structure or framework that organises prior experiences by abstracting out their important and stable components. A schema of a restaurant for example would include general information about different attributes that belong to a restaurant (e.g. menus, chefs, chairs, kitchen, waiters) and the relationships between these attributes (e.g. waiters bring menus, the chef is in the kitchen). Scripts and plans form specific classes of schemas that are much narrower defined. A script provides information about the sequence of events that happen in a particular context, such as a restaurant visit (Abelson, 1981; Schank & Abelson, 1975). Plans are responsible for the deliberate behaviour of a person and provide links between scripts and contextually appropriate actions. In other theories, however, schemas are more loosely defined structures of interrelated information that represent generic concepts (Rojahn & Pettigrew, 1992; Rumelhart & Ortony, 1976).

While there is little agreement about the structure and organisation of schemas, there is surprising consensus on its function. Schemas are often interpreted as key units of comprehension that guide our behaviour and interpretation (Bartlett, 1932; Ghosh & Gilboa, 2014; Minsky, 1974; Rumelhart & Ortony, 1976). Schemas are active knowledge structures that interact with incoming information at all stages of the mnemonic processing, namely, acquisition, consolidation and retrieval. Schemas affect the encoding of new information by guiding our attention (Brewer & Nakamura, 1984; Rojahn & Pettigrew, 1992; Rumelhart & Ortony, 1976; Shea et al., 2008) and facilitating inferential elaboration (Bransford & Johnson, 1972; Rumelhart, 1980). They guide the retrieval of information by influencing memory search and memory reconstruction (Anderson, 1984; Bartlett, 1932; Brewer & Nakamura, 1984; Rumelhart, 1980). But the most striking phenomenon of schemas is their beneficial effect on memory (also called the schema effect). A great variety of different experiments has demonstrated that information that relates to a pre-existing schema is remembered better than information that is unrelated or inconsistent (Brewer & Nakamura, 1984; Ghosh & Gilboa, 2014).
Chapter 1. General introduction

mura, 1984; Brod et al., 2013; Morris, 2006; Rumelhart & Ortony, 1976; van Kesteren et al., 2012). The first studies in this row demonstrated using stories and pictures that the recall of meaningful material was much better than the recall of meaningless material (Bartlett, 1932; Bransford & Johnson, 1972; Brent, 1969; Chiesi et al., 1979; Mandler & Johnson, 1977). Other studies showed that participants with certain backgrounds (e.g. baseball players) that related to new information (e.g. baseball stories) remembered that information better than participants without that background knowledge (Chase & Simon, 1973; Chiesi et al., 1979; Steffensen & Colker, 1982).

1.3.4 Schema assimilation model

Even though the idea that schemas serve as a scaffolding to preserve schema-related information has been around since many years (Bransford & Johnson, 1972; Brewer & Nakamura, 1984) only recently research has started to investigate the underlying mechanisms of the schema effect (McClelland, 2013; Tse et al., 2007, 2011; van Kesteren et al., 2010b,a, 2012, 2013b,a, 2014; Wang et al., 2013). Evidence from research in rodents, humans and computational modelling suggests that the degree to which new information links into pre-existing knowledge influences the rate of systems consolidation (McClelland, 2013; Tse et al., 2007; van Kesteren et al., 2013b). See Figure 1.3 for an illustration. In order to prevent interference with existing neocortical knowledge structures, memory consolidation has long been held to be a very slow and gradual process (McClelland et al., 1995; Nadel & Moscovitch, 1997). However, if the newly acquired information fits well into existing neocortical representations it can rapidly become assimilated (Morris, 2006; Tse et al., 2011; McClelland, 2013). Schemas appear to act as catalysts for memory consolidation by inducing a shift in processing between neocortex and hippocampus and in the interaction between these two systems (McClelland et al., 1995; van Kesteren et al., 2012). In a sequence of human fMRI studies, van Kesteren et al. (2010, 2013, 2014) demonstrated that during the encoding of new information, congruency to prior knowledge modulated the contribution of neocortex (especially the mPFC) and hippocampus. This schema-dependent shift in the contribution of neocortex and hippocampus during encoding is thought to initiate differences in the subsequent consolidation mechanisms, which in turn may underlie the beneficial effect of schemas on memory (van Kesteren et al., 2012, 2013a). Tse et al. (2007) demonstrated that memory consolidation was accelerated when the newly learned information could be integrated into a pre-existing schema. They trained rats over a couple of weeks to associate six flavour cues with locations in a complex spatial environment. After this schema was successfully learned a single trial of learning was sufficient to consolidate a new flavour-location pair in the same environment. The schema engaged a rapid consolidation process such that after only 48 hours the integrity of the hippocampus was already unnecessary for retrieval of that newly learned pair-associate, demonstrating that the memory was no longer hippocampal dependent. No such effect was seen without the schema or for inconsistent information. Additional findings reported in Tse et al. (2011) provided evidence that the hippocampal-dependent learning of new paired associates was tied to an up-regulation of immediate early genes in the medial prefrontal cortex, and that pharmacological interventions targeted at that
area could prevent both new learning and the recall of remotely and even recently consolidated schema-related information. These findings suggest that accelerated neocortical encoding mediates the schema benefit. Importantly, new simulations extending those reported in McClelland et al. (1995) and inspired by the findings of Tse et al. (2007, 2011), demonstrated that within the CLS framework new information that is consistent with existing neocortical knowledge structures can indeed be learned rapidly and without interference (McClelland, 2013). Based on this recent research Ghosh et al. (2014) made a new attempt to define the term schema as knowledge structures that show the schema effect. They identified four essential and sufficient features of a schema. A schema has an associative network structure and is composed of units and their interrelations (1); schema knowledge lacks context-detail (2) but is composed of extracted commonalities across events and based on multiple episodes (3); schemas are flexible and can be updated with new information (4). Features schemas are sensitive to but that are not necessary are chronological or hierarchical relationships, cross-connectivity and overlapping attributes between sub-schemas and the direct relationship to behaviour.

Figure 1.3: Schema assimilation model. Systems memory consolidation is accelerated when newly acquired information links well into pre-existing cortically-based knowledge structures (schemas), which facilitate the assimilation process (Tse et al., 2007). Figure adapted from Frankland & Bontempi (2005).

1.3.5 Relationship between semantic memory and schemas

Semantic memory (Tulving, 1972) and schema theories (Bartlett, 1932; Minsky, 1974; Spiro, 1977) share certain features. Especially theories, which define schemas as knowledge structures that represent concepts and stereotypes (Ghosh & Gilboa, 2014; Rojahn & Pettigrew, 1992; Rumelhart & Ortony, 1976) largely overlap with definitions of semantic memory. Rumelhart and Ortony (1976, 1980) for example described schemas as interacting knowledge structures that represent the generic concepts for objects and events and
allow for higher level conceptualisation, which is very similar to contemporary interpretations of semantic memory (Lambon Ralph et al., 2010; Lambon Ralph, 2014; Patterson et al., 2007). Similarly, the observation that prior knowledge affects memory and guides the interpretation of new incoming information applies evenly to schemas and semantic memory (Bartlett, 1932; Ghosh & Gilboa, 2014; Morris, 2006; Rumelhart & Ortony, 1976; Rumelhart, 1980; Tulving, 1972; van Kesteren et al., 2012). But even though there are clear overlaps between schemas and semantic memory there are likewise apparent differences. While semantic memory is clearly defined as part of declarative memory, schemas are much broader and can cover skills and procedural memory. In many schema theories (e.g. Minsky, 1975; Norman, 1972) the key function of a schema is to provide a summary of our past experiences by representing a frame for events and situations, which can have a strong temporal component. In this view schemas help to organise semantic content of a situation by providing information about the interrelations and connections between individual attributes (Gureckis et al., 2011). Importantly, however, and independent of the exact definition of schemas, semantic memory acts as a schema in terms of the schema effect. Thus, new information can be rapidly incorporated into semantic networks when the new information relates to pre-existing knowledge. This aspect of the formation of semantic memory is addressed in Chapters 4 and 5.

1.4 Sleep physiology

This section provides a brief overview of sleep physiology. The focus hereby lies on sleep patterns that are assumed to be involved in memory processing, which will be covered in section 1.5. Sleep is broadly divided into four different stages, namely stage 1, stage 2, slow wave sleep (SWS) and rapid-eye-movement (REM) sleep, which show distinct electroencephalography (EEG) oscillatory patterns. REM sleep periods and nonREM sleep periods, including sleep stages 1, 2 and SWS, alternate through the night in a cyclical fashion, each cycle lasting approximately 90 minutes. While the first part of the night is characterised by high amounts of SWS, REM sleep prevails during the second half (Fuller et al., 2006; Iber et al., 2007; Rechtschaffen & Kales, 1968).

1.4.1 Sleep stages

In the following the characteristic EEG patterns of the four stages of sleep are described. An exemplary illustration of each stage is provided in Figure 1.4. As SWS and Stage 2 are particularly important in the context of memory function the focus is on these two stages. Sleep onset is usually characterised by stage 1, a transitional stage between wakefulness and sleep which typically only lasts a couple of minutes (~5% of total sleep time (TST), Saletu 2001). During stage 1, conscious awareness gradually disappears and the EEG shows a low voltage, mixed frequency, predominating in the 8-12 Hz alpha and 4-7 Hz theta range. Sharply contoured waves called vertex sharp waves, lasting < 0.5 s, are a typical feature of stage 1 (Fuller et al., 2006). Stage 1 is usually followed by stage 2, which takes up approximately 56% of the TST (Saletu, 2001). Stage 2 is characterised by two pronounced oscillatory events: K-complexes and spindles (9-16 Hz). K-complexes
Figure 1.4: Sleep physiology. A) Hypnogram. Human sleep alternates in cycles between rapid eye movement (REM) sleep and nonREM sleep (including stage 1, 2 and slow wave sleep (SWS)). SWS dominates in the first half of the night, while REM sleep prevails in the second half. B) Each sleep stage is characterised by specific patterns of electrical field potential oscillations. K-complexes and sleep spindles are key features of stage 2 sleep, while slow oscillations and delta waves prevail during SWS.

are generated in the cortex and are composed of a short negative sharp wave (< 0.5 s), followed by a slower, larger positive component. K-complexes provide an isolated cortical down-state and can be evoked by sensory stimuli, suggesting that they are involved in sleep maintenance (Cash et al., 2009). Others interpret K-complexes as the expression of spontaneously occurring, cortically generated slow oscillations, which are described in more detail below (Genzel et al., 2014; Steriade, 2006). Sleep spindles are periodically reoccurring EEG rhythms, lasting 0.5 to 3 s, which appear as brief episodes of waning-and-waxing field potentials within a frequency range of 9-16 Hz. Spindles are a hallmark of nonREM sleep and are prevalent during stage 2 sleep compared to SWS (Achermann & Borbély, 1997; Andrillon et al., 2011; Dijk et al., 1993; Loomis et al., 1935; Steriade et al., 1985; Zeitlhofer et al., 1997). Spindles result from interactions between inhibitory thalamic reticular nucleus (TRN) cells and excitatory thalamo-cortical (TC) neurons (Ha-
Chapter 1. General introduction

lassa et al., 2011; Steriade et al., 1985, 1993b). Via an intra-thalamic feedback loop TC and TRN neurons increasingly recruit cells into synchronised burst firing, which has been suggested to underlie spindle waxing (Krosigk et al., 1990). TC neurons transmit these rhythmic thalamic oscillations to cortical neurons in a distributed, topographically organized fashion, where they are further amplified (Andrillon et al., 2011; Kandel & Buzsáki, 1997; Lüthi, 2013). Individual EEG spindle waves are scalp reflections of these currents generated by cortical neurons. Neocortical efferents to TRN cells allow a feedback control and enable a widespread synchronisation (Amzica & Steriade, 2000; Contreras et al., 1997). Increasing evidence suggests that sleep spindles are diverse in frequency and topographic distribution. In humans spindles are usually divided into slow spindles (11-13 Hz), which predominate in frontal cortices and fast spindles (13-16 Hz), which predominate in centro-parietal areas (Anderer et al., 2001; Andrillon et al., 2011; Gennaro & Ferrara, 2003; Jobert et al., 1992; Nakamura et al., 2003; Schabus et al., 2007; Ueda et al., 2000; Zeitlhofer et al., 1997). Differences in spindle frequencies are thought to reflect the preserved topographical organization between thalamic nuclei and sub-regions in the TRN (Andrillon et al., 2011; Guillery & Harting, 2003; Steriade & Timofeev, 2003). Spindles are key elements in the reduced sensory responsiveness during sleep as they distort the transmission of sensory information to the cortex by inhibiting incoming messages in the thalamus (Dang-Vu et al., 2011; Schabus et al., 2012). Besides their role in cortical disconnection spindles enable epochs of heightened plasticity in the neocortex (Steriade, 2006). Several experiments demonstrated that mimicking spindles by stimulating the thalamus and neocortex within the spindle frequency range increased synaptic responsiveness of cortical neurons (Bazhenov et al., 1998; Castro-Alamancos & Connors, 1996; Steriade & Timofeev, 1997) and could induce long-term potentiation (Rosanova & Ulrich, 2005; Timofeev et al., 2002).

SWS, also called deep sleep, is defined by four oscillatory rhythms: spindle (9-16 Hz), delta (1-4 Hz), slow oscillation (0.5-1 Hz) and ripple activity in the hippocampus (Steriade et al., 1993a; Steriade & Nuieie, 1993a,b). Slow oscillations are generated in the neocortex and solely depend on neocortical integrity. The underlying cellular mechanisms, however, are not fully understood (Amzica & Steriade, 1995; Lemieux et al., 2014; Sanchez-Vives & McCormick, 2000; Steriade & Nuieie, 1993a; Timofeev et al., 1996). Slow oscillations originate mainly from prefrontal cortical areas and recruit as travelling waves all parts of the neocortex in an anteroposterior direction (Massimini et al., 2004; Sheroziya & Timofeev, 2014). Slow oscillations have a peak frequency of ~0.8 Hz (Achermann & Borbély, 1997) and are characterised by alternating states of neuronal silence and increased neuronal activity, which are visible in the EEG. The silencing period is driven by a long-lasting hyperpolarising (down) phase that affects cortical and TC neurons, which remain silent for a few hundred milliseconds (Cissé et al., 2007; Timofeev et al., 1996). The excitation period is driven by a prolonged (0.2-0.8 s) depolarizing (up) phase, which creates a strong excitatory feedback on the thalamus via cortico-TRN synapses and on TC neurons (Contreras et al., 1997; Steriade & Timofeev, 2003; Sanchez-Vives & McCormick, 2000). While slow oscillations are usually considered as global events, i.e. occurring in
phase across most brain regions, (Steriade & Timofeev, 2003; Genzel et al., 2014), some evidence exists supporting the hypothesis that slow oscillations can be locally regulated (Nir et al., 2011), for example as a function of prior activity during wake (Huber et al., 2004, 2006). Delta waves only arise partially in the neocortex, but are primarily generated in single thalamo-cortical cells (Steriade, 2006; Steriade & Nuiiez, 1993a). On a macroscopic EEG level, delta waves are only seen when thalamo-cortical neurons that express delta activity are synchronised, possibly by TRN input, which in turn is synchronised by slow oscillations arising in the neocortex (Steriade, 1991; Steriade et al., 1993a). Both slow and delta (0.5-4 Hz) oscillations are implicated in cortical plasticity and have been shown to induce long term plasticity (Chauvette et al., 2012; Frank et al., 2001). All three SWS rhythms (spindles, slow oscillations and delta waves) are associated with prolonged hyperpolarisation of TC and cortical neurons and therefore inhibit the signal transmission from thalamus to cortex, reducing sensory responsiveness during sleep (Steriade, 2006).

Hippocampal sharp wave ripples (SWR) constitute a major mode of hippocampal activity (Buzsáki et al., 1992; Chrobak & Buzsáki, 1996; Siapas & Wilson, 1998), and are a common feature of SWS (Buzsáki et al., 1992; Clemens et al., 2007; Suzuki & Smith, 1987) but also occur during REM sleep (Louie & Wilson, 2001) and quiet wakefulness (Kudrimoti et al., 1999). SWR are composed of two components, ripples and sharp waves. Sharp waves are fast depolarizing events, generated in the CA3 region of the hippocampus, on which the high-frequency oscillations, called ripples (100-300 Hz, lasting 30-200 ms) originating in the CA1 region, are superimposed (Buzsáki, 1986; Csicsvari et al., 1999). SWR are rapidly transmitted to the subiculum and deep entorhinal cortex, and possibly excite additional target structures, including basolateral amygdala and neocortex (Pennartz et al., 2004). SWR functionally couple neurons into transient ensembles (Bukalo et al., 2013). Those neurons display an antidromic firing pattern, in which action potentials are generated in the axon and propagate to the soma in the opposite direction to normal. This process enhances the responsiveness of the neuron and reduces the LTP threshold (Bukalo et al., 2013). SWR are also thought to induce LTP themselves (Buzsáki, 1986) and the occurrence of SWR is facilitated in synaptic circuits that were previously potentiated (Behrens et al., 2005). Even though most research on SWR comes from rodent studies, hippocampal ripples have also been reported in humans (Bragin et al., 1999; Staba et al., 2002).

REM sleep is defined by the concomitant appearance of low amplitude, mixed frequency, wake-like (30-80 Hz) EEG activity, sharp, frequent rapid-eye movements and muscle atonia. REM sleep is associated with visually detailed and perceptually vivid dreaming (reviewed in Hobson et al., 2000), which has been shown to be mediated by heightened activity across a number of brain regions including visual cortex, thalamus and amygdala (Maquet et al., 1996).

1.4.2 Synchrony of sleep-related rhythms

During natural sleep, oscillatory rhythms occur in temporal coordination resulting in complex wave sequences (Steriade, 2006). Especially during SWS the brain displays a coalescence of the four cardinal oscillatory events. A major role is attributed to slow oscillations,
which are thought to orchestrate delta, spindle and SWR activity, by driving neurons to fire in a synchronous manner (Battaglia et al., 2011; Mölle et al., 2006; Sirota et al., 2003; Steriade, 1991; Steriade & Nuiiez, 1993a; Steriade, 2006). Although slow oscillations are a cortical phenomenon, the synchronisation spreads via efferent pathways (e.g. cortico-TRN projections) to other structures including thalamus and hippocampus, mediating the generation of spindles and SWR (Buzsáki & Draguhn, 2004; Mölle et al., 2002, 2004). Spindle and SWR occurrences are increased during the depolarising positive phase of the slow wave and decreased during the hyperpolarising negative phase (Steriade & Timofeev, 2003). Importantly, a strong temporal correlation has also been demonstrated between spindles and SWR (Clemens et al., 2007, 2011; Mölle et al., 2006; Siapas & Wilson, 1998; Sirota et al., 2003). Spindles and SWR coincide during the up-phase of the slow oscillation, whereby SWR tend to precede spindle onset (Siapas & Wilson, 1998; Sirota et al., 2003).

Through reciprocal connections the neocortex and thalamus form a unified oscillatory network and enable synchrony across large parts of the brain (Amzica & Steriade, 2000), but oscillatory rhythms can also occur independently of each other in localised cortical regions (Nir et al., 2011).

1.4.3 Synaptic plasticity during sleep

While some studies showed that spindles and slow oscillations can enhance plasticity (Chauvette et al., 2012; Frank et al., 2001; Rosanova & Ulrich, 2005; Timofeev et al., 2002), Tononi and co-workers (Tononi & Cirelli, 2003, 2006, 2014) propose in the synaptic homeostasis hypothesis (SHY) that slow oscillations induce a global synaptic downscaling via synaptic de-potentiation. SHY suggests that sleep plays a major role in the regulation of synaptic weights. Due to the constant interaction with the environment during wakefulness plastic changes occur across many cortical circuits, often resulting in long-term potentiation (LTP). As a consequence total synaptic strength increases across the day and reaches a maximum just before sleep (Klintsova & Greenough, 1999; Knott et al., 2002). As increases in the net synaptic strength are associated with higher energy and space demands, an imbalance towards potentiation is created and a down-scaling mechanism is necessary to ensure sustainability (Desai et al., 2002; Miller & MacKay, 1994). SHY claims that this function is fulfilled by sleep, which actively reduces global synaptic strength to a baseline level that is energetically sustainable (Bushey et al., 2011; Cirelli et al., 2004; Donlea et al., 2010, 2011; Maret et al., 2011; Vyazovskiy et al., 2008). A central role is attributed to slow oscillations, which, according to SHY, actively promote a global depression/de-potentiation through the alternating up- and down-phases. An important aspect of SHY is that synaptic strength is reduced proportionally, preserving relative differences in synaptic connections.
1.5 The role of sleep in systems memory consolidation and semanticisation

This section covers the role of sleep in systems memory consolidation and introduces an influential theory, the Active Systems Consolidation model (ASC), which proposes a mechanism by which sleep may facilitate systems consolidation and the semanticisation of memories. The observation that sleep has a beneficial effect on memory retention dates back to Ebbinghaus (1885). Initial theories (e.g. Jenkins 1924) proposed that the benefit of sleep on memory results from a passive protection against interference, which remained a prominent hypothesis for decades (Rickard et al., 2008; Vertes, 2004; Wixted, 2004). However, a range of behavioural observations, including sleep-related performance gains in procedural memory tasks (Fischer et al., 2006; Gais et al., 2000, 2002; Korman et al., 2007; Mednick et al., 2003; Plihal & Born, 1999; Stickgold et al., 2000b,a; Walker et al., 2003b,a) and sleep-related transformations towards more integrated and generalisable representations in declarative tasks (Gais et al., 2007; Orban et al., 2006; Wagner et al., 2004), could not be explained by a passive role of sleep. By now, there is substantial evidence that during sleep memories can be actively strengthened and reorganised (Diekelmann & Born, 2010; Ellenbogen et al., 2006; Gais & Born, 2004; Lewis & Durrant, 2011; Mölle & Born, 2011; Rasch et al., 2007; Rasch & Born, 2013; Ribeiro et al., 2004; Tononi & Cirelli, 2014; Vorster & Born, 2014; Walker, 2008).

1.5.1 Active systems consolidation model

The ASC, introduced by Born et al. (2006), forms an extension to the standard two stage model for memory consolidation and claims that sleep plays an active role in this process (see Figure 1.5). In the standard consolidation model it is assumed that repeated reactivation of newly formed memory traces induces a gradual redistribution of cortical-cortical connections (Frankland & Bontempi, 2005; McClelland et al., 1995; Squire & Alvarez, 1995). Even though memory reactivation occurs during explicit recall, quite wakefulness and sleep (Bridge & Paller, 2012; Dudai, 2012; Maquet et al., 2000; Nader et al., 2000; Pavlides & Winson, 1989; Peigneux et al., 2004; Wilson & McNaughton, 1994), the ASC proposes that memory reactivation that actually benefits systems memory consolidation happens preferentially during epochs of SWS. During sleep hippocampal memory reactivations are thought to be linked to SWR. Due to this linkage memory reactivations can be tied into complex wave sequences, which were described in section 1.4.2. The ASC suggests that the depolarising cortical up-states of slow oscillations repetitively drive SWR/reactivation events, and orchestrate these with the occurrence of thalamo-cortical spindles and other neocortical activity. SWR/reactivation events provide information about the original hippocampal-dependent memory trace, while spindles facilitate plastic changes in the neocortex. This synchronous feedback from hippocampus and spindles to the neocortex is thought to induce long-term plastic changes within cortical-cortical connections, which enable a reorganisation of individual memory traces in line with systems memory consolidation. Specifically, sleep is assumed to facilitate a shift in the neural substrates that support memory from hippocampus to neocortex and to promote the se-
manticisation of memories. Although the ASC has been proposed for declarative memory it is also thought to account for other memory systems, such as procedural memory (Born et al., 2006; Diekelmann & Born, 2010; Rasch & Born, 2013; Yotsumoto et al., 2009). In the next sections evidence for the ASC is described. First general support for the hypothesis that memories are reactivated and processed during sleep is presented. Then evidence for the view that sleep facilitates systems consolidation and the semanticisation of memories is summarised.

Figure 1.5: Active systems consolidation model. Newly acquired memory traces, which depend on the hippocampus, are repeatedly reactivated during hippocampal sharp wave ripples (SWR), which may underlie their gradual redistribution to the neocortex. The depolarising up-phase of slow oscillations drives these reactivation events and synchronises them to the occurrence of sleep spindles. This coordinated activity is thought to strengthening cortico-cortical connections and to promote the hippocampal-neocortical dialogue, which underlies systems memory consolidation. Figure adapted from Born & Wilhelm (2012).

1.5.2 Evidence that memories are processed during sleep

1.5.2.1 Crucial role of SWS and spindles for memory processing

The ASC proposes that slow oscillations, which are present in nonREM sleep and prevail during SWS, and spindles are crucially involved in memory consolidation. This hypothesis is supported by a broad range of studies, which found associations between memory consolidation and SWS or spindles. Spindle activity, for example, has been reported in numerous studies to correlate positively with overnight memory retention in declarative tasks (Clemens et al., 2005, 2006; Cox et al., 2012; Fogel et al., 2014; Gais et al., 2002; Genzel et al., 2009; Holz et al., 2012; Mander et al., 2014; Saletin et al., 2011; Schabus et al., 2004), and with sleep-related performance gains in procedural tasks (Fogel & Smith, 2006; Holz et al., 2012; Nishida & Walker, 2007; Tucker & Fishbein, 2009; Walker et al., 2002). Other studies showed that early nocturnal sleep, which is rich in SWS, but not late REM-rich sleep, is beneficial for memory consolidation (Fowler et al., 1973; Gais et al., 2000; Plihal & Born, 1999). Positive correlations between the amount of SWS obtained and post-sleep memory performance are also frequently reported (Durrant et al., 2011, 2013; Lau et al., 2011b; Wilhelm et al., 2011). While these studies only provide indirect support that sleep plays a role in memory processing, evidence for a direct association between learning and sleep came from studies, which showed that sleep is locally regu-
lated by prior learning. Learning before sleep has been shown to increase amplitude and coherence of slow oscillations in those brain regions that were originally involved in the learning (Huber et al., 2004; Mölle et al., 2004, 2009). Importantly, this local change in slow oscillation activity also predicted the improvement in task performance after sleep (Huber et al., 2004). Similarly, increases in spindle densities were observed after learning in a range of different tasks, including word-learning, spatial mapping, motor learning and picture association tasks (Fogel & Smith, 2006; Gais et al., 2002; Ruch et al., 2012; Schabus et al., 2004; Schmidt et al., 2006) and some of these studies also reported positive correlations between the increase in spindle activity and memory retention (Schabus et al., 2004; Schmidt et al., 2006). Together, these studies suggest that the use of neural networks before sleep, locally intensifies slow oscillation and spindle activity within these networks, which in turn seems to reflect enhanced memory processing. First evidence for a causal role of slow oscillations in memory consolidation was provided by Marshall et al. (2006) who induced slow-oscillation like field potentials in healthy participants with electrical brain stimulation during early SWS-rich nocturnal sleep. The resulting increase in slow oscillation activity was associated with improved overnight retention of word-pairs. Subsequent studies confirmed these results using different methods to manipulate slow oscillations (Marshall et al., 2011; Ngo et al., 2013). These findings provided direct evidence that, in line with the ASC, slow oscillation activity is actively involved in memory processing. Evidence that sleep spindles are causally involved in memory consolidation was provided by Mednick et al. (2013) who demonstrated that a pharmacologically-induced increase in spindle density produced significantly better verbal memory. Together, these studies provide substantial evidence that memories are actively processed during sleep, and that slow oscillations and spindle activity are crucial components in this processing.

1.5.2.2 Memories are spontaneously reactivated during sleep

A central hypothesis of the ASC is that memory strengthening and reorganisation during sleep relies on the reactivation of individual memory traces. Most evidence for memory reactivation during sleep was provided by research in rodents using hippocampal-dependent maze tasks, which showed that single neurons and neuron assemblies that were active during memory encoding were also active during subsequent sleep (Kudrimoti et al., 1999; Pavlides & Winson, 1989; Qin et al., 1997; Sutherland & McNaughton, 2000; Wilson & McNaughton, 1994). Wilson and McNaughton (1994) for example recorded neuronal firing patterns from ensembles of hippocampal place cells during spatial behavioural tasks and subsequent SWS (important to note is that SWS and stage 2 is not distinguished in rodents). They found that cells that fired together when the animal occupied particular locations during wakefulness exhibited an increased tendency to fire together during subsequent sleep, suggesting that information acquired during active behaviour was re-expressed in hippocampal circuits during sleep. The order of neuronal firing during wakefulness seems to be preserved in reactivations during sleep (Lee & Wilson, 2002; Nadasdy et al., 1999; Skaggs & McNaughton, 1996), but in a temporally compressed manner (Lee & Wilson, 2002). Memory reactivations during sleep have also been observed in non-human primates (Hoffman & McNaughton, 2002) and songbirds (Dave & Margoliash,
Evidence that memory reactivation during sleep is related to memory consolidation was provided by Dupret et al. (2010) who showed that the frequency of memory reactivations during sleep in rodents predicted subsequent memory performance. In humans evidence for spontaneous memory reactivation during sleep is still relatively sparse due to the methodological difficulties. Using positron emission tomography Peigneux et al. (2004) demonstrated that hippocampal areas that were activated during route learning in a virtual town were likewise activated during subsequent SWS. The amount of this hippocampal reactivity correlated positively with the improvement of performance in route retrieval on the next day. While this study only showed that brains areas involved in the task were reactivated during sleep, Deuker et al. (2013) provided evidence for the reactivation of specific memories during sleep. In this study multivariate pattern classification analysis was applied to fMRI data recorded during memory encoding and subsequent sleep. Patterns that were identified during memory encoding reoccurred spontaneously during post-learning sleep and the frequency of reactivation predicted subsequent memory for individual items. These findings provide important human evidence that memory reactivation underlies the beneficial effect of sleep on memory consolidation. Importantly, research in rodents has shown that hippocampal reactivations during SWS are linked to SWR (Csicsvari & Dupret, 2014; Dupret et al., 2010; Girardeau & Zugaro, 2011; Kudrimoti et al., 1999; Nádasdy et al., 1999; Pennartz et al., 2004). This association between memory reactivations and SWR is crucial to the ASC, as it provides a mechanism by which memory reactivation can be coordinated with other sleep oscillatory rhythms (see section 1.4.2). A causal role for SWR in memory consolidation was provided by studies showing that the selective elimination of SWR impaired the consolidation of recently acquired memories (Ego-Stengel & Wilson, 2010; Jadhav et al., 2012; Girardeau et al., 2009). In humans, so far, only one study exists, which demonstrated an association between SWR during sleep and subsequent memory performance (Axmacher et al., 2008).

### 1.5.2.3 Cued memory reactivation as a tool to influence sleep-related memory processing

While evidence for spontaneous memory reactivations in humans is still very sparse indirect evidence that memory reactivation underlies memory processing during sleep from studies using a method called 'cued memory reactivation' is accumulating. It is well established that incoming stimuli can be processed during sleep (Bastuji et al., 2002; Brualla et al., 1998; Ibáñez et al., 2006; Kouider et al., 2014). On this basis cued memory reactivation has been used to influence memory consolidation during sleep (Oudiette & Paller, 2013). In context cued memory reactivation memory encoding is associated with a contextual cue, like an odour or a sound, which is represented during subsequent sleep. The first study that demonstrated a beneficial effect of context cued reactivation on memory retention was conducted by Rasch et al. (2007). In this study an odour was used as contextual cue during a picture-learning task. Representing the odour during subsequent SWS enhanced memory retention. While in context cued reactivation the whole task is associated with a cue, cued reactivation can also be highly specific and only target individual memories as shown by Rudoy et al. (2009). In this study participants learned
object-location associations and each object was paired with its characteristics sound (e.g. dog - bark). Half of the items were cued during nonREM (item cued reactivation) by representing the sounds of the corresponding objects. After sleep participants recalled locations more accurately for the items that were cued during sleep, suggesting that specific memories can be individually targeted and strengthened during sleep. The positive effect of cueing during nonREM on memory retention has been confirmed by several studies for declarative memory (Diekelmann et al., 2011; Schreiner & Rasch, 2014; Rilm et al., 2013; van Dongen et al., 2012) and also for skill learning tasks (Antony et al., 2012; Cousins et al., 2014; Schönauer et al., 2014). Importantly, the effect cued memory reactivation is specific to sleep and usually not observed when the cues are represented during wakefulness (Antony et al., 2012; Cousins et al., 2014; Rudoy et al., 2009; Schreiner & Rasch, 2014). Under certain circumstances cued reactivation during wakefulness can even lead to a destabilisation of the memory (Diekelmann et al., 2011). In line with the ASC this suggests that the combination of memory reactivation with sleep oscillatory rhythms is crucial for the consolidation benefit. A general assumption made by studies using cued memory reactivation is that representing the cue during sleep influences spontaneously occurring memory reactivations and thereby modulates memory consolidation. Important evidence for this hypothesis was provided by Bendor & Wilson (2012) who demonstrated in rodents that cued reactivation biased the occurrence of spontaneous reactivations towards the cued memory. Similarly, Dave & Margoliash (2000) showed that the presentation of a bird’s own song during sleep induced a firing pattern in motor neurons corresponding to the firing pattern during daytime singing. Overall, cued memory reactivation seems a powerful tool for the investigation of sleep-dependent memory benefits in humans and together these studies provide substantial evidence that memory reactivation underlies memory processing during sleep.

Collectively, these studies provide convincing evidence that the mechanisms proposed by the ASC underlie memory processing during sleep. However, the above described beneficial effects of sleep on memory could be accounted for by a strengthening of the original hippocampal-dependent memory traces and do not necessarily support the view that sleep facilitates systems memory consolidation and semanticisation. The synaptic homeostasis hypothesis (SHY), which was introduced in section 1.4.3, could equally explain these findings by global synaptic downscaling (Tononi & Cirelli, 2014). The following section summarises evidence that sleep promotes memory reorganisation, which provides strong support that sleep plays an active role in systems memory consolidation.

1.5.3 Evidence that sleep supports systems memory consolidation

The standard model for systems memory consolidation proposes that memories are re-organised over time. As described in section 1.3.2 this reorganisation involves a shift in the underlying neural substrates from hippocampus to neocortex and a qualitative memory change from detailed context-bound memory towards abstract and decontextualised representations. In the following sections research findings, which support the hypothesis that sleep facilitates these processes, are summarised.
1.5.3.1 Neural substrates that support memory are reorganised during sleep

Evidence that a gradual shift in the brain circuits that support memory preferentially occurs during sleep was provided by several neuroimaging studies (Durrant et al., 2013; Gais et al., 2007; Orban et al., 2006; Payne & Kensinger, 2011; Sterpenich et al., 2007). Orban et al. (2006) showed for example by using a spatial memory task that brain activity involved in memory recollection shifted from hippocampus to striatum after sleep but not after sleep deprivation. Comparable results were reported by Durrant et al. (2013) who found that a gradual shift from the hippocampal to the striatal memory system, which was predicted by SWS, underlay abstraction in a statistical learning task. Further support comes from a study by Takashima et al. (2006), which showed that hippocampal activity during memory retrieval decreased and neocortical activity increased over the course of 3 months. Interestingly, SWS during a nap after the initial encoding session correlated positively with memory retention and hippocampal activity tested directly after the nap, possibly suggesting that during post-learning sleep the ground is set for systems memory consolidation. Together, these studies support the view that sleep promotes a reorganisation of the brain circuits that support memory, broadly in line with systems memory consolidation.

1.5.3.2 Sleep supports processes of semanticisation

Systems memory consolidation implies a qualitative memory change resulting in more abstract and decontextualised representations (McClelland et al., 1995; Nadel & Moscovitch, 1997; Stickgold, 2005; Winocur et al., 2010). A range of studies showed that sleep promotes this process of semanticisation by facilitating i) the extraction of regularities, ii) the integration of distinct elements into unified concepts, and iii) the assimilation of new information with prior knowledge (Inostroza & Born, 2013; Lewis & Durrant, 2011; Rasch & Born, 2013; Walker & Stickgold, 2010). The first study showing a qualitative memory change during sleep was conducted by Wagner et al. (2004). In this study participants performed a number reduction task, in which sudden insight into a hidden rule can be gained. Wagner et al. (2004) showed that sleep, compared to wakefulness facilitated the insight into the hidden rule, suggesting that during sleep memory representations were reorganised, such that underlying regularities were set apart. Subsequent findings from the same group support the hypothesis that SWS plays an important role in this process (Yordanova et al., 2008, 2009, 2012). These studies revealed that early-night SWS-rich sleep was necessary for the sleep-related gain in insight (Yordanova et al., 2008), and that the behavioural effect was related to a topographic redistribution of slow cortical potentials (Yordanova et al., 2009). Very similar sleep-benefits were obtained with the serial reaction time task (SRTT), in which explicit knowledge of a hidden sequence emerged preferentially after sleep (Drosopoulos et al., 2011; Fischer et al., 2006). By now, a variety of studies that implemented probabilistic patterns (Djonlagic et al., 2009; Durrant et al., 2011, 2013), language learning (Fenn et al., 2003; Gómez et al., 2006; Hupbach et al., 2009), and concept knowledge (Diekelmann et al., 2010; Lau et al., 2011a; Payne et al., 2009), have reported that sleep facilitates the extraction of regularities and memory for
'gist' information. However, while some studies reported a clear association with SWS, (Durrant et al., 2011; Yordanova et al., 2012), in other studies behavioural performance was associated with REM sleep (Cai et al., 2009; Djonlagic et al., 2009) and some studies did not observe any association with sleep at all (Lau et al., 2011a). Apart from the emergence of underlying regularities, semanticisation can also be reflected in more integrated memory representations. Accordingly, sleep has been shown to promote the linkage of distantly-related elements into unitised or integrated representations (Cai et al., 2009; Ellenbogen et al., 2007; Lau et al., 2011b). This was, for instance, demonstrated in a transitive interference task by Ellenbogen et al. (2007). Participants learned a hierarchy of pairwise presented elements (A>B,B>C,C>D,D>E) but were unaware of the overall hierarchical structure (A>B>C>D>E). Sleep had a beneficial effect on binding these elements together, allowing superior performance for the more distant inferential judgements. Similar results were obtained by Lau et al. (2011b) using a relational memory task. Interestingly, they further showed that the amount of SWS obtained in the retention interval was correlated with the ability to form connections between distantly linked elements. These results suggest that SWS is involved in this process of semanticisation. Another crucial step in systems memory consolidation is the assimilation of new information into existing knowledge structures. So far, three studies have investigated the impact of sleep on the integration of newly learned information into the mental lexicon (Dumay & Gaskell, 2007; Tamminen et al., 2010, 2013). Participants learned novel spoken words (e.g., cathedruke) that overlapped phonologically and therefore competed with familiar words (e.g., cathedral). Dumay & Gaskell (2007) showed that this lexical competition effect only emerged after sleep, suggesting that sleep plays a crucial role in the integration process. Tamminen et al. (2010) showed that the lexical competition effect was association with sleep spindle activity. Participants with higher spindle densities showed larger overnight increases in the lexical competition effect, reflecting enhanced integration, than participants with lower spindle densities. In the third study semantic content was added to the newly learned words (e.g. cathedruke: rabbit that eats meat), so that half of the items fell into dense semantic neighbourhoods and the other half into sparse semantic neighbourhoods (Tamminen et al., 2013). Results showed that semantic neighbourhood density influenced sleep architecture, with participants exhibiting more spindles and slow-wave activity after learning the sparse compared with the dense neighbourhood words. Together these studies provide first evidence that spindles and slow wave activity (SWA) play a role in the integration of new information into existing semantic networks. These findings further raise the question whether sleep spindles might mediate the accelerated assimilation of new information that fits well to prior knowledge, which was described in section 1.3.4. Chapters 4 and 5 address this question. Overall, these examples demonstrate that sleep can qualitatively change memories towards generalisable, unified schema-like representations. This change in memory quality reflects semanticisation and supports the view that systems memory consolidation occurs - at least partly - during sleep.
1.5.3.3 Increased hippocampal-neocortical dialogue during SWR

The two previous sections summarised evidence that memory reorganisation can take place during sleep. The ASC proposes that memory reorganisation results from reactivation-induced hippocampal-neocortical dialogue. In line with this hypothesis research has shown that during SWR hippocampal-neocortical interactions are increased (Sirotta et al., 2003; Siapas & Wilson, 1998). SWR modulate the firing of neurons in deep layers of the retro-hippocampal cortices, which in turn mediate hippocampal efferents to the neocortex (Girardeau & Zugaro, 2011). SWR therefore synchronise neurons across multiple downstream brain regions within short time windows of enhanced plasticity (Bukalo et al., 2013). Through the coupling with hippocampal memory reactivation SWR might provide a mechanism by which selective memory traces can be strengthening and redistributed within neocortical networks (Chrobak & Buzsáki, 1996; Csicsvari & Dupret, 2014; Mölle et al., 2009; Qin et al., 1997). Consistent with this idea memory reactivation has been reported in sub-cortical and cortical regions like the ventral striatum (Pennartz et al., 2004), thalamus (Ribeiro et al., 2004), posterior parietal (Hoffman & McNaughton, 2002; Qin et al., 1997), visual (Ji & Wilson, 2007), (medial) prefrontal (Benchenane et al., 2010; Peyrache et al., 2011) and somatosensory (Hoffman & McNaughton, 2002) cortex. Further support comes from findings, which showed that hippocampal reactivations tend to precede downstream neocortical activity (Ji & Wilson, 2007; Peyrache et al., 2011; Siapas & Wilson, 1998). Importantly, however, direct evidence that memory reorganisation is causally related to memory reactivation is still missing. Gupta et al. (2010) found in rodents that not only memory traces that were formed during prior experience were replayed during wakefulness, but in addition they observed the construction of never-experienced novel-path sequences. This provides evidence that memory reactivation can underlie processes of abstraction and integration, but whether this also happens during sleep remains unknown. So far no direct evidence exists that memory reactivation underlies sleep-related memory reorganisation, as proposed by the ASC.

Overall, there is strong evidence that memories can be reorganised during sleep. In line with system memory consolidation this reorganisation seems to involve a shift in the brain circuits that support memory from hippocampus to neocortex and a transformation in memory quality towards more integrated and abstract representations. These findings support the idea that sleep promotes systems memory consolidation and facilitates processes that contribute to semanticisation. However, many open questions remain regarding the underlying mechanisms. Especially, evidence that memory reactivation underlies the reorganisation of memories during sleep is largely missing. Similarly, very little is known about the role of sleep in the assimilation of new information into existing semantic networks.
1.6 Summary

Semantic memory refers to our general knowledge of the world, which arises from regularities and repeated occurrences in our experience. The formation of coherent semantic representations poses computational challenges, including the i) integration of information in a time- and modality invariant fashion, the ii) abstraction of statistical regularities, and the iii) assimilation of new information into existing semantic networks (Lambon Ralph, 2014; Rogers & McClelland, 2004). These challenges have been identified in the context of the hub-and-spoke model, which represents an influential framework for how well-established semantic memory is organised in the brain, but evenly apply to the formation of new, abstract semantic representations. Though there may be various routes towards creating conceptual knowledge, the semanticisation of episodic memory seems to represent a main one. Semanticisation is assumed to be linked to systems memory consolidation and describes a process in which semantic representations evolve from episodic memory via the aforementioned mechanisms (McClelland et al., 1995). During systems consolidation the repeated reactivation of hippocampal-dependent memory traces is thought to drive a gradual redistribution, such that memories are qualitatively altered and integrated into the long-term memory store, the neocortex (Dudai, 2004; McClelland et al., 1995). Although memory reactivations are also observed during active retrieval and quite wakefulness, those that drive systems memory consolidation and semanticisation have been suggested to occur preferentially during sleep (Born et al., 2006; Inostroza & Born, 2013). During sleep memory reactivations are embedded in complex wave sequences, which are thought to increase neocortical receptivity and enhance hippocampal-neocortical interactions, providing optimal conditions for systems memory consolidation. Sleep has been shown to support the reorganisation of memories, by facilitating the integration of information into unified concepts, the abstraction of statistical regularities, and the integration of new information with prior knowledge. Overall, this clear overlap between the processes involved in the formation of semantic memory and those that seem benefit from sleep-dependent memory consolidation suggest that sleep might play a role in the formation of semantic memory. However, this relationship has received little attention in research so far and many open questions remain.

1.7 Research objectives

The overarching aim of this thesis was to investigate sleep-related memory reorganisation with a focus on the mechanisms that are thought to be involved the formation of semantic memory. Several processes that contribute to the semanticisation of memories have been shown to benefit from sleep, but other important aspects of semanticisation have not been addressed yet. The integration of cross-modal information plays an important role in the formation of semantic memory. While several studies showed that sleep promotes the linkage of distinct elements, it is not yet known whether sleep also facilitates the integration of information from different sensory modalities. In Chapter 2 we aimed to mimic the formation of abstract semantic representations by reducing this process to two of its key
computational challenges, the integration of cross-modal information and the extraction of statistical regularities. We then explored its evolution over an offline retention period, and investigated the impact of wakefulness and sleep within the retention interval. Even though some processes of semanticisation clearly benefit from sleep, little is known about the underlying mechanisms. The ASC proposes that sleep-related memory reorganisation underlies the same reactivation-driven mechanisms as memory strengthening. Evidence, however, is still very sparse. In Chapter 3 we aimed to address this question using cued memory reactivation. We asked whether cued reactivation during SWS could further enhance the beneficial effect of sleep on abstraction. Another important aspect of the formation of semantic memory is the assimilation of new information into existing semantic networks. While this has long been held to be a very slow and gradual process, recent research has shown that it can be very rapid, when the new information relates to prior knowledge. Whether sleep plays a role in this accelerated consolidation process is unknown. In Chapters 4 and 5 we aimed to address this issue. In Chapter 4 sleep-related differences in the consolidation of newly acquired memories that either related to prior knowledge or were completely unrelated were assessed with fMRI and PSG. Building on the results of Chapter 4 in Chapter 5 we investigated how closely information must be related to prior knowledge to trigger the schema benefit and the association with sleep.
Chapter 2

Time- but not sleep-dependent memory consolidation promotes the emergence of conceptual knowledge

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2.1 Abstract

Conceptual knowledge about objects comprises a diverse set of multi-modal and generalisable information, which allows us to bring meaning to the stimuli in our environment. The formation of conceptual representations requires two key computational challenges: integrating information from different sensory modalities and abstracting statistical regularities across exemplars. Although these processes are thought to be facilitated by offline memory consolidation, investigations into how cross-modal concepts evolve offline, over time, rather than with continuous category exposure are still missing. Here, we aimed to mimic the formation of new conceptual representations by reducing this process to its two key computational challenges and exploring its evolution over an offline retention period. Participants learned to distinguish between members of two abstract categories based on a simple one-dimensional visual rule. Underlying the task was a more complex hidden indicator of category structure, which required the integration of information across two sensory modalities. In two experiments we investigated the impact of time- and sleep-dependent consolidation on category learning. Our results show that offline memory consolidation facilitated cross-modal category learning. Surprisingly, consolidation across wake, but not across sleep showed this beneficial effect. By demonstrating the importance of offline consolidation the current study provided further insights into the processes that underlie the formation of conceptual representations.

Keywords: Memory consolidation, sleep, category learning, abstraction, cross-modal object representations

2.2 Introduction

Every day we automatically discriminate between hundreds of objects, and assign meaning to them. This process often requires the integration of information from different modalities. For instance, when discriminating a donkey from a mule, information about its shape, the colour of its fur, or its location overlaps between the two species and is therefore, individually, not sufficient for correct categorisation. However, when the information is integrated, the two exemplars can be pulled apart, which allows us to rapidly discriminate between them. To account for this ability and to allow for generalisation to novel objects or situations, the conceptual representation of an object enables the capture of regularities and variations across the different modalities (Lambon Ralph et al., 2010; Lambon Ralph, 2014; Medin & Rips, 2005). The formation of many real-world concepts therefore seems to depend on two crucial mechanisms: the abstraction of the statistical variation across exemplars and the integration of information from different modalities (Lambon Ralph et al., 2010; Rogers et al., 2004). How new conceptual representations form with on-going category training has been studied in great detail (Ashby & Maddox, 2005; Jiang et al., 2007; Kumaran et al., 2009; Van der Linden et al., 2008, 2010, 2011; Smith & Minda, 2002). To date, however, very little research has focused on how conceptual representations evolve over time (Djonlagic et al., 2009).
Memory consolidation describes a post-encoding process of reorganisation, through which new memories become stabilised and integrated into long-term memory (Frankland & Bontempi, 2005). In addition to its stabilising effect, memory consolidation, including that which occurs across sleep, has been associated with a qualitative change of memories towards more abstract and general representations (McClelland et al., 1995; Walker & Stickgold, 2010; Winocur et al., 2010). Specifically, memory consolidation has been shown to facilitate the integration of distinct elements into coherent constructs (Ellenbogen et al., 2007; Kuriyama et al., 2004; Lau et al., 2011a; Walker & Stickgold, 2010). This has been demonstrated, for example, using a relational memory task in which participants were taught objects pairs, embedded in a hidden hierarchy (Ellenbogen et al., 2007). Consolidation across sleep promoted the links between individual items and the hierarchical structure. A similar but weaker benefit was observed during sleep-independent consolidation. Other evidence suggests that sleep-dependent consolidation facilitates the incorporation of newly learned information into the network of pre-existing knowledge (Tamminen et al., 2010). Besides this integrative function, memory consolidation also seems to play a role in the abstraction of rules (Gómez et al., 2006; Sweegers et al., 2014; Wagner et al., 2004), statistical patterns (Fischer et al., 2006), and the generalisation of information (Tamminen et al., 2010). Durrant et al. (2011, 2013), for instance, showed that sleep-dependent and, less strongly, sleep-independent consolidation promoted the abstraction of an implicit probabilistic structure in sequential auditory stimuli. Given that both the integration of information as well as the abstraction of statistical patterns seem to present fundamental mechanisms in the formation of conceptual representations, a key target of the current study was to explore how memory consolidation, possibly dependent on sleep, facilitates these aspects of concept formation. A study by Maddox et al. (2009) partially tackled this question by investigating the effect of sleep deprivation on information-integration category learning. The information-integration category learning task has been extensively studied in category learning (Ashby & Maddox, 2005). Key features of this task are that: the category structure cannot be easily verbalised; categorisation accuracy is only maximised when information from two or more stimulus dimensions is integrated at some predecisional stage (Ashby & Gott, 1988); and, categories can display strong within-category variation along different dimensions. The information-integration category learning task, therefore, nicely mimics the basic mechanisms involved in the formation of many natural concepts, as described above. The study conducted by Maddox et al. (2009) showed that sleep deprivation led to an overall performance deficit in the information integration category learning task. In the context of the current study more importantly, they also found a significant performance increase in the information-integration category learning task over a 24-hour off-line consolidation period, in which participants received a normal night of sleep. This performance increase cannot be directly attributed to a consolidation benefit as there was no control group, which performed the task without a consolidation break, but it does suggest that sleep may benefit this type of category-learning.

The current study investigated the effect of consolidation on the emergence of cross-modal category representations in more detail. The formation of conceptual representations in real life is usually unintentional - fostered by the incidental exposure to category members.
This type of category learning is assumed to be mediated by an implicit, procedural system (Ashby & Maddox, 2005; Smith et al., 2012). By modifying the information-integration category learning task (Ashby & Gott, 1988), we attempted to mimic the emergence of natural concepts, reduced to its two key mechanisms: the integration of cross-modal information and the abstraction of statistical regularities. We developed a paradigm in which an information-integration structure, across two different sensory modalities (auditory and spatial), was learned through a simple rule-based categorisation task. The abstract nature of this task prevented participants from drawing on prior knowledge and allowed us to track category learning from its very early stages. We conducted two experiments to investigate the effect of time-dependent consolidation (Experiment A) and the effect of sleep-dependent consolidation (Experiment B) on category learning. We predicted that the underlying information-integration category structure would be picked up implicitly during the training and enhanced by time- and sleep-dependent consolidation.

2.3 Methods

2.3.1 Participants

Experiments A and B involved 26 participants each. Informed consent was obtained from all participants prior to the study, approved by the University of Manchester Research Ethics Committee. Participants were not familiar with Asian orthographic characters, had normal or corrected-to-normal vision and hearing, and no prior history of psychiatric, learning or sleep disorders. Participants were required to be free of psychological drugs, alcohol and caffeine, and to refrain from daytime napping for 24 h preceding and throughout the study period. In Experiment A participants were randomly assigned to either a 15 min consolidation group (15 min group, n=13, mean age: 24.00, S.D.: 4.51, 6 F) or a 24 h consolidation group (24 h group, n=13, mean age: 24.14, S.D.: 3.59, 5 F). In Experiment B participants were randomly assigned to either a 12 h day consolidation group (12 h day, n=13, mean age: 19.50, S.D.: 1.22, 11 F) or a 12 h night consolidation group (12 h night, n=13, mean age: 20.00, S.D.: 1.30, 11 F).

2.3.2 Stimuli and stimulus generation

Each stimulus was defined by a combination of spatial, auditory and visual information, and belonged to one of two categories. In the spatial dimension, each stimulus was characterised by a specific location along the horizontal screen axis, in the auditory dimension by a particular pitch (between 200 and 1000 Hz) and in the visual dimension by an image of an Asian orthographic character. Category assignment was predefined based on obvious image characteristics. However, the same category assignment could be achieved by integrating the information about location and pitch. Stimuli were first created in spatial and auditory dimensions, in which the category structure was based in terms of an information-integration structure (Ashby & Gott, 1988). The visual dimension was added to each stimulus in a second step. Stimuli were generated by drawing 72 random samples from each of two bivariate normal distributions, forming the two stimulus categories. Dis-
Table 2.1: Parameters of bivariate normal distributions used for the stimulus generation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Category 1</th>
<th>Category 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_x$</td>
<td>-0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>$\mu_y$</td>
<td>0.8</td>
<td>-0.8</td>
</tr>
<tr>
<td>$\sigma_x$</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>$\sigma_y$</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>$\rho_{xy}$</td>
<td>1.92</td>
<td>1.92</td>
</tr>
</tbody>
</table>

Distribution parameters are shown in Table 2.1. Transformations of the original values $(x, y)$ into the two stimulus dimensions, space $(x', \text{ min: } -400 \text{ pixels, max: } 400 \text{ pixels from the centre})$ and tone $(y', \text{ min: } 200 \log_2 \text{Hz, max: } 1000 \log_2 \text{Hz})$, were performed according to Formulas (1) and (2).

\[
(x + 400) \frac{(x'_\text{max} - x'_\text{min})}{800} + x'_\text{min} \quad (1)
\]

\[
y'_\text{min} 2^{\frac{(y-200)}{800} \log_2 \frac{y'_\text{max}}{y'_\text{min}}} \quad (2)
\]

To visualise the category structure, each stimulus can be represented graphically by a point in the two-dimensional stimulus space as shown in Figure 2.1. In a second step, each two-dimensional stimulus was paired with an image of an Asian orthographic character. All orthographic characters were distinct and could be easily distinguished. Stimuli of category 1 were paired with characters, which had at least one enclosed space; stimuli of category 2 were paired with characters without an enclosed space (see Figure 2.1 for examples). Important to note is that this category structure allowed correct categorisation of a stimulus based on its image (‘open’ or ‘closed’) as well as based on integrating its information coded on location and tone dimensions. Stimuli for the cross-modal category learning task and the explicit memory tasks were randomly drawn from this pool of stimuli, such that 50% fell in each category.

### 2.3.3 Experimental tasks

All tasks were presented using Cogent 2000 developed by the Cogent 2000 team at the FIL and the ICN. They were written and executed using MATLAB® 7.5 on a desktop PC with dual core Xeon processor. Sounds were heard through a pair of Sennheiser® HD207 noise-cancelling headphones. Stimuli were presented on a 17” computer screen on black background.

#### 2.3.3.1 Cross-modal category learning task

For each participant 48 stimuli (24 stimuli per category) were randomly drawn from the pool of stimuli. Each time it was confirmed by plotting the selected stimuli that the selected set was representative of the distribution. The cross-modal category learning
Chapter 2. Role of sleep in cross-modal category learning

Figure 2.1: Visualisation of the category structure (A) and the CMCL-task trial structure (B).
(A) An asterisk denotes stimuli from category 1. Stimuli from category 2 are indicated by open circles. The abscissa corresponds to the location along the horizontal screen axis, the space dimension of a stimulus. The ordinate corresponds to the pitch (frequency in log₂(Hz)), the auditory dimension of a stimulus. In this two-dimensional space the category structure is an information-integration structure (Ashby & Gott, 1988). Each two-dimensional stimulus is paired with an image of an orthographic character. Stimuli of category 1 are paired with characters, which have an enclosed space (for visualisation purpose coloured in grey); stimuli of category 2 are paired with open shaped characters. Category membership can be detected either based on a simple rule regarding the image (‘open’, ‘closed’) or by integrating information on location and tone. (B) Every trial started with the simultaneous presentation of just the auditory and the spatial dimension of a stimulus for 500 ms, before the orthographic character appeared. The three-dimensional stimulus was presented for 1200 ms.

(CMCL) task, in both experiments, consisted of four or five repeated blocks depending on the group. In each block all 48 stimuli were presented once, in randomised order. Every trial started with the simultaneous presentation of the auditory and spatial information of the stimulus. The spatial information was indicated by a white square (4x4 cm²) appearing at the specific location. After 500 ms the orthographic character was presented within the white square. The 3-dimensional stimulus was presented for 1200 ms. Using correspondingly labelled keys on the computer keyboard (C: closed, O: open), participants were instructed to categorise the stimulus as quickly and accurately as possible according to the image into one of the two categories ‘open’ or ‘closed’. The last response given during the 1700 ms stimulus presentation period was counted and the reaction time for this response was recorded. This gave participants the chance to correct their responses and therefore encouraged participants to respond more quickly. Stimulus presentation was followed by 800 ms blank screen and initiation of the next trial. After each block participants had a self-determined break and received feedback on their average reaction time, the number of mistakes and if they had improved compared to previous blocks. Participants were not aware of the underlying implicit category structure and the aim of the study.

Crucial to our design was that the integrated information about the location and the tone of a stimulus, which always preceded the image, actually predicted the category membership of the image. Hence, use of the spatial and auditory information for categorising the stimuli would be reflected in accelerated response times. We hypothesised that, with training, participants would start to abstract the underlying cross-modal category structure and use this information for categorisation. A relative decrease in the average response time compared to the control (see next paragraph) served as indicator
for the emergence of category knowledge. While the first few blocks of the CMCL-task were considered as training, the final block served as test block and was used for the analysis.

2.3.3.2 Control task

The control task was used to determine individual reaction time baselines for categorising the images of the CMCL stimuli into the two categories 'open' or 'closed'. In the control task the same 48 stimuli that were used in the CMCL-task were presented once in their visual dimension only (i.e., the orthographic character without location or tone information). Each trial started with the presentation of a white square (4x4 cm²) in the middle of the screen. After 500 ms the orthographic character was displayed for 1200 ms within the square. No spatial or auditory information was given. Stimulus presentation was followed by 800 ms blank screen and initiation of the next trial. Task instructions and measures were identical to the CMCL-task. As control trials differed from CMCL-task trials only in the absence of auditory and spatial information, response time differences between the control and the CMCL-task could be attributed to the use of this information for categorising the stimuli. The difference in the average response time between the control and the last block of the CMCL-task served as measure for category learning in both experiments.

2.3.3.3 Explicit memory tasks

Three additional tasks were conducted to investigate whether explicit memory components contributed to the reaction time performance in the CMCL-task. In all tasks responses were given by pressing correspondingly labelled keys on the keyboard. No feedback was received. Novel stimuli were randomly drawn from the pool of the remaining stimuli, whose generation was described in Section 2.3.2 with the constraint that half fell in each category.

1. Recognition task: This task addressed how well individual stimuli were remembered. Therefore, 24 out of the 48 CMCL-task stimuli were randomly chosen with the constraint that half fell in each category and presented simultaneously in all 3 dimensions intermixed with 24 novel stimuli. Participants were instructed to indicate if they recognised each stimulus. Each trial was response terminated.

2. Association task: In this task, the memory for the combination of the visual dimension (image) with the auditory and spatial information was tested. Participants were tested on the 48 CMCL-stimuli. 24 of these stimuli were presented in their original three-dimensional combination. The other 24 stimuli were recombined. Therefore we kept the combination of spatial and auditory information fixed and shuffled the images between these stimuli within one category. Of the 24 stimuli presented as familiar items in the recognition task, 12 were recombined and 12 were presented in their original combination. We did not control for the similarity distance between the old and the recombined items. The stimuli were presented, one at a time, in
randomised order. Participants were instructed to indicate for each stimulus if the image and the space-tone combination was the same as in the CMCL-task or not. Each trial was response terminated.

3. Categorisation task: This task was used to test if participants could correctly categorise stimuli based on their spatial and auditory information only. The CMCL-task stimuli were presented once, in random order, under this categorisation condition. In each trial location and tone information of a stimulus was simultaneously presented for 1700 ms and participants were instructed to indicate if the stimulus would have an 'open' or a 'closed' shape in its visual dimension.

2.3.4 Procedure

Both experiments consisted of two experimental sessions, which were separated by a consolidation interval. This interval differed across four conditions. In Experiment A, the two experimental sessions were either separated by 24 h (± 30 min) or by 15 min. Both sessions took place between 10 a.m. and 5 p.m. (mean starting time: 13:30, S.D.: 2 h 14 min). In Experiment B, the two sessions were separated by a 12 h (± 1 h) interval which took place either during the night or during the day. Sessions took place in the morning at 8 a.m. (± 1 h) and in the evening at 8 p.m. (± 1 h). The 12 h day group completed the first session in the morning and the 12 h night group completed the first session in the evening, followed by a normal night of sleep. A schematic illustration of the procedure is shown in Figure 2.2. Session one started with a brief training round familiarising participants with stimuli and instructions. Subsequently participants performed the CMCL-task. Stimuli for the CMCL-task were randomly selected for each participant from the pool of 72 stimuli in each category. The CMCL-task was followed by the control task and the explicit memory tasks. The association task was performed by participants in Experiment B only. After completion of this session, which took about 45 min, participants were instructed to leave and carry on with their usual daily activities (12 h wake group, 24 h group), to have a 15 min break outside of the testing room (15 min group) or to return home and have a normal night of sleep (12 h night group). Session two started with the CMCL-task on 48 novel stimuli. In experiment A the CMCL-task in this session included 4 blocks only. Subsequently participants performed the control and the explicit memory tasks. This session lasted for 45 min. At the beginning of both sessions participants of Experiment B filled out a Karolinska Sleepiness Scale (KSS).

2.3.5 Statistical analysis

The same statistical analysis was conducted on Experiments A and B. Category learning was assessed in each session by comparing response times of the last CMCL-block with the corresponding control. Therefore, a 2x2 mixed analysis of variance (ANOVA) with within-subjects factor task (CMCL, control) and between-subjects factor group (Experiment A: 24 h and 15 min; Experiment B: 12 h day and 12 h night) was conducted, separately for each session, on the response times (in ms) to assess category learning before consolidation.
Chapter 2. Role of sleep in cross-modal category learning

Figure 2.2: Schematic illustration of the experimental procedures of experiments A and B. Both experiments consisted of two experimental sessions, separated by a consolidation interval. Consolidation interval characteristics differed between conditions as indicated above the arrows. Each session comprised several blocks of the cross-modal category learning (CMCL) task, with the respective final block serving as test block of interest, the control task and two (in Experiment B three) additional memory tasks.

2.4 Results

2.4.1 Experiment A

2.4.1.1 CMCL-task

In Experiment A we sought to assess how a post-learning consolidation interval would influence cross-modal category learning. One participant of the 15 min group was excluded from the analysis as the response times deviated by more than three standard deviations from the group average. Results are shown in Figure 2.3A. In session one there was no difference in the response times of the CMCL-task and the control, F(1,23)=0.43, p=0.53, and no difference in the performance between the two groups, F(1,23)=0.48, p=0.50. The interaction between the factors task and group was also not significant, F(1,23)=0.57, p=0.46. These results suggested that before the consolidation interval, no
Figure 2.3: Reaction time results for Experiment A (24 h and 15 min group) and Experiment B (12 h day and 12 h night group). Average response times are shown for all blocks of the CMCL-task and the control (C), for each experimental session. Standard error bars are included. In each session the final block of the CMCL-task was considered as test block (grey box) and response time differences between this block and the control (white box) served as measure for category learning. (A) Session 2: The 24 h group performed significantly faster in the final CMCL-task block than in the corresponding control, indicating the use of integrated auditory and spatial information. This difference was not significant for the 15 min group. (B) Session 2: The 12 h day group showed a significant reaction time decrease in the CMCL-task block compared to the corresponding control. This difference was not significant for the 12 h night group. The data points plotted in light grey correspond to the response times of experiment A. *p < 0.05, **p < 0.01.

category learning had taken place in either group. In session two there was again no main effect of group, F(1,24)=0.47, p=0.50. Importantly, however, in this session the overall response times for the CMCL-task were significantly lower (M=983.10 ms, SD=119.90 ms) than for the control (M=1032.30 ms, SD=73.00 ms), F(1,23)=7.22, p=0.01, indicating that information of the underlying information-integration category structure was used for categorisation. The interaction between task and group did not reach significance but displayed a trend, F(1,23)=3.38, p=0.08. Planned comparisons, using Bonferroni adjusted alpha levels of 0.025, showed that while for the 24 h group there was a significant difference in response times between the CMCL-task and the control, t(12)=2.82, p=0.015, this difference was not significant for the 15 min group, t(11)=0.74, p=0.47. Showing subtle but important differences between the two groups, these results suggest that category learning was dependent on the presence of the consolidation interval.

2.4.1.2 Explicit memory tasks

Two explicit memory tasks were conducted at the end of each experimental session to investigate how well participants could remember the individual items (recognition task) and if they had acquired explicit knowledge about the underlying information-integration category structure (categorisation task). The results are summarised in Table 2.2. Performance did not differ between groups (Recognition task: F(1,23)=2.55, p=0.12; Categorisation task: F(1,23)=0.11, p=0.74), or sessions (Recognition task: F(1,23)=2.54, p=0.13; Categorisation task: F(1,23)=2.58, p=0.12) in either task, and the interaction between session and group was not significant (Recognition task: F(1,23)=0.61, p=0.44; Categorisation task: F(1,23)=1.92, p=0.18). These results suggest that the overall reaction time decrease in the CMCL-task compared to the control observed in the second session
was not due to improved item recognition or improved explicit categorisation performance within the second session. Performance was above chance in the recognition task, using Bonferroni adjusted alpha levels of 0.0125, for each group in each session ($t \geq 5.78$, $p \leq 0.001$). Interestingly, for the categorisation task only the performance of the 24 h group in the second session was above chance ($M=29.30$, $SD=6.20$), using Bonferroni adjusted alpha levels of 0.125, $t(12) = 3.08$, $p = 0.01$. All other performances were at chance level ($t \leq 1.69$, $p \geq 0.12$).

### Table 2.2: Results of the explicit memory tasks of Experiment A.

<table>
<thead>
<tr>
<th></th>
<th>15 min group</th>
<th></th>
<th>24 h group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1</td>
<td>S2</td>
<td>S1</td>
<td>S2</td>
</tr>
<tr>
<td>Recognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>task</td>
<td>1.05 ± 0.4</td>
<td>1.16 ± 0.6</td>
<td>0.71 ± 0.5</td>
<td>1.01 ± 0.4</td>
</tr>
<tr>
<td>Categorisation</td>
<td>26.9 ± 5.1</td>
<td>27.2 ± 4.6</td>
<td>25.9 ± 4.1</td>
<td>29.3 ± 6.2</td>
</tr>
</tbody>
</table>

Data for the recognition task are $d'$ ± SD. Data for the categorisation task are means ± SD. Correct trials for a session are out of a total of 48.

### 2.4.2 Experiment B

#### 2.4.2.1 CMCL-task

Experiment B sought to assess how post-learning sleep or wakefulness would influence cross-modal category learning. Results are shown in Figure 2.3B. The analysis of session one showed no significant difference between the response times of the CMCL-task and the control, $F(1,24)=0.40$, $p=0.53$, no difference between groups, $F(1,24)=0.71$, $p=0.41$, and no interaction between the factors task and group, $F(1,24)=0.01$, $p=0.91$. Consistent with the results of Experiment A, no abstraction of the underlying category structure seemed to have occurred before the consolidation interval. In session two we found no difference between groups, $F(1,24)=0.47$, $p=0.50$, but a significant main effect of task, $F(1,24)=13.02$, $p=0.001$. Response times were quicker for the CMCL-task ($M=992.99$ ms, $SD=59.66$ ms) than for the control ($M=1026.95$ ms, $SD=66.19$ ms). Importantly, there was also a significant interaction between task and group, $F(1,24)=5.97$, $p=0.02$. Simple effects analysis, using Bonferroni adjusted alpha levels of 0.025, revealed that this interaction was driven by a significantly lower response time for the CMCL-task ($M=973.70$ ms, $SD=67.60$ ms) than for the control ($M=1030.70$ ms, $SD=69.90$ ms) in the 12 h day group, $t(12)=4.00$, $p=0.002$. For the 12 h night group the difference between CMCL and control tasks was not significant, $t(12)=0.89$, $p=0.39$. In line with the results of Experiment A, these results suggest that category learning occurred in the second session and was modulated by the consolidation interval. Surprisingly, the 12 h consolidation interval including wake and not sleep seemed to have a beneficial effect on category learning.

#### 2.4.2.2 Explicit memory tasks

In additional to the recognition and the categorisation tasks used in Experiment A, Experiment B also tested how well participants could remember the association between the visual orthographic character and the correct space-tone information (association task). The
results are summarised in Table 2.3. There was no difference between groups (Recognition task: \(F(1,24)=1.78, p=0.20\); Association task: \(F(1,24)=0.14, p=0.72\); Categorisation task: \(F(1,24)=1.85, p=0.19\)), or sessions (Recognition task: \(F(1,24)=0.02, p=0.89\); Association task: \(F(1,24)=3.10, p=0.09\); Categorisation task: \(F(1,24)=1.53, p=0.23\)), and no interaction between session and group in any task (Recognition task: \(F(1,24)=0.12, p=0.73\); Association task: \(F(1,24)=0.45, p=0.51\); Categorisation task: \(F(1,24)=0.09, p=0.77\)). In the recognition task performance was above chance, using Bonferroni adjusted alpha levels of 0.0125, for both groups in both sessions (\(t \geq 5.78, p \leq 0.001\)). In the association task, only performance of the 12 h night group in the second session was above chance, \(t(12)=3.31, p=0.006\), all other scores were at chance (\(t \leq 2.84, p \geq 0.015\)). In line with the finding of Experiment A, only the performance of the 12 h day group on the categorisation task in the second session was above chance, \(t(12)=3.50, p=0.004\). All other scores were at chance (\(t \leq 2.12, p \geq 0.06\)). Interestingly, in both experiments, only the group, which showed a significant effect in the CMCL-task, performed above chance in the categorisation task. This finding suggests that, as expected, our reaction time measure captured the initial steps in the emergence of category knowledge.

<table>
<thead>
<tr>
<th></th>
<th>12 h day group</th>
<th></th>
<th>12 h night group</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>S1</td>
<td>S2</td>
<td>S1</td>
<td>S2</td>
</tr>
<tr>
<td>Recognition task</td>
<td>1.11 ± 0.5</td>
<td>1.16 ± 0.5</td>
<td>0.92 ± 0.5</td>
<td>0.90 ± 0.5</td>
</tr>
<tr>
<td>Association task</td>
<td>0.11 ± 0.5</td>
<td>0.35 ± 0.4</td>
<td>0.23 ± 0.4</td>
<td>0.34 ± 0.4</td>
</tr>
<tr>
<td>Categorisation task</td>
<td>27.4 ± 6.6</td>
<td>29.5 ± 5.7</td>
<td>25.4 ± 6.0</td>
<td>26.7 ± 4.6</td>
</tr>
</tbody>
</table>

Data for recognition and association tasks are \(d' \pm SD\). Data for the categorisation task are means \(\pm SD\). Correct trials for a session are out of a total of 48.

### 2.4.2.3 Circadian effects

As previous research has demonstrated that circadian rhythms may interact with memory formation, there is a potential danger of circadian confounds in memory studies (Gerstner & Yin, 2010; Siegel, 2001). Since experimental sessions were conducted at different times of day (e.g., in the morning after sleep and in the evening after wake), it is possible that our results were influenced by circadian factors. To test for this possibility, we conducted a 2x2 mixed ANOVA with factors time of day (evening, morning) and group (12 h day, 12 h night) on the response times of the control task, as performance on this task was expected to be constant between groups and sessions. Importantly, there was no main effect of time of day, \(F(1, 24)=1.69, p=0.21\). We further found no main effect of group, \(F(1,24)=0.05, p=0.83\), and no interaction between time of day and group, \(F(1,24)=2.24, p=0.15\). Circadian influences were assessed using the same ANOVA on alertness measures of the KSS. Results showed again no main effect of the time of day, \(F(1,24)=0.01, p=0.93\), no difference between groups, \(F(1,24)=0.01, p=0.95\) and no interaction, \(F(1,24)=1.79, p=0.19\). These results suggest that the differences in performance observed after retention across intervals including wakefulness or sleep were not due to circadian variations.
2.5 Discussion

The current study investigated the influence of time- and sleep-dependent consolidation on the acquisition of cross-modal conceptual representations. Participants learned to distinguish between members of two abstract categories based on a simple one-dimensional rule (in form of an orthographic character). Underlying the task was a hidden, more complex indicator of category structure, which required the integration of information across two sensory modalities. The response times in both experiments demonstrated that, at the end of the second session, participants benefitted from this additional cross-modal information, indicating that at least some initial category learning had occurred. The results of Experiment A suggested that this learning was dependent on the presence of a consolidation interval. In Experiment B we found that the state of consciousness during this consolidation interval had an impact on the consolidation that occurred. The results of the additional explicit memory tasks did not reveal any performance differences between groups or sessions - indicating that the CMCL reaction time-based task is more sensitive to the initial phases of category learning. Overall, the current data suggest that our task captured the very early stages in the emergence of cross-modal categorical representations.

Our results of Experiment A are in line with the performance increase observed by Maddox et al. (2009) in an information-integration category learning task over a 24 h consolidation period. The current study extends this finding by providing evidence that this type of category learning is indeed facilitated by post-exposure consolidation. The information-integration category learning task is assumed to be mediated by a system that proceeds relatively automatically and without explicit awareness (Ashby & Maddox, 2005; Helie & Ashby, 2010). There is strong evidence in the literature that consolidation benefits skill learning. This has mainly been demonstrated for motor memory (Albouy et al., 2008; Brashers-Krug et al., 1996; Dayan & Cohen, 2011), sequencing (Karni et al., 1994; Press et al., 2005; Robertson et al., 2005) and visuo-motor (Krakauer et al., 2005; Reis et al., 2013) tasks. In addition to the abstraction of statistical patterns or rules, which often presents a crucial component to skill learning, the information-integration category learning task requires the integration of information at a predecisional stage. Perhaps for the first time, the current study demonstrated that cross-modal probabilistic category learning also requires post-exposure consolidation across time. During consolidation, memory representations are assumed to be restructured (Frankland & Bontempi, 2005; McClelland et al., 1995), and this process has been associated with a qualitative change in which information is unitised and general patterns emerge (McClelland et al., 1995; Walker & Stickgold, 2010). Because the consolidation benefit only emerged after additional training, reorganisation of memory representations during the consolidation interval may have led to subtle changes, which then allowed a more effective abstraction of the underlying category structure during subsequent training.

A beneficial effect of sleep on simple procedural memory tasks, such as perceptual or motor learning (Gais et al., 2000; Huber et al., 2004; Walker et al., 2002, 2003b) is well
established. Much less is understood about the role of sleep in more complex skill learning tasks, which involve the abstraction of rules or patterns, and the evidence up to date is inconclusive. While some studies show a beneficial effect of sleep-dependent consolidation (Debas et al., 2010; Durrant et al., 2011, 2013; Fischer et al., 2006), other studies demonstrated consolidation benefits that are independent of sleep (Nemeth et al., 2010; Robertson et al., 2004) or even specific to wakefulness (Song et al., 2007). The impact of sleep on probabilistic category learning was investigated by Djonlagic et al. (2009) using the weather prediction task. This study showed a sleep-dependent benefit on category learning, which seemed to be mediated by rapid eye movement (REM) sleep. In the current study we found a clear dissociation between day-time and sleep-related processes but in contrast to Djonlagic et al. (2009), only consolidation across wake facilitated category learning. Taken together, the results from Experiments A and B suggest that a certain amount of wake was necessary in order for the consolidation benefit to occur in our specific task. Similar to our results, a recent study conducted by Werchan and Gomez (2013) in young children showed a beneficial effect of wake but not sleep on the generalisation of word learning. Werchan and Gomez argued that, for successful abstraction and generalisation, the forgetting of irrelevant memories plays a key role (Vlach et al., 2012). As the strengthening of memories and the prevention of forgetting is an important function of sleep-based processes, a period of sleep could possibly inhibit conceptual generalisation by strengthening irrelevant memories. Wakefulness on the other hand seems to promote the forgetting of details and hence might provide a better basis for generalisation (Werchan & Gómez, 2013). This raises the question of when sleep promotes abstraction and when it does not. Werchan and Gomez (2013) suggested that it may depend on the generalisation ability of the participant, which influences the encoding of new memories. While adults are able to inhibit irrelevant information during encoding, young children cannot. Sleep-related processes may contribute, therefore, to the preservation of irrelevant details, which could slow up the abstraction of common patterns (Werchan & Gómez, 2013). Given that this notion is based on differences in the encoding process rather than the age of the participant, this hypothesis could also be applied to our results. Our category learning task presented a highly abstract and novel category to participants. In this particular situation, adult participants are in fact more like children with yet-to-be-learned familiar stimuli since, in both cases, there is limited availability of prior knowledge to distinguish between relevant and irrelevant information, which in turn might have influenced the sleep-dependent process. However, even if this novelty aspect makes an important contribution, it is unlikely to be the only factor that determines if memories show a sleep- or daytime-related enhancement, since other studies also using novel category or probabilistic structures showed sleep-dependent consolidation benefits (Djonlagic et al., 2009; Durrant et al., 2011). Another important aspect could be explicit awareness as suggested by Robertson et al. (2004), who showed that offline learning was sleep dependent for explicit skills, but time dependent for implicit skills. The importance of awareness for consolidation was also demonstrated by Song et al. (2007) by using a probabilistic variant of the serial reaction time task. This study showed that when learning occurred implicitly, sleep did not enhance general skill or sequence-specific learning. Daytime enhancement,
however, occurred for general skill. Our results are in line with this hypothesis as our
task was largely implicit and information-integration category learning is assumed to be
mediated by an implicit, procedural system (Ashby & Maddox, 2005; Smith et al., 2012).
We did not observe any significant improvements for the explicit memory tasks. Differ-
ences in awareness could also explain the different results found by Djonlagic et al. (2009),
since in contrast to our study, participants showed explicit knowledge of the probabilistic
structure. Generally, and more importantly, these different results highlight the many
open questions about the function of sleep and wake for memory consolidation.

In summary, our data show that the basic computational mechanisms in the formation
of cross-modal conceptual representations are facilitated by offline consolidation across
wake. Our study therefore contributes to a better understanding of the mechanisms for
how representations of real-world concepts evolve over time.

Acknowledgements
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Chapter 3

Cued memory reactivation during SWS abolishes the beneficial effect of sleep on abstraction

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This chapter is based on a manuscript that is being prepared for submission for peer review
3.1 Abstract

Extracting regularities from stimuli in our environment and generalising these to new situations is a fundamental process in human cognition. Recently, sleep has been shown to facilitate this process, but the underlying physiological mechanisms remain unclear. Here we used an auditory statistical learning task to determine whether cued memory reactivation during slow wave sleep (SWS) further enhanced the beneficial effect of sleep on the extraction of statistical regularities. Participants were exposed to a sequence of tones that was probabilistically determined, and subsequently tested for recognition of novel, short auditory and visual sequences adhering to this same statistical pattern in both immediate- and delayed-recall sessions. Overnight sleep between the recall sessions was monitored with polysomnography (PSG) and in one group of participants the auditory exposure sequence was replayed during SWS. Participants who did not receive any replay performed well above chance in the recall tasks of the delayed session, indicating that they abstracted the underlying pattern. In this group of participants the overnight performance change was associated with the amount of SWS obtained. Surprisingly, participants who received the replay during SWS, showed an impairment in performance across sleep, no association with SWS, and no abstraction of the underlying statistical pattern. In a third group of participants who received the replay during wakefulness it was established that the negative effect of replay on task performance was specific to replay during sleep. The current results suggest that replaying the probabilistic sequence during SWS disrupted or interfered with the abstraction of the underlying statistical structure. These findings raise important questions about the scope and the underlying mechanisms of cued memory reactivation.

**Keywords:** Memory consolidation, sleep, statistical learning, abstraction, and cued memory reactivation

3.2 Introduction

Often we encounter new exemplars of an object, such as the different cars that we see on our way to work. Even though we have not experienced these specific exemplars before and they might vary in colour, shape or sound, we can easily identify them. Our semantic representations enable us to do so by capturing the deep statistical structure that links conceptually related stimuli together (Lambon Ralph et al., 2010; Rogers et al., 2004). Extracting statistical regularities from our environment and integrating them across different modalities are therefore fundamental processes in the formation of abstract semantic representations (Lambon Ralph et al., 2010; Rogers et al., 2004; Sweegers et al., 2014). Recently, these processes have been shown to benefit from sleep (Stickgold & Walker, 2013; Walker & Stickgold, 2010). The important role of sleep in memory consolidation has been firmly established over the past years (Born et al., 2006; Diekelmann & Born, 2010; Rasch & Born, 2013; Walker, 2008). In addition to a direct retention benefit, sleep seems to facilitate the reorganisation of memory traces (Frankland & Bontempi, 2005). Memory
reorganisation over sleep can be reflected in increased knowledge of hidden rules or underlying patterns (Djonlagic et al., 2009; Durrant et al., 2011; Fischer et al., 2006; Wagner et al., 2004), strengthened connections between distinct elements (Ellenbogen et al., 2007; Lau et al., 2011a,b), and enhanced integration of new information with pre-existing knowledge (Cai et al., 2009; Tamminen et al., 2010, 2013). Overall, a variety of studies suggests that sleep promotes a change in memory quality from detailed context-bound memory to more abstract and generalised representations by facilitating the extraction of statistical regularities and integrative processing (Inostroza & Born, 2013; Rasch & Born, 2013; Walker & Stickgold, 2010). The spontaneous and repeated reactivation of recently formed memory traces during sleep has been proposed to underlie both the stabilisation and the reorganisation of memories during sleep (Born et al., 2006; Diekelmann & Born, 2010; Oudiette & Paller, 2013). Recent studies have experimentally manipulated spontaneously occurring reactivations by using cued memory reactivation (or replay). For cued memory reactivation auditory or olfactory cues are paired with the new information during memory encoding. The memory cues are represented during subsequent sleep and thought to bias or trigger spontaneously occurring reactivations and thereby manipulating the consolidation process (Bendor & Wilson, 2012; Dave & Margoliash, 2000). Although cued memory reactivation has been successfully applied during non-REM sleep to enhance and stabilise specific memories (Rudoy et al., 2009; Rihm et al., 2013; Schreiner & Rasch, 2014; Antony et al., 2012) its influence on memory reorganisation such as the extraction of statistical regularities remains largely unknown. To our knowledge so far only one study has addressed a similar question (Cousins et al., 2014). A modified version of the serial reaction time task was used to demonstrate that cued memory reactivation during sleep promoted the emergence of explicit sequence knowledge, possibly reflecting a reorganisation of the underlying memory traces (Cousins et al., 2014).

The current study aimed to further assess this question by exploring whether cued memory reactivation during SWS enhanced the beneficial effect of sleep on the abstraction of statistical regularities. We used the auditory statistical learning task that was used by Durrant et al. (2011, 2013), as in this paradigm the association between SWS and abstraction performance has been firmly established. In this task participants are exposed to a sequence of tones that is probabilistically determined. Subsequently they are tested for recognition of short new, randomly generated, sequences adhering to this same statistical structure. Performance in the recognition task therefore reflects whether the underlying statistical structure has been abstracted and can be applied to new exemplars. Additionally, a visual version of the recall test exists (Durrant et al., submitted), which allows to measure whether the abstracted knowledge is tied to the auditory modality or can generalise to the visual domain. To examine the effect of cued reactivation during sleep, chunks of the probabilistic auditory sequence were re-presented during SWS in one group of participants. Another group, in which no cued reactivation was done, served as control. To assess whether the effect of cued reactivation was specific to sleep the auditory sequence was re-presented during wakefulness directly before sleep, in a third group of participants. Based on previous findings (Durrant et al., 2011, 2013) we expected to find an overnight
performance improvement, further enhanced by cued reactivation during SWS.

3.3 Methods

3.3.1 Participants

Forty-two right-handed healthy volunteers participated in this experiment after informed consent was obtained, approved by the Research Ethics Committee of the University of Manchester. All had normal or corrected-to-normal vision, no hearing problems, and no history of neurological, psychiatric or sleep disorders. Participants reported a regular sleep pattern over the month preceding the experiment and followed a standardised sleep schedule (11 p.m. - 7 a.m.) for three days prior to study begin. Participants were randomly assigned to one of three experimental groups: SWS-replay (SWS-R) group (n = 14, mean age: 22.9, SD: 3.5, 5 females), control group (n = 14, mean age: 22.5, SD: 3.4, 6 females) and pre-sleep-replay (PS-R) group (n = 14, mean age: 20.5, SD: 3.0, 6 females), which differed in terms of the replay.

3.3.2 Stimuli

The same stimuli as in Durrant et al. (2013) and Durrant et al. (submitted) were used in the current experiment. The stimuli were made up of sequences of pure tones (lasting 200 ms each) with seven different frequencies (261.63, 288.86, 318.93, 352.12, 388.77, 429.24, and 473.92 Hz), which were obtained by dividing an octave into seven equal intervals in pitch space. These intervals are not heard in Western tonal music and were used in order to avoid creating melodic fragments familiar to Western listeners. Tones were sampled with a frequency of 44100 Hz, had a fixed amplitude and were Gaussian modulated to avoid aliasing edge effects. Tones in a sequence were separated by 20 ms gaps. The stimuli involved one exposure stream and 168 short test streams. The exposure stream consisted of 1818 tones and lasted 6 min and 40 s. The test streams consisted of 18 tones, lasting 3.96 s, each. In addition to the auditory test streams the stimuli also involved 84 visual test streams (Figure 3.1C), in which a yellow circle moved from left to right across a black background on the computer screen along 18 defined locations. On a computer screen with a resolution of 1024 x 768 pixels the circle started in a location 62 pixels from the left edge of the screen, where it remained for 200 ms. It then disappeared for 20 ms and appeared in its next location 53 pixels to the right, where it again remained for 200 ms. This process continued for 18 horizontal locations, giving the appearance of a circle moving across the screen in a series of discrete events. The vertical position for each event could take one of seven evenly spaced vertical locations (-250 pixels, -167 pixels, -83 pixels, 0 pixels, 83 pixels, 167 pixels, 250 pixels, relative to the centre of the screen). The seven vertical locations were chosen in analogy with the seven possible pitch heights in the auditory sequence. Auditory and visual sequences both consisted of discrete events over time, varying equally in height and following the same timings. Participants were not aware of this analogy.
Figure 3.1: Generation of structured and unstructured sequences. A) Transition matrix for the exposure stream and structured test sequences. Rows index the last tone that has occurred and columns tones that could occur next. The probability for each transition is reflected in the colour with white = 0.9 and black = 0.0167. Tones occur overall with an equal frequency, ensuring that this cannot provide additional structural information. B) Examples of a structured test stream and an unstructured test stream. Each test stream consisted of 18 tones. The sequence of structured test streams was determined based on the transition matrix, with the constrain that the number of high probability transitions was between 10 and 16. The sequence of unstructured test streams was generated randomly with an equal probability of 0.143 for each transition, resulting in four high probability transitions in this particular case. Low probability transitions are indicated in red. C) Analogous to the auditory test streams, the visual test streams were sequences of a yellow circle moving from left to right across a black background. The circle started in the left edge of the screen and appeared at 18 distinct horizontal locations (indicated by vertical lines), giving the impressing that it was moving from left to right. The vertical position could take one of seven evenly spaced locations, analogous to the seven pitch heights of the auditory streams. Structured and unstructured visual test streams were created analogue to auditory test streams.
The exposure stream, 42 of the auditory test streams and 42 of the visual test streams followed a probabilistic structure (structured condition). The probability for each potential transition between the current item (tone for the auditory stream and screen height for the visual stream) and the next item was determined by a transition matrix, forming a first-order Markov chain (see Figure 3.1). In the transition matrix each row contained one likely transition \( p = 0.9 \), shown in white in Figure 3.1A) and six unlikely transitions \( p = 0.0167 \), shown in black in Figure 3.1A). This ensured that a given item was followed by a particular item 90% of the time, and by any of the other six items 10% of the time, making the sequences probabilistic. All seven items occurred overall with an equal probability, assuring that participants had to acquire sequence knowledge rather than just information on how frequently individual items occurred. The other half of the auditory and visual test streams (42 each) were generated randomly, with an equal probability for each tone/height at every position in the sequence (unstructured condition). As all test streams of the structured condition had the same probabilistic structure as the exposure stream, those test streams were considered as similar to the exposure stream, while the test streams of the unstructured condition were not similar to the exposure stream. For the replay the exposure stream was divided into six fragments, each 66 s long. The replay stream contained all fragments twice, in randomised order and with 10 s gaps between consecutive fragments.

### 3.3.3 Experimental task and design

All three experimental groups followed the same basic protocol (shown in Figure 3.2), which involved two experimental sessions, one in the evening at 9 p.m. ± 1 h and one in the following morning at 8 a.m. ± 1 h. All participants slept the night (approximately from 11 p.m. to 7 a.m.) between the two sessions in a bedroom in the Sleep Research Laboratory at the University of Manchester and their sleep was monitored using polysomnography (PSG). Before each session alertness was measured using the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973) and the Karolinska Sleepiness Scale (KSS; Glenville & Broughton, 1978).

Session one started with a learning phase in which the auditory exposure stream was presented, in order to familiarise participants with the transition probabilities. While the exposure stream was played, the term ‘Tone Stream’ was presented in the middle of the computer screen, in order to focus participants’ attention towards the auditory stream. As in the study by Durrant et al. (2013) participants were informed that an immediate and a delayed recall task would follow. Directly after the learning phase participants conducted the immediate recall task. In this task 42 structured and 42 unstructured auditory test streams were presented in randomised order. While a test stream was played, the instruction ‘Listen’ as well as the number of the current trial out of the total number was presented in the middle of the computer screen (‘Trial 18 of 84: Listen’). Subsequently a 5-s response period (indicated by the phrase ‘Trial 18 of 84: Respond now’) followed, in which participants indicated whether or not the test stream sounded similar to the exposure stream, by pressing correspondingly labelled buttons (‘familiar’ or ‘unfamiliar’) on
Chapter 3. Memory replay during SWS manipulates the abstraction of regularities

Figure 3.2: Experimental design. All groups encoded the exposure stream at 9 p.m., followed by an immediate recall test session. Subsequently, participants completed a 2-back working memory task. Overnight sleep was monitored with polysomnography. At 8 a.m. participants undertook a delayed recall session, followed by the visual recall task. In the SWS-replay (SWS-R) group the replay-stream was presented during SWS and in the pre-sleep-replay (PS-R) group during the 2-back task. The control group did not receive any replay. PS-R: pre-sleep-replay, SWS-R: SWS-replay.

the computer keyboard. Participants were instructed to give their response as soon as they were sure. They were also informed in advance that half of the test streams were similar to the exposure stream and that the other half was unfamiliar. After the immediate recall task a 2-back task (adapted from Kane et al. 2007), lasting 15 min, followed. In each trial one of eight phonologically distinct letters (B, F, K, H, M, Q, R, X) was displayed in the middle of the screen for 500 ms, followed by a blank 2500 ms inter-stimulus interval. For each trial starting from trial number three, participants attempted to press one button (‘Yes’) if the current letter matched the letter that appeared 2 items ago (B-f-b) and another button (‘No’) if the two letters did not match. Participants were instructed to respond as quickly and accurately as possible. Participants could give their response as soon as the letter appeared on the screen and until the end of the inter-stimulus interval. Following a short practice run, participants performed six blocks of 48 trials each. Within each block each letter appeared six times, once as a target and five times as a foil. To prevent recognition based on perceptual features only, letters appeared randomly in either upper or lower case. Participants were asked to maintain their focus on the task. After each block feedback was given on accuracy and participants were encouraged to try to improve their performance in the following block. While participants completed this
task brown noise was played. Session two started with the delayed auditory recall task followed by the visual recall task. Trial structure and instructions of the delayed auditory recall task were analogue to the immediate recall task, but 42 novel structured and 42 novel unstructured test streams were used. In the visual recall task participants were presented with the 84 visual test sequences, in randomised order, and asked to indicate within the subsequent 5-s response period, whether or not the visual test streams was similar to the auditory exposure stream. Written instructions and the trial number out of the total number of trials were presented prior to each trial. In order to prevent that participants imagined the auditory analogue to the visual sequence, the seven different auditory tones were randomly played while the visual sequence was presented. Participants were instructed to ignore those tones and use only the visual information in their judgement.

The three experimental groups differed in the presentation of the replay stream. In the SWS-R group the replay stream was presented softly during the first two cycles of SWS. The replay started in the first extended period of SWS and was stopped immediately upon arousal or leaving SWS. In the PS-R group the replay stream was presented during the 2-back task. In both groups the replay stream was played on PC speakers, with an approximate intensity of 48 dB, embedded in brown noise. In the control group no replay was done. As in the PS-R group the replay stream was presented during wakefulness the 2-back task, which is a demanding working memory task, served as distractor task and aimed to prevent rehearsal or active listening for a better comparison with the covert replay in the SWS-R group. To avoid differences in the experimental design, which could potentially influence memory performance, the 2-back task was conducted in all groups.

3.3.4 Equipment

The experimental tasks were realised using Cogent 2000 developed at the Functional Imaging Laboratory (University College, London), implemented using MATLAB® 7.5. Sound was generated using the onboard SoundMAX® digital audio chip, and heard through a pair of Sennheiser® HD207 noise-cancelling headphones.

3.3.5 Behavioural data analysis

Data were analysed with SPSS® 20.0 and MATLAB® 7.5. The sensitivity index d-prime (d’ = z-score(hits) - z-score(false alarms)) was calculated for the detection of the structured sequences for each session from the number of hits (correct identification of structured sequences) and the number of false alarms (incorrect identification of unstructured sequences as being structured). In cases where maximum hits or no false alarms occurred, half a trial was added or subtracted from the proportion correct when considering all test trials of the session (e.g. 0.5/84) in order to avoid an infinite z-score (Stanislaw & Todorov, 1999). The difference between the performance on the delayed and the immediate recall session gave a measure of consolidation. A 2 x 3 mixed measures analysis of variance (ANOVA), with within-subject factor session (levels: immediate, delayed) and between-subject factor
group (levels: SWS-R group, PS-R group, control group) was used on the d’ measures to investigate performance differences between groups. A one-way ANOVA on the d’ measures of the visual recall task was used to assess differences between groups. In all our results, we considered p < 0.05 as significant and all tests were 2-tailed. Significant effects were further explored with Bonferroni-corrected t-tests. One-sample t-tests were used to test whether performance was above chance. For each round of the 2-back task the sensitivity index d-prime was calculated from the number of hits and false alarms. Differences between groups were assessed using a 2 x 6 mixed measures ANOVA with factors round (levels: round 1 to 6) and group.

3.3.6 PSG data acquisition and analysis

An Embla© N7000 system was used for the EEG recording (200 Hz sampling rate). Six scalp electrodes were positioned using the international 10-20 system (F3, F4, C3, C4, O1, O2) with contralateral mastoid references. Two electrooculographic channels monitored eye movements and three chin electromyographic channels monitored muscle tone; a ground electrode was also attached. NuPrep© exfoliating agent was used to prepare the scalp and electrodes were attached using EC2© electrogel. Impedance of less than 5 kΩ was verified at each electrode. Sleep data were visually scored using RemLogic© 1.1 software, in 30 s epochs, bandpass filtered between 0.3 and 35 Hz, by two trained sleep researcher according to the AASM Manual (American Academy of Sleep Medicine, Westchester, IL, 2012). The proportion of time spent in each sleep stage (stage 1, stage 2, SWS, REM) and the overall sleep duration were calculated. As previous studies showed that the amount of SWS predicted a performance increase from the immediate to the delayed recall session (Durrant et al., 2011, 2013), we measured the correlation between SWS and overnight performance change for all experimental groups. A multivariate analysis of variance (MANOVA) on the time spent in each sleep stage was used to examine group differences in the sleep structure. For spindle detection raw EEG data of non-rapid-eye movement sleep (nonREM: including stage 2 and SWS) were cleaned of artefacts and band-pass filtered (12-15 Hz) using a linear finite impulse response filter in EEGLab v.9.0. An automated detection algorithm (Ferrarelli et al., 2007), which counts amplitude fluctuations in the filtered time series, which exceed a predetermined threshold, as spindles, was used to determine the number of spindle events at each electrode. Reported results are averaged across frontal and central channels. Group differences were assessed using a one-way ANOVA. Power spectral density during SWS was analysed on central (averaged across C3 and C4) and frontal (averaged across F3 and F4) channels using Welch’s method. This utilized a 4 s Hamming window length with 50% overlap, focussing on frequency bands that are prominent during SWS, i.e. slow oscillation (0.3-1Hz), delta (1-4 Hz) and sigma/spindle (12-15Hz) bands. A MANOVA was used to assess group differences. As replay during sleep could have potentially caused sleep disruptions, resulting in reduced sleep quality, sleep quality was examined and compared between the three experimental groups. The following measures regarding sleep quality, which have been used in the literature (Martin et al. 1997, Buysse et al., 1998) were considered: time awake after sleep onset (in min), sleep efficiency (total sleep time in percentage of the time from sleep...
onset until the last wake event), the number of transitions from one sleep stage to another, the transition index (number of transitions per hour of sleep), the number of awakenings (> 15 s), the awakening index (number of awakenings per hour of sleep), the number of arousals and the arousal index (number of arousals per hour of sleep). A MANOVA examined group differences on these variables. To assess more subtle changes in sleep quality related to SWS, the sleep stage in which the replay was presented, the arousal index, the transition index and the awakening index (number of events per time spent in SWS) for SWS only, were calculated and analysed with a MANOVA.

3.4 Results

3.4.1 Auditory recall task

The behavioural results are presented in Figure 3.3A. A 2x3 mixed measures ANOVA with factors session and group revealed no significant main effect of session, F(1,39) = 0.008, p = 0.930, no difference between groups, F(2,39) = 2.214, p = 0.123, but, importantly, a significant session x group interaction, F(2,39) = 5.421, p = 0.008. While the SWS-R group showed a significant decrease in performance across the two recall sessions, at a Bonferroni-corrected α-level of 0.017, (mean S1: 1.129, SE: 0.144, mean S2: 0.767, SE: 0.122), t(13) = 2.794, p = 0.015, the performance in the control group (mean S1: 1.248, SE: 0.111, mean S2: 1.339, SE: 0.151), t(13) = 0.738, p = 0.474, and the PS-R group (mean S1: 1.157, SE: 0.142, mean S2: 1.450, SE: 0.226), t(13) = 1.684, p = 0.116, did not change across sessions. As expected performance between groups did not differ in the immediate recall session, t(26) ≤ 0.652, p ≥ 0.520, indicating that all groups had a comparable performance prior to the consolidation interval. After sleep, in the delayed recall session the SWS-R group performed significantly worse than the control group, t(26) = 2.937, p = 0.007, and the PS-R group, t(26) = 2.659, p = 0.013, at a Bonferroni-corrected α-level of 0.017. Performance between control and PS-R group did not differ, t(26) = 0.410, p = 0.685. Importantly, performances in each session in each group were significantly greater than chance, t(13) ≥ 6.274, p < 0.001, demonstrating that participants in all conditions were successful in conducting the task.

3.4.2 Visual recall task

The behavioural results of the visual recall task are presented in Figure 3.3B. One participant of the SWS-R group did not complete the visual recall task due to a technical failure. A one-way ANOVA revealed a marginal significant difference in performance between the three experimental groups, F(2,38) = 3.098, p = 0.057. Planned post hoc comparisons, using a Bonferroni-corrected α-level of 0.025, showed that the SWS-R group performed significantly worse than the control group, t(25) = 2.490, p = 0.020, and marginally worse than the PS-R group, t(25) = 2.253, p = 0.033. Performance was above chance for the control group and the PS-R group (Bonferroni-corrected α-level of 0.017), t(13) ≥ 2.884, p ≤ 0.013, demonstrating that they were successful in conducting the task. Performance of the SWS-R group did not exceed chance level, t(12) = 0.785, p = 0.448.
Chapter 3. Memory replay during SWS manipulates the abstraction of regularities

Figure 3.3: Behavioural results. A) Auditory recall task. While in the immediate recall session there was no difference in the performance between groups, a difference emerged in the delayed recall session (assessed by t-tests). The SWS-replay group showed a significant decrease in correct recognition of structured and unstructured sequences after consolidation, whereas the control group and the pre-sleep-replay group showed no change in performance. This group difference in the performance change across consolidation was significant in a 2x3 analysis of variance with factors session and group. B) Visual recall task. The control group and the pre-sleep-replay group exhibited strong performance, while the SWS-replay group performed at chance. The difference in performance between the SWS-replay and the two other groups was significant. **p < 0.001, *p < 0.05, n.s.: p > 0.1.

3.4.3 Alertness and response times

Differences in alertness between the three experimental groups were assessed with one-way ANOVAs on the average scores of the KSS and the SSS for each session. Groups did not differ in both sessions on both scales, F(2,39) ≤ 1.869, p ≥ 0.168, suggesting that there was no difference in alertness between groups in either session. The change in alertness between S1 and S2 did also not differ between groups neither for the KSS, F(2,39) = 0.896, p = 0.416, nor for the SSS, F(2,39) = 0.992, p = 0.380. In line with previous studies (Durrant et al., 2011, 2013), response times (in seconds) were faster on correct than incorrect trials for both the immediate-recall (correct mean: 0.791, SE: 0.243; incorrect mean: 0.946, SE: 0.299; comparison: t(41) = 4.773, p < 0.001) and delayed-recall (correct mean: 0.776, SE: 0.232; incorrect mean: 0.877, SE: 0.333; comparison: t(41) = 3.210, p = 0.003) sessions, confirming that response time is a sensitive measure in the statistical learning paradigm. There was no significant main effect of group (immediate-recall: F(2,39) = 0.206, p = 0.815; delayed recall: F(2,39) = 0.636, p = 0.535) and no significant interaction between group and trial correctness in either session (immediate-recall: F(2,39) = 1.396, p = 0.260; delayed-recall: F(2,39) = 1.816, p = 0.176), confirming that all groups had a similar pattern of response times. Together, these results suggest the observed group differences in performance were not due to differences in alertness.

3.4.4 N-back task

Data from one participant of the control group were lost due to a technical failure. A 6x3 mixed measures ANOVA (factors: round and group) was used to assess differences in performance on the 2-back task between experimental groups. Importantly, we observed no difference between groups, F(2,38) = 1.797, p = 0.180, or group x round interaction,
F(10,190) = 1.350, p = 0.207. The main effect of round was significant, F(5,190) = 6.703, p ≤ 0.001, with increasing performance across rounds. These results suggest that the PS-R group was not distracted by the presentation of the replay stream and focused comparably on the 2-back task as to the other groups.

### 3.4.5 Association between overnight performance change and SWS

For one participant of the control group no PSG data were available, due to technical difficulties during the sleep monitoring. Results of the PSG analysis of the remaining participants are presented in Table 3.1. The two previous studies using this paradigm showed that the amount of SWS predicted the behavioural performance change from the immediate to the delayed recall session of the auditory recall task (Durrant et al., 2011, 2013). Therefore this association was also assessed in the current study, shown in Figure 3.4. The control group showed as expected a positive correlation between the proportion spend in SWS and the behavioural performance change from immediate to delayed recall, r(13) = 0.587, p = 0.035. Participants with a large proportion of SWS showed an overnight improvement in performance, while participants with little SWS showed an impairment. This correlation was specific to SWS; no other sleep stage (S1, S2, REM, TST) showed a significant correlation, r(14) ≤ 0.108, p ≥ 0.726. The SWS-R group showed no association between the change in performance and SWS, r(14) = -0.123, p = 0.674, or any other sleep stage, r(14) ≤ 0.316, p ≥ 0.271. The PS-R group showed a strong correlation between SWS and the behavioural performance change, but surprisingly this association was negative, r(14) = -0.704, p = 0.005. Participants with a high proportion of SWS showed a decrease in performance, while participants with a low proportion of SWS, showed an improvement. This correlation was specific to SWS; no other sleep stage showed a significant correlation, r(14) ≤ 0.431, p ≥ 0.124.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SWS-R group</th>
<th>Control group</th>
<th>PS-R group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sleep Time (min)</td>
<td>458.71 ± 19.12</td>
<td>432.96 ± 12.74</td>
<td>428.25 ± 13.96</td>
<td>0.34</td>
</tr>
<tr>
<td>REM (%)</td>
<td>18.71 ± 1.32</td>
<td>18.71 ± 1.57</td>
<td>19.69 ± 1.05</td>
<td>0.83</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>5.96 ± 1.08</td>
<td>5.68 ± 0.87</td>
<td>4.52 ± 0.84</td>
<td>0.52</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>63.72 ± 1.41</td>
<td>61.83 ± 1.53</td>
<td>58.38 ± 1.83</td>
<td>0.07</td>
</tr>
<tr>
<td>SWS (%)</td>
<td>11.61 ± 1.52</td>
<td>13.78 ± 1.52</td>
<td>17.41 ± 1.38</td>
<td>0.03*</td>
</tr>
<tr>
<td>nonREM spindle density</td>
<td>0.77 ± 0.09</td>
<td>0.83 ± 0.10</td>
<td>0.91 ± 0.10</td>
<td>0.62</td>
</tr>
</tbody>
</table>

SWS-R: SWS replay, PS-R: pre-sleep-replay, nonREM: non-rapid-eye-movement sleep (including SWS and stage 2 sleep). Spindle density is measured as number per minute. Data are means ± SE, p values are from one-way ANOVAs. * Significance at p = 0.05 level.
Chapter 3. Memory replay during SWS manipulates the abstraction of regularities

Figure 3.4: Relationship between slow wave sleep (SWS) and behavioural performance in the auditory recall task. The SWS-replay (SWS-R) group showed no association between SWS and the overnight performance change. In the Control group the improvement in task performance from the immediate- to the delayed-recall session was significantly correlated with the amount of SWS obtained. The Pre-sleep-replay (PS-R) group showed a significant but negative association. Participants with a high proportion of SWS showed a decrease in performance from the immediate- to the delayed-recall session while participants with a low proportion of SWS showed an improvement.

3.4.6 Differences between groups in sleep structure

A MANOVA on the proportions spent in each sleep stage was used to investigate differences between groups in their sleep structure. The analysis showed no significant multivariate effect of group, $F(8,72) = 1.420, p = 0.203$. To assess more subtle differences between groups, univariate F-tests were examined for each variable. The results are presented in Table 3.1. These analyses revealed a significant effect for SWS, $F(2,38) = 4.049, p = 0.025$. This effect was driven by significantly more SWS in the PS-R group compared to the SWS-R group, $t(26) = 2.824, p = 0.009$, and a trend towards more SWS of the PS-R group compared to the control group, $t(25)= 1.775, p = 0.088$. Importantly, however, there was no difference between the SWS-R group and the control group, $t(25) = 1.008, p = 0.323$, which could have explained the difference in performance. Univariate analyses also revealed a marginal significant effect for stage 2 sleep, $F(2,38) = 2.919, p = 0.066$. This was driven by significantly more S2 in the SWS-R group compared to the PS-R group, $t(26) = 2.315, p = 0.029$, but again there was no difference between the other groups $t \leq 1.435, p \geq 0.164$. We further assessed with a MANOVA differences in the power spectral density of SWS, in slow oscillation, delta and spindle frequency bands of central and frontal electrodes (Table 3.2). The multivariate group effect was not significant, $F(12,68) = 1.094, p = 0.380$. Planned univariate F-tests on all dependent variables also showed no differences between groups, $F(2,38) \leq 2.049, p \geq 0.143$. 

73
Table 3.2: Power spectral density (\(\mu V^2/Hz\)) during slow wave sleep (SWS).

<table>
<thead>
<tr>
<th>Position</th>
<th>Frequency band</th>
<th>SWS-R group</th>
<th>Control group</th>
<th>PS-R group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>SO (0.3-1Hz)</td>
<td>988.7 ± 112.9</td>
<td>871.0 ± 101.3</td>
<td>1138.9 ± 127.8</td>
<td>0.28</td>
</tr>
<tr>
<td>Central</td>
<td>Delta (1-4Hz)</td>
<td>201.0 ± 24.6</td>
<td>227.8 ± 25.6</td>
<td>272.2 ± 36.7</td>
<td>0.24</td>
</tr>
<tr>
<td>Central</td>
<td>Sigma (12-15Hz)</td>
<td>2.5 ± 0.4</td>
<td>3.1 ± 0.5</td>
<td>3.1 ± 0.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Frontal</td>
<td>SO (0.3-1Hz)</td>
<td>1043.0 ± 103.6</td>
<td>952.3 ± 106.6</td>
<td>1276.3 ± 132.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Frontal</td>
<td>Delta (1-4Hz)</td>
<td>265.0 ± 34.4</td>
<td>301.1 ± 35.1</td>
<td>386.2 ± 65.6</td>
<td>0.20</td>
</tr>
<tr>
<td>Frontal</td>
<td>Sigma (12-15Hz)</td>
<td>2.6 ± 0.6</td>
<td>3.6 ± 0.6</td>
<td>3.5 ± 0.6</td>
<td>0.43</td>
</tr>
</tbody>
</table>

SO: Slow oscillations, SWS-R: SWS replay, PS-R: pre-sleep-replay. Data are means ± SE.

3.4.7 Differences between groups in sleep quality

As replay during sleep could potentially disrupt sleep and impair sleep quality, which might in turn explain the observed performance decrease in the SWS-R group, sleep quality was assessed with respect to awakenings, arousals and sleep stage transitions. The results are summarised in Table 3.3. A MANOVA was used to examine group differences. The multivariate effect of group was not significant, \(F(16,64) = 0.988, p = 0.480\). To assess more subtle differences between groups, univariate F-tests were examined for each variable (shown in Table 3.3), but none of the variables showed a significant effect, \(F \leq 1.858, p \geq 0.170\). Furthermore, mean occipital alpha power during nonREM sleep, which can be an indicator of arousal or brief awakenings (Rudoy et al., 2009), was assessed but did not differ between groups (SWS-R: 3.43 ± 0.42 (SE) \(\mu V^2/Hz\), PS-R: 3.74 ± 0.31 (SE) \(\mu V^2/Hz\), Control: 4.73 ± 0.55 (SE) \(\mu V^2/Hz\); \(F(2,38) = 2.313, p = 0.113\)).

Table 3.3: Overall sleep quality.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SWS-R group</th>
<th>Control group</th>
<th>PS-R group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time awake (min)</td>
<td>28.18 ± 4.21</td>
<td>33.12 ± 6.03</td>
<td>40.93 ± 10.72</td>
<td>0.49</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>94.31 ± 0.71</td>
<td>92.87 ± 1.33</td>
<td>91.64 ± 2.06</td>
<td>0.44</td>
</tr>
<tr>
<td>No. transitions</td>
<td>94.14 ± 8.02</td>
<td>100.85 ± 12.91</td>
<td>75.93 ± 6.94</td>
<td>0.17</td>
</tr>
<tr>
<td>Transition index</td>
<td>11.71 ± 1.00</td>
<td>12.92 ± 1.56</td>
<td>9.77 ± 0.90</td>
<td>0.17</td>
</tr>
<tr>
<td>No. awakenings</td>
<td>12.86 ± 1.73</td>
<td>17.23 ± 4.09</td>
<td>11.57 ± 1.47</td>
<td>0.30</td>
</tr>
<tr>
<td>Awakening index</td>
<td>1.67 ± 0.19</td>
<td>2.42 ± 0.59</td>
<td>1.63 ± 0.22</td>
<td>0.26</td>
</tr>
<tr>
<td>No. of arousals</td>
<td>81.14 ± 12.46</td>
<td>91.46 ± 8.18</td>
<td>76.86 ± 5.77</td>
<td>0.53</td>
</tr>
<tr>
<td>Arousal index</td>
<td>10.66 ± 1.79</td>
<td>12.72 ± 1.10</td>
<td>10.83 ± 0.79</td>
<td>0.48</td>
</tr>
</tbody>
</table>

SWS-R: SWS replay, PS-R: pre-sleep-replay, Index: number of events per hour of sleep, Sleep efficiency: Time awake/Sleep Period*100. Data are means ± SE.

Since the replay was presented during SWS and hence might have affected this sleep stage in particular, we examined sleep quality of SWS only. A MANOVA was used on the dependent variables: SWS transition index, SWS awakening index and SWS arousal index. Results are presented in Table 3.4. The multivariate group effect was not signifi-
Chapter 3. Memory replay during SWS manipulates the abstraction of regularities

cant, F(6,74) = 1.749, p = 0.122. Planned univariate F-tests revealed a significant group difference in the SWS arousal index, F(2,38) = 0.640, p = 0.039, driven by a marginal significantly higher arousal index for the Control group compared to the SWS-R group (t(25) = 2.004, p = 0.056) and the PS-R group (t = 2.013, p =0.055). The SWS arousal index did not differ between the SWS-R group and the PS-R group, t(26) = 0.191, p = 0.850. These results suggest that the sleep quality was not impaired by the replay.

Table 3.4: Sleep quality of slow wave sleep (SWS).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SWS-R group</th>
<th>Control group</th>
<th>PS-R group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWS transition index</td>
<td>0.35 ± 0.08</td>
<td>0.41 ± 0.10</td>
<td>0.22 ± 0.04</td>
<td>0.16</td>
</tr>
<tr>
<td>SWS awakening index</td>
<td>0.012 ± 0.004</td>
<td>0.010 ± 0.007</td>
<td>0.010 ± 0.004</td>
<td>0.96</td>
</tr>
<tr>
<td>SWS arousal index</td>
<td>0.054 ± 0.011</td>
<td>0.104 ± 0.025</td>
<td>0.053 ± 0.008</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

SWS-R: SWS replay, PS-R: pre-sleep-replay, SWS index: number of events during SWS divided by the total amount of SWS (in min). Data are means ± SE. *Significance at p = 0.05 level.

3.5 Discussion

In the current study we explored whether cued memory reactivation during SWS further enhanced the beneficial effect of sleep on the extraction of statistical regularities, a process thought to be involved in the formation of abstract semantic representations. Surprisingly, we found that the beneficial effect of sleep on abstraction was abolished when the probabilistic auditory sequence was replayed during SWS. While the overnight performance change in the detection of structured and unstructured auditory sequences was positively correlated with the amount of SWS in the control group, the group which received the reply during SWS, showed no such association and performance was impaired after sleep. This negative effect on task performance was specific to replay during SWS and not observed when the replay was presented during wakefulness. Importantly, sleep structure and sleep quality did not differ between the groups, indicating that the replay did not affect or disrupt the sleep itself, but may have interfered with the consolidation process. These results suggest that sleep-related mechanisms involved in the abstraction of statistical regularities were disrupted by presenting the probabilistic auditory sequence during SWS.

That sleep facilitates processes of abstraction and generalisation has been observed in a range of different tasks involving verbal concepts (Lau et al., 2011a), probabilistic rules (Djonlagic et al., 2009), number sequences (Wagner et al., 2004) and grammar-learning in infants (Gómez et al., 2006; Huber et al., 2008). The beneficial effect of sleep on the extraction of the auditory probabilistic sequence used in the current task was established by Durrant and colleagues (2011, 2013, submitted). They consistently reported that performance in this task improved after sleep and that the level of improvement was predicted by the amount of SWS obtained (Durrant et al., 2011, 2013, submitted). Although we did not observe an overall performance improvement across sleep, which may be explained by...
a lack of power due to our small sample size, we replicated the association between SWS and performance change in our control group. In line with the previous studies participants with a high proportion of SWS showed an improvement in performance across sleep, while participants with a low proportion of SWS showed an impairment. These findings support the hypothesis that processes during SWS mediate the abstraction of statistical regularities. The beneficial effect of sleep on memory stabilisation and reorganisation is thought to result from repeated, hippocampal-driven reactivation of memory traces during SWS (Buzsáki, 1996; Diekelmann & Born, 2010; Maquet et al., 2000; Rasch & Born, 2013; Wilson & McNaughton, 1994). Memory reactivations during SWS are assumed to occur within hippocampal sharp wave ripples (Axmacher et al., 2008; Buzsáki et al., 1992; Kudrimoti et al., 1999). The active systems consolidation model (Born et al., 2006; Diekelmann & Born, 2010), which is widely accepted, proposes that slow oscillations, which are a key feature of SWS, orchestrate the occurrence of sharp wave ripples (and hence memory reactivations) and thalamo-cortical spindles, which have been shown to provide brief windows of enhanced neocortical plasticity (Rosanova & Ulrich, 2005). This temporal synchrony between memory reactivation and increased neocortical receptivity is assumed to enable hippocampal-neocortical information exchange and a reorganisation of the memory traces that are reactivated (Rasch & Born, 2013; Sirota et al., 2003). Functional imaging results from Durrant et al. (2013) suggest that the underlying mechanisms of abstraction in the current task indeed involve a SWS-mediated reorganisation of the brain circuits that support memory. Specifically, this study demonstrated that the overnight performance change was associated with a gradual shift from the hippocampal to the striatal memory system and that this change in the underlying neural substrates was predicted by the amount of nocturnal SWS (Durrant et al., 2013). iOTA (‘Information Overlap to Abstract’) is a recent model, which offers a mechanism by which reactivation-induced memory reorganisation could result in the abstraction of regularities (Lewis & Durrant, 2011). Under this model, reactivation of experience-specific memories results in a selective strengthening of shared elements across the different memories. Therefore repeated reactivation of memories in different contexts and with slightly varying features progressively builds schematic representations of overlapping features and relationships between stimuli. Based on this theory our hypothesis for the current study was that cued reactivation would, by manipulating the occurrence of spontaneous reactivations (Oudiette & Paller, 2013), promote the abstraction process through a selective enhancement of the highly likely transitions. Surprisingly, however, we observed the opposite: cued reactivation impaired task performance for both auditory and visual versions of the task and abolished the association with SWS. These findings suggest that representing the probabilistic sequence during SWS interfered with the process of abstraction.

An ongoing debate in statistical learning concerns the nature of the memory representations used by participants to solve the task (Durrant et al., 2013; Perruchet & Pacton, 2006; Tunney & Altmann, 2001). The auditory recall task can be solved either by abstracting transition statistics (i.e. the probabilistic sequence) or by using episodic memory of concrete fragments of the exposure sequence (Durrant et al., 2013). The visual recall
task, however, can only be solved by applying knowledge about the probabilistic structure as the visual stimuli share no superficial characteristics with the auditory exposure stream, but only coincide with the underlying statistical pattern (Durrant et al., 2013, submitted). Importantly, findings by Durrant et al. (submitted) showed that solving the visual recall task required sleep. These results provide evidence that in the current task the abstraction of the underlying statistical pattern occurs during sleep (Durrant et al., submitted). Supporting the hypothesis that the replay interfered with the abstraction process, the replay-driven overnight impairment in performance was also reflected in the visual recall task. While participants of the control and pre-sleep replay group performed well above chance on this task, clearly demonstrating some knowledge of the statistical structure, performance of the SWS-replay group was at chance level. This suggests that the SWS-replay group had no knowledge of the statistical structure after sleep, possibly explaining their low performance in both recall tasks. Our findings suggest that the replay of the probabilistic sequence during SWS interfered with the abstraction of the underlying pattern. From our study no conclusion can be drawn in terms of the underlying mechanisms. A purely speculative explanation is that the probabilistic nature of the replay cue caused the interference. Supported by the finding that abstraction of the transition probabilities only emerges over sleep (Durrant et al., submitted), it has been suggested that during initial encoding small episodic (concrete) fragments of the auditory sequence are stored in hippocampal-dependent representations (Durrant et al., 2013, submitted). According to the iOtA model, the extraction of the most likely transitions (i.e. the perfect sequence) would emerge from the dominating overlap of these transitions during spontaneous memory reactivation. As we used the probabilistic sequence as memory cue during SWS, which is highly variable, the cue and the stored memory representations of the concrete fragments did not perfectly overlap. Therefore the spontaneous reactivation of the concrete fragments might have been disrupted through the presentation of the partially overlapping memory cue. This could explain the impaired performance and lack of association with SWS. Even though this is speculative, it raises important questions about the nature of cued memory reactivation. So far in all studies that successfully applied cued memory reactivation to enhance the sleep benefit on memory stabilisation, only ‘absolute’ stimuli that did not vary were used. Cousins et al. (2014) for example used a fixed (not probabilistically-determined) auditory sequence as memory cue during SWS and reported enhanced sequence knowledge after sleep. Therefore the question arises whether partially overlapping memory cues might have the potential to disrupt the beneficial effect of sleep on memory reorganisation. Further studies are needed to address this question.

The comparable performance between the pre-sleep replay group and the control group suggests that the negative effect of the replay on task performance was specific to replay during sleep. Surprisingly, however, the replay during wakefulness also had an interfering effect and reversed the association with SWS. Participants with a low proportion of SWS showed an overnight improvement in performance while participants with a high proportion of SWS got worse. These results may indicate that SWS in this group was associated with the consolidation of the wrong thing, such as for example unnecessary details like
low probability transitions. As participants in this group received with the replay another presentation round of the exposure stream after the test phase it is likely that they perceived the exposure stream differently and focused on other aspects compared to the initial encoding. Why this causes impairment, remains unclear. Interestingly, the pre-sleep replay group also showed a slight difference in the sleep structure with a higher proportion of SWS than the two other groups, which might suggest that some different processing occurred in this group. Importantly however, participants performed well above chance in the visual recall task and showed unlike the group who received the replay during SWS, no impairment in the auditory recall task, indicating that this group had abstracted the underlying statistical structure. Therefore the interference with the abstraction of the underlying statistical structure was specific to the replay during SWS.

A clear limitation of the current study is the between-subject design. The observed negative effect of the replay on task performance could also be explained by a mechanical disruption of sleep, independent of the memory cue itself. A disruption of SWS through the auditory cues for example might also disrupt SWS-mediated consolidation processes. This explanation, however, is unlikely to explain the current findings since superficial features of SWS, such as SWS amount, spectral power of frequency bands that are dominant during SWS and SWS quality measures did not differ between the SWS-replay group and the control group. Another possibility is that the replay caused a general impairment of sleep quality, resulting in a less restorative function of sleep and increased tiredness, which could theoretically explain the impaired performance of the replay group. However, comparable sleep quality and alertness measures between all groups, suggest that it is highly unlikely that the replay impaired sleep quality and that the differences in performance were due to differences in alertness. Overall, our findings suggest that the replay-related impairment was caused through a specific interference with the consolidation process and not through a mechanical disruption of sleep. But even though we tried to rule out mechanical disruption as possible explanation, we cannot completely be exclude it.

In conclusion, the current results suggest that representing the probabilistic auditory sequence during SWS interfered with the abstraction process and therefore impaired subsequent performance in both auditory and visual recall tasks. These findings raise important questions about the scope and the underlying mechanisms of cued memory reactivation, which need to be addressed in future studies.

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Chapter 4

Sleep spindles mark hippocampal to neocortical consolidation of schema-related memories

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4.1 Abstract

Information that relates to prior knowledge is memorised better than information that does not relate to a pre-existing schema. Recent research has started to unravel the underlying neural mechanisms of this schema effect. One key process seems to be accelerated memory consolidation, as schema-related memories can be assimilated into neocortical networks more quickly. Whether sleep plays a role in this schema-dependent consolidation process is unknown. To address this question the current study investigated whether differences in the consolidation of schema-related and unrelated memories were associated with sleep. Participants established a schema over several days before new facts that were either related to the schema or completely unrelated were memorised. This encoding was undertaken in two sessions separated by 24 h, including a night of sleep. Memory performance on the newly-learned facts was tested directly after the second encoding. We used functional magnetic resonance imaging (fMRI) during the recall to assess differences in brain activity related to consolidation and schema-linkage. Our behavioural results showed that the beneficial effect of schemas on memory increased across the 24 h consolidation period, driven by a protection of schema-related memories against decay. The increase in the schema effect was predicted by spindle density. We also found that higher spindle densities were associated with decreased hippocampal engagement across time, specifically for schema-related memories. These results suggest that the rate of sleep spindles marks the process of assimilating new information into existing long-term memory.

Keywords: Schema, prior knowledge, sleep, spindles, and memory consolidation

4.2 Introduction

The assimilation of new information into existing knowledge is a fundamental component of the formation of long-term memory. Recent evidence from research in rodents, humans and computational modelling suggests that the degree to which new information relates to a pre-existing schema influences this consolidation process (McClelland, 2013; Tse et al., 2007; van Kesteren et al., 2013a). Schemas refer to coherent frameworks of knowledge and are thought to interact with incoming information at different stages of the mnemonic processing, such as acquisition, consolidation and retrieval (Bartlett, 1932; Bransford & Johnson, 1972; Brewer & Nakamura, 1984; Minsky, 1974; Rumelhart, 1980). A striking phenomenon of schemas, known as the schema effect (van Kesteren et al., 2013b), is their beneficial effect on memory: new information that links coherently into a schema is memorised better than information that does not relate to any present schema (Bartlett, 1932; Bransford & Johnson, 1972; Brent, 1969; Brewer & Nakamura, 1984; Chase & Simon, 1973; Johnson, 1970; Mandler & Johnson, 1977; van Kesteren et al., 2012, 2013a, 2014). Tse et al. (2007) suggested that one mechanism underlying this schema effect is accelerated memory consolidation. This hypothesis was based on findings in rodents, which showed that in the presence of an associative schema, newly formed memories became independent of the hippocampus more quickly and were retained for a longer period of time (Tse et al., 2007,
During memory consolidation the hippocampus is thought to promote a gradual incorporation of newly acquired information into long-term memory by binding, reactivating and strengthening distributed cortical-cortical connections (Frankland & Bontempi, 2005; McClelland et al., 1995). In order to prevent interference with existing neocortical knowledge structures memory consolidation is usually thought to be a very slow and gradual process (McClelland et al., 1995). However, recent evidence from research in rodents and computational modelling suggests that if the newly acquired information is consistent with existing neocortical representations, it can be rapidly assimilated (McClelland, 2013; Tse et al., 2011). Taken together, these findings suggest that in the presence of an associative schema new information can be rapidly incorporated into the neocortex and hippocampal independence is accelerated (McClelland, 2013; Tse et al., 2011; van Kesteren et al., 2012).

Another aspect which plays an important role in memory consolidation is sleep (Diekelmann & Born, 2010). Sleep has been shown to promote various aspects of memory consolidation including the strengthening and reorganisation of memories traces (Diekelmann & Born, 2010; Frankland & Bontempi, 2005; Rasch & Born, 2013; Stickgold & Walker, 2013). During sleep, slow oscillations synchronise neocortical activity with the occurrence of sleep spindles, which are thought to induce plasticity in the neocortex (Rosanova & Ulrich, 2005), and hippocampal sharp wave ripples (SWR), which have been linked to memory reactivation (Mölle et al., 2006; Siapas & Wilson, 1998; Siroti et al., 2003; Steriade & Timofeev, 2003). Due to this orchestrating function of slow oscillations, sleep seems to provide ideal conditions for the hippocampal-neocortical dialogue that underlies memory consolidation (Buzsáki, 1996; Hasselmo, 1999). Furthermore, sleep has been implicated in the process whereby new memories become part of existing knowledge structures. Results from Tamminen et al. (2010, 2013) suggested that sleep spindles, in particular, are associated with the integration of new information with existing knowledge. Together, these findings raise the question of how sleep, and specifically sleep spindles, might be related to the accelerated consolidation of memories that link into a schema. The aim of the present study was to explore the role of sleep for memory consolidation in the context of the schema effect. We addressed this question using a paradigm in which participants first established a schema and then memorised new information that was either related to the schema (schema-related facts) or completely unrelated (non-schema facts). We were interested in differences between the schema-related memories and the non-schema memories that evolved across time.

Participants established a schema by learning information about arthropods (schema A) or cells (schema B) over six separate sessions. In two subsequent encoding sessions, which were spaced by 24 h, participants memorised schema-related and non-schema facts. During the night between the two encoding sessions sleep was monitored with polysomnography (PSG). Directly after the second encoding session, participants were tested in a recall task on how well they remembered the newly learned facts. The recall task took place inside a magnetic resonance imaging (MRI) scanner. A schematic illustration of the procedure is shown in Figure 4.1. This design allowed us: i) to compare recent versus remote memory
with respect to consolidation, as the difference between these two conditions served as approximation for the overnight change in memory; ii) to compare the difference between schema-related and non-schema memory, which served as a measure for the schema effect; iii) to explore how the schema effect changed across consolidation, which was approximated by the difference in the schema effect between the recent and the remote condition; and, iv) to assess whether an overnight change in the schema effect was associated with certain sleep physiological features.

Figure 4.1: Experimental design. Participants were randomly assigned to schema A or schema B. Sessions one to six, spaced across two weeks, comprised the schema learning. In two encoding sessions, spaced by 24 h, participants memorised new schema-related (S) and non-schema (NS) facts. Sleep was monitored in the night between the two encoding sessions with polysomnography (PSG). The recall took place inside an MRI scanner immediately after the second encoding.

4.3 Results

The behavioural results are presented in Figure 4.2. As expected, memory performance was better for schema-related than for non-schema facts, $F(19) = 46.47, p < 0.001$, indicating that the schema manipulation was successful. Importantly, we found a significant interaction, with the schema effect being greater for the remote than the recent condition, $F(19) = 5.24, p = 0.034$, suggesting that the schema effect increased across consolidation. A multiple regression analysis was conducted to determine whether sleep parameters predicted this increase in the schema effect from the recent to the remote condition. The overall regression model with the explanatory variables: total sleep time, stage 1, rapid-eye-movement sleep, slow wave sleep (SWS), stage 2 sleep spindle density, was significant, $F(5,13) = 5.627, p = 0.006$ and predicted 56.2% of the variance in the interaction scores (adjusted $R^2; R = 0.83$). The main factors influencing the overnight change of the schema effect were spindle density ($t = 4.114, p = 0.001$) and SWS ($t = -3.049, p = 0.009$). No other variable was significant ($t \leq 1.573, p \geq 0.140$). Further analyses revealed that while SWS only showed a trend for a correlation with the interaction score ($r(19) = -0.423, p = 0.071$), the spindle density was strongly correlated with the interaction score ($r(19) = 0.603, p = 0.006$), with higher spindle densities associated with greater increases in the schema effect across consolidation as shown in Figure 4.2B. To explore what was driving this correlation we conducted a median split analysis based on the spindle density (Figure 4.2D). Interestingly, we found a significant 3-way (time x schema x spindle group) interaction, $F(17) = 22.124, p < 0.001$. For the non-schema condition there was no difference in the overnight change (recent - remote) in the proportion of correctly remember
facts, between high and low spindle density group, F(17) = 0.693, p = 0.417. For the schema-related facts, however, this difference was significant, F(17) = 20.510, p < 0.001, suggesting that spindle density is a marker for the retention of schema-related memories. Furthermore, the low spindle group showed a significant decrease in the number of correctly remembered items from the recent to the remote condition, t(9) = -7.468, p < 0.001 (mean remote: 1.08 ± 0.05 (SE), mean recent: 1.28 ± 0.05 (SE)), while performance in the high spindle group was roughly constant across time, t(8) = 0.592, p = 0.570 (mean remote: 1.17 ± 0.04 (SE), mean recent: 1.141 ± 0.04 (SE)). Overall, the results of the median split analysis suggest that the greater schema effect of the remote condition compared to the recent condition was driven by the fact that memory for schema-related items decayed very little in participants with high spindle densities.

![Figure 4.2: Behavioural results.](image)

A) The proportion of correctly remembered facts for the schema group and the control group. For the schema group, there was a clear schema benefit that was greater for the remotely than the recently encoded facts. B) This increase in the schema effect across consolidation, which was measured by the interaction score, was predicted by the stage 2 spindle density. C) The difference in memory performance between the recent and the remote conditions for the schema group and the control group. While the schema group showed significantly less decay of schema-related memories than non-schema memories, the control group exhibited an equivalent decay rate for strongly and weakly encoded items. This suggests that the schema manipulation, and not the difference in encoding strength between the schema-related and non-schema memories, was driving the increase in the schema effect over time in the schema group. D) Results of the median split analysis on the spindle densities of the schema group. For the non-schema condition there was no difference in the overnight change in memory performance between the low and the high spindle density group. For the schema-related condition, the high spindle density group showed no overnight memory change, while the low spindle group showed significant memory decay, indicating that the reduced decay of schema-related items was associated with participants who had high spindle densities. Data are presented as Mean ± SE. Statistical analyses were performed on the arcsine-transformed proportion of correctly remembered facts. Low Sp.: Low spindle density group; High Sp.: High spindle density group. ***p < 0.001, **p < 0.01, *p < 0.05, n.s. p > 0.1.

Functionally, we first assessed differences in hippocampal activity during the recollection
of recently and remotely encoded facts \textit{[recent > remote]}. We observed a cluster in the right hippocampus, shown in Figure 4.3A (peak: [34 -18, -12], cluster size: 93 voxels; see supplemental material (SM) Table 4.4 for details). Within this hippocampal cluster, beta estimates revealed that the overnight change in activity did not differ between schema-related and non-schema memories, \(t(19) = 0.016, p = 0.99\) (Figure 4.3B).

To assess whether other regions of the hippocampus showed differences in the overnight activation change between the schema-related and the non-schema condition, we examined the interaction between the factors schema and time \(\text{NS(recent > remote) > S(recent > remote)}\). However, no significant effects were observed within our region of interest (see SM Table 4.5 for details). As the behavioural results suggested a role for sleep spindles in the retention of schema-related memories, we explored whether spindle density was associated with the observed decrease in hippocampal engagement across consolidation. Separately for the schema-related and the non-schema condition, we examined correlations between spindle density and the parameter estimates for the overnight change in activity within the identified hippocampal cluster. Interestingly, sleep spindles predicted an
overnight change for the schema-related condition (Figure 4.3C), \( r(19) = 0.692, p = 0.001 \), but not for the non-schema condition, \( r(19) = 0.321, p = 0.180 \), at a Bonferroni-corrected \( \alpha \)-level of 0.025. These findings suggest that spindles may be specifically associated with the consolidation of schema-related memories.

In the behavioural analysis we found that the rate of sleep spindles predicted how the schema effect changed across consolidation. To investigate the underlying neural substrates of this effect we examined brain regions in which spindles predicted differences in the overnight activity change between the schema-related and the non-schema condition. Specifically, we included the stage 2 spindle density as covariate into a whole brain fMRI analysis of the interaction contrast \([S(\text{recent} > \text{remote}) > NS(\text{recent} > \text{remote})]\). Interestingly, this showed that spindle density mediated activity in a bilateral posterior hippocampal cluster (Right peak MNI coordinates: \([34 -26, -10]\), cluster size: 96 voxels; Left peak MNI coordinates: \([-28 -42 4]\), cluster size: 170 voxels, see SM Table 4.6 for more details). Thus, in this region of the hippocampus, the difference in the overnight change in activity between the schema-related and the non-schema condition was predicted by the rate of sleep spindles. Higher spindle densities were associated with a greater change in hippocampal activity for the schema-related condition than the non-schema condition, while low spindle densities predicted the opposite. Notably, while the cluster in the right hemisphere, including the peak, clearly fell within the hippocampus, a large proportion of the left cluster, including the peak, fell in the ventricle. We will focus, therefore, in subsequent analyses on the right hemispheric cluster (Figure 4.4A). Equivalent analyses and results for the left hemispheric cluster are reported in the SM 5.1. To determine whether the relationship between spindles and the activity of the interaction contrast was driven by one of the two conditions (S or NS), we examined correlations between spindle density and the parameter estimates for the \([\text{recent} > \text{remote}]\) - contrast, separately for the schema-related and the non-schema condition (Figure 4.4C/D). For schema-related facts, the spindle density was strongly associated with the overnight change in hippocampal activity, \( r(19) = -0.715, p = 0.001 \). Participants with higher spindle densities showed a greater overnight decrease in hippocampal involvement than participants with lower spindle densities. For non-schema facts there was no such association, \( r(19) = 0.204, p = 0.402 \). The difference in strength between the two correlations was marginally significant, \( t(16) = 2.014, p = 0.061 \) (assessed by the Hotelling/Williams test). In parallel to our behavioural analysis, a median split analysis, in which participants were divided based on their spindles into a low and a high spindle density group, was conducted on the parameter estimates of this hippocampal cluster (Figure 4.4B). While there was a clear difference in the overnight change in hippocampal activity between the low and the high spindle group for the schema-related condition, \( t(17) = 4.351, p < 0.001 \), no difference was observed for the non-schema condition, \( t(17) = 0.072, p = 0.94 \). The interaction between the conditions was significant, \( p < 0.01 \). As an additional confirmation that the relationship between spindles and the interaction in hippocampal activity between schema and time was driven by the schema-related condition, we calculated separate linear t-contrasts of the overnight change \([\text{recent} > \text{remote}]\) at the first level for schema-related facts and non-schema facts. The resulting contrast images were carried forward to second-level one sample t-tests, in
which stage 2 sleep spindle density was included as covariate. Because this analysis served to confirm the association between spindles and the overnight activation change of the right hippocampus cluster, a hippocampal mask for the right hemisphere was applied. For the non-schema condition no significant activation was found. For the schema-related condition a cluster (48 voxels), which overlapped by 21 voxels with the cluster identified in the interaction contrast, was observed (see SM 5.2 for details), suggesting that higher spindle densities predict decreased hippocampal engagement across consolidation for the schema-related items only.

Finally, we observed a three-way correlation between spindles, behaviour and hippocampal activation in the right hippocampal peak (MNI coordinates: [34 -26 -10]). The parameter estimates of this peak, in which spindles predicted the difference in the overnight activation change between the schema-related and the non-schema condition, also correlated with the behavioural interaction score, $r(20) = -0.571$, $p = 0.009$. Thus, participants with higher spindle densities who showed less forgetting of schema-related facts compared to non-schema facts also showed a greater overnight change in hippocampal activity for schema-related facts compared to non-schema facts. Overall, these results suggest that the rate of
stage 2 spindles marks the difference in the consolidation between schema-related and non-schema memories. A higher rate of spindles predicts a better retention of schema-related memories and decreased hippocampal involvement across consolidation.

Control group

Since the behavioural schema advantage was present immediately after encoding, the overnight increase in the schema effect could potentially be due to differences in encoding strength independent of the schema manipulation. To control for this possible confound, we tested an additional group (n=20), in which all facts were learned in the non-schema condition only and memory performance was matched to the performance of the original schema group on the recently encoded schema-related and non-schema facts. Thus the differences in memory performance of the recent condition of the schema group were intentionally mimicked in this control group by modulating encoding strength independently of a schema. Participants of this group performed two encoding sessions, separated by 24 h, in which they memorised the same facts as the original schema group but without prior schema knowledge. To create the necessary differences in encoding strength, one half of the facts was encoded more than twice as many times (9x) as the other half (4x). The same recall task that was used for the schema group was administered (without fMRI), directly after the second encoding session. Detailed information about the control group and the procedure is provided in the SM 6. The results are presented in Figure 4.2. A 2x2 mixed measures ANOVA, with factors Group (levels: schema, control) and Encoding Strength (Levels: strongly encoding, weakly encoding; note that in the schema group these levels refer to the schema-related and non-schema condition) revealed that memory performance in the recent condition did not differ between the two groups, $F(1,38) = 0.436, p = 0.513$. The same ANOVA was applied to the remote condition. Here we observed a significant difference between groups, $F(1,38) = 6.464, p = 0.015$, and critically a significant interaction, $F(1,38) = 5.535, p = 0.024$. This interaction was driven by lower performance of the control group compared to the schema group on strongly encoded facts, $t(38) = 3.639, p = 0.001$. Performance on weakly encoded facts did not differ between schema and control group, $t(38) = 1.073, p = 0.290$. These results suggest that encoding strength alone was not driving the observed differences in the overnight change between the schema-related and the non-schema condition. Instead, the performance difference was specific to the schema manipulation, which seemed to have led to a protection of the schema-related memories against forgetting. To assess whether the association between spindles and the change in the schema effect was specific to the schema manipulation or driven by differences in encoding strength, we conducted a regression analysis with the same explanatory variables as for the schema group, for this control group. The regression model was not significant, $F(5,14) = 0.830, p = 0.549$, and none of the variables had a significant contribution, $t \leq 1.7, p \geq 0.1$. We also explored whether stage 2 sleep spindle densities correlated with the behavioural interaction score but the correlation was not significant, $r(20) = -0.064, p = 0.790$. Moreover, the correlations between spindle densities and behavioural interaction scores were significantly stronger in the schema compared to the control group, $z(38) = 2.217, p = 0.027$. This suggests that the association between spindles and the overnight
change of the schema effect was specific to the schema manipulation.

4.4 Discussion

In the current study we explored whether sleep was associated with differences in the consolidation between schema-related and non-schema memories. We found that the rate of sleep spindles predicted an overnight increase in the schema effect, driven by a protection of the schema-related memories against decay. Our results further showed that higher spindle densities were associated with reduced hippocampal engagement across time, specifically for schema-related memories. These results suggest that the rate of sleep spindles marks schema-dependent neocortical consolidation, possibly through a role in the integration of new information with a pre-existing schema.

Only recently has research started to investigate the neural mechanisms behind the beneficial effect of schemas on memory, or in short the schema effect. Tse et al. (2007) demonstrated, using a flavour-place associations task in rodents, that the consolidation of new information into schemas engaged a rapid consolidation process such that, after a very short time period (< 48 hours), the integrity of the hippocampus was already unnecessary for memory retrieval. In two subsequent studies they showed that schema-dependent rapid hippocampal disengagement was accompanied by increasing involvement of the neocortex (Tse et al., 2011; Wang et al., 2012). These findings challenged the long-standing view, based on the complementary learning systems theory (CLS), that the rapid integration of new information into neocortical structures is avoided to prevent catastrophic interference with structured knowledge representations (McClelland et al., 1995). However, new simulations extending those reported in McClelland et al. (1995) and inspired by the findings of Tse et al. (2007, 2011), demonstrated that new information that is consistent with existing neocortical knowledge structures can indeed be learned rapidly and without interference (McClelland, 2013). In a sequence of human fMRI studies, van Kesteren et al. (2010a, 2013a, 2014) demonstrated that differences in the underlying neural substrates were already present during memory encoding. Encoding schema-related information was associated with increased medial prefrontal cortex activity (van Kesteren et al., 2010a, 2013a, 2014) and decreased medial temporal lobe activity (van Kesteren et al., 2014) compared to the encoding of unrelated and inconsistent information. Van Kesteren and colleagues suggested that this schema-dependent shift in the contribution of neocortex and hippocampus during encoding initiates differences in the subsequent consolidation mechanisms (van Kesteren et al., 2012, 2013b). Together these findings provide strong evidence that schemas act as catalysts for memory consolidation by accelerating the shift in the representational division of labour in favour of neocortical over hippocampal regions (McClelland, 2013; Tse et al., 2007; van Kesteren et al., 2012).

Until the present study, how sleep-dependent memory consolidation links into this process, however, was completely unknown. The results from the current investigation suggest that the rate of sleep spindles marks the superior retention of schema-related memories over
non-schema memories. These human findings build on the rodent results from Tse et al. (2007) by demonstrating that sleep spindles are associated with the augmented overnight consolidation of schema-related memories. Sleep spindles have been linked with declarative memory consolidation in a range of studies (Rasch & Born, 2013). Spindle activity has been found to correlate positively with memory performance after sleep (Clemens et al., 2005; Gais et al., 2002; Schabus et al., 2004), increases in spindle densities have been observed after learning (Gais et al., 2002; Schmidt et al., 2006), and a pharmacologically-induced increase in spindle density has been associated with enhanced declarative memory performance (Mednick et al., 2013). Importantly, sleep spindles have also been implicated in the integration of new information with existing knowledge (Tamminen et al., 2010, 2013). Using lexical competition as measure for integration Tamminen et al. (2010) demonstrated that participants with higher spindle densities showed larger overnight increases in the lexical competition effect, reflecting enhanced integration, which is in line with the findings of the current study.

Functionally we observed that sleep spindles predicted an overnight reduction in hippocampal engagement, specifically for schema-related memories. Thus, the high spindle densities seem to be a marker of more efficient neocortical consolidation and less hippocampal dependence after sleep (i.e., consistent with McClelland’s complementary learning systems model, in which there is a greater shift in the division of labour for schema-related new information). What might the role be of sleep spindles in the integration of new information into existing neocortical knowledge structures? One hypothesis is that spindles trigger neural plasticity in the neocortex (Rosanova & Ulrich, 2005; Timofeev et al., 2002). For example, Rosanova and Ulrich (2005) demonstrated that the natural firing pattern recorded in an anaesthetized cat during sleep spindles was able to induce long-term potentiation at excitatory connections in pyramidal cells in vitro. These epochs of heightened plasticity, induced by spindles, tend to occur in close temporal correlation with hippocampal SWR, (Clemens et al., 2007; Siapas & Wilson, 1998; Sirotta et al., 2003). SWR are linked to the reactivation of memories and are thought to play a crucial role in memory consolidation (Buzsaki, 1989; ?; Girardeau et al., 2009; Lee & Wilson, 2002; Ramadan et al., 2009; Wilson & McNaughton, 1994). The coupling of these network events is an effective way to link neocortical and hippocampal cell assemblies (Sirotta et al., 2003) and seems to provide ideal conditions for a coordinated hippocampal-neocortical information exchange (Siapas & Wilson, 1998; Sirotta et al., 2003). These proposed mechanisms for spindle activity could provide the basis for the integration of newly encoded hippocampal-dependent memories into existing neocortical networks. If new information is consistent with existing neocortical representations, it is assimilated more efficiently (McClelland, 2013) and therefore might benefit more from the proposed integrative function of spindles, as observed in the current study. In short, spindle activity might mark hippocampal-to-neocortical consolidation, in general (cf. Tamminen et al., 2010) and thus information that is more readily assimilated into existing knowledge (i.e., schema-consistent) might be more strongly indexed by spindle rates. Thus participants who showed an increase in the schema effect across consolidation (i.e., they had a better retention of schema-related than non-schema memories), assimilated schema-related memories more efficiently into the neocortex, which
was reflected in higher spindle densities. Consistent with this hypothesis, besides the correlation between spindles and the hippocampal activity of the interaction, we also observed a correlation between brain activity and the behavioural interaction score. Participants with high spindle densities who exhibited less forgetting of schema-related compared to non-schema memories (i.e. a greater interaction score) also showed a greater overnight reduction in hippocampal activity for the schema-related compared to the non-schema memories. Thus spindle-correlated neocortical consolidation of new information is accompanied by a concomitant reduction in hippocampal support.

In conclusion, the current study provided first evidence for a potential role of sleep spindles in the consolidation of schema-related memories. Due the nature of our study we cannot attribute a causal role to spindles in this process, but the rate of sleep spindles clearly correlates with the process of assimilating new information into existing long-term memory structures.

4.5 Methods

4.5.1 Participants

Twenty two native English students (mean age: 21.55, SD: 2.61, 6 males, randomly assigned to one of the two schemas) participated in this study. All had normal or corrected-to-normal vision, no hearing problems, and no history of neurological, psychiatric or sleep disorders. Participants had a regular sleep-wake cycle for at least four weeks preceding the study and were required to have no post-GSCE knowledge or special interest in biology, medicine, chemistry and zoology. Informed consent was obtained from all participants prior to the study, approved by the University of Manchester Research Ethics Committee. Two participants had to be excluded due to technical problems during the encoding. Therefore 20 individuals were included in the analysis.

4.5.2 Stimuli

Two schemas were created. Schema A contained information about arthropods and schema B contained information about cells. Each schema had a hierarchical structure and consisted of two sub-categories (Schema A: ants and crabs; Schema B: cell types and organelles), each containing six individual category members. The schema comprised detailed information about the characteristics of these 12 category members. For each category member we also created six new facts, which were not part of the schema but related to information in the schema (schema-related facts). These facts served as new information that was learned in the encoding sessions. Each fact consisted of two similar versions: one was used for the encoding and the other served as false choice for the recall. The facts that were used as schema-related facts for participants who learned schema A, served as unrelated (non-schema) facts for participants who learned schema B and vice versa. More specific information regarding schemas and facts can be found in the SM.
4.5.3 Procedure

A schematic illustration of the procedure is shown in Figure 4.1. Before the study began participants completed a pre-test related to the assigned schema to assure that prior knowledge did not interfere with the study. The actual experiment consisted of two parts. The first part served the schema learning and was subdivided into six sessions, which were spaced across approximately two weeks. In these sessions participants learned information about the schema-category. This involved a range of different tasks such as reading texts, picture naming or multiple choice questions. After successful establishment of the schema participants completed the second part of the experiment which involved the learning of new facts that were either related to the schema (schema-related facts) or completely unrelated (non-schema facts). This part comprised two encoding sessions and a recall session, which took place inside an MRI scanner. On the day following the last schema learning session participants completed the first encoding session. A second encoding session followed 24 h (± 1.5 h) later. In both sessions 72 new facts (36 schema-related and 36 non-schema facts) were presented in pseudorandom order and participants were instructed to memorise them. All facts were shown four times. In the night between the two encoding sessions participants slept in the Sleep Research Laboratory at the University of Manchester, where they were monitored with PSG. Immediately after the second encoding, participants were placed in a 3 Tesla MRI scanner where they undertook the recall, in which all 144 facts were tested. In the recall task each fact was presented together with its false choice and the participant selected the correct answer within the 6 s presentation time by pressing the corresponding button on a button box. A 'Don’t know' option was provided to avoid guessing. More specific information regarding the procedure, the tasks and the equipment used can be found in the SM.

4.5.4 PSG data acquisition and analysis

Polysomnographic monitoring was carried out using an Embla® N7000 sleep monitoring system, with Ag-AgCl electrodes attached using EC2® electrogel after the scalp was first prepared with NuPrep® exfoliating agent. Scalp electrodes were attached at six standard locations using the 10-20 system, C3, C4, F3, F4, O1, and O2, each referenced to the contralateral mastoid (M1 and M2). Left and right electrooculogram, left, right, and upper electromyogram, and a ground electrode were also attached. All electrodes were verified to have a connection impedance of less than 5 kΩ. All signals were digitally sampled at a rate of 200 Hz. Sleep structure was analysed using RemLogic® 1.1 software. Sleep data were organized into 30 s epochs, bandpass filtered between 0.3 and 35 Hz to remove low-frequency drift and high-frequency noise, and visually scored independently by two experienced sleep researchers according to the standardised sleep scoring criteria of Rechtschaffen and Kales (1968). The proportion of time spent in each sleep stage and the overall sleep duration were calculated (Results are reported in the SM 4.3). The spindle analysis involved artefact-rejected, stage 2 non-rapid-eye movement (nonREM) sleep. Raw EEG data were band-pass filtered (12-15 Hz) using a linear finite impulse response filter. Automated detection (Ferrarelli et al., 2007) derived the number of discrete
spindle events: for each channel, amplitude fluctuations in the filtered time series exceeding a predetermined threshold counted as spindles. Thresholds were calculated relative to the mean channel amplitude (eight times the average amplitude). This algorithm is similar to others and has been widely used (e.g. Tamminen et al., 2013). Reported results are averaged across channels (individual channel results and the division into fast and slow spindles are provided in the SM 4.5). We focused in our analysis on stage 2 sleep spindles (results for SWS spindles are reported in the SM 7.) as previous research has shown that during stage 2 sleep and associated with the appearance of stage 2 spindles there is increased connectivity between the hippocampus and the neocortex (Andrade et al., 2011), providing ideal conditions for hippocampal-neocortical dialogue, which is assumed to underlie sleep-dependent memory consolidation and plays a crucial role in the integration of new memories into a schema (Genzel et al., 2014; van Kesteren et al., 2010a). Furthermore, Tamminen et al. (2010) demonstrated that nonREM spindles, but in particular stage 2 spindles, were associated with the magnitude of a lexical competition effect, which served as measure for the integration of newly learned information with existing knowledge. Overall, these findings suggest that stage 2 spindles, in particular, might be linked to schema-dependent consolidation.

4.5.5 Statistical analyses

A factorial design with factors schema (schema-related, non-schema) and time (recent, remote) was used, which allowed us to compare memory performance across four conditions: schema-related (S) remote, non-schema (NS) remote, schema-related recent and non-schema recent. Behavioural performance was assessed by calculating the proportion of trials in which the learned fact was correctly identified. Proportions were arcsine-transformed for analyses to better meet the assumption of normality (Judd et al., 2009). We were interested in the performance difference between the schema-related and the non-schema condition, which served as a measure for the size of the schema effect, and how this changed across time [recent - remote]. This was assessed using a 2x2 repeated measures ANOVA, with factors schema and time. Reaction times were recorded as a secondary measure and results are provided in the SM 4.2. To investigate whether sleep physiological aspects explained the increase of schema effect across time, which was measured by the behavioural interaction score [Remote(S-NS) - Recent(S-NS)], we conducted a simultaneous regression analysis with the following explanatory variables: total sleep time (TST, in min), REM sleep (% of TST), Stage 1 sleep (% of TST), SWS (% of TST), Stage 2 spindle density (number of spindles per min), and the behavioural interaction score as dependent variable. Multicollinearity was assessed according to the variance inflation factor (VIF); as stage 2 sleep was correlated with SWS and REM sleep it was not included in the regression model (see SM 4.4 for details). The remaining predictor variables were found to be not collinear. The association between the schema effect and the stage 2 spindle density was further explored by a median split analysis, in which participants were divided into two groups based on their spindle density (see SM 4.6 for more information). A 2x2x2 repeated measures ANOVA, with factors schema, time and spindle group (levels: high spindle group, low spindle group) was used to assess whether the overnight change of the
Chapter 4. Spindles mark hippocampal to neocortical consolidation of schema-related memories

The schema effect differed between participants with high spindle densities from those with lower spindle densities. In all our results we considered $p < 0.05$ as significant and all tests were two-tailed. For post-hoc tests Bonferroni corrections were applied.

4.5.6 fMRI data acquisition and analysis

Functional MRI time series data were acquired using a 3T Allegra MR scanner (Siemens) with an 8-channel head coil. Blood oxygen level dependent signal was recorded using T2*-weighted fMRI images obtained with a gradient echo-planar sequence. Fifty oblique transaxial slices tilted at $15^\circ$ were acquired in an ascending sequence with a voxel size of $3 \times 3 \times 2.8 \text{ mm}^3$ including an interslice gap of 40%, matrix size of $64 \times 64$, time repetition (TR) of 2960 ms, time echo (TE) of 30 ms, and flip angle of $80^\circ$. Functional imaging data were processed using the Statistical Parametric Mapping 8 software (SPM8; Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm). Functional images were realigned to correct for motion artefacts and corrected for slice acquisition time differences. Images were then transformed into standard stereotaxic space, corresponding to the Montreal Neurological Institute (MNI) canonical brain. This was accomplished by registering the mean EPI volume (acquired during realignment) to SPMS’s EPI template and applying the subsequent transform to all image volumes. Finally, a spherical Gaussian smoothing kernel with a full width half-maximum of 8 mm was applied to the normalised data of each participant. Data analysis was conducted with a two level, random effects general linear model (Friston et al., 1995). At the first level, the design matrix contained five regressors. These were the four different memory conditions, schema-related remote (S-remote), non-schema remote (NS-remote), schema-related recent (S-recent), non-schema recent (NS-recent), and button presses. Each regressor was convolved with a canonical haemodynamic response function. Movement parameters were included as six non-convolved regressors of no interest. Based on previous research (van Kesteren et al., 2012; Tse et al., 2007) we focused our analyses on our a-priori region of interest, the hippocampus. In the first analysis a linear t-contrast of the recent versus remote condition [recent > remote] was calculated at the first level, masked by the hippocampus, to establish the region that displayed an overnight reduction in activity. To assess group effects, the resulting contrast image was carried forward to a second-level one sample t-test. Beta estimates, from the whole cluster, were extracted separately for the four conditions (S remote, NS remote, S recent, NS recent) using Marsbar (Brett et al., 2002). Differences between conditions were examined using t-tests. Correlations between the parameter estimates for the overnight change [recent > remote] and spindle densities were examined, separately for schema-related and non-schema facts. To assess whether other hippocampal regions showed differences in the overnight activity change between schema-related and non-schema memories, a linear t-contrast of the interaction [NS(recent > remote) > S(recent > remote)] was calculated at the first level and the resulting contrast image was carried forward to a second-level one sample t-test. In a third analysis we explored in line with our behavioural findings, brain regions in which spindles predicted an overnight difference in brain activity between schema-related and non-schema memories. Therefore a linear t-contrast of the negative interaction [S(recent > remote)
> NS(recent > remote)] was calculated at the first level. The resulting contrast image was carried forward to a second-level one sample t-test and stage 2 spindle density was included as covariate. Beta estimates of the resulting activation cluster were extracted using Marsbar and further analyses, including a median split analysis and correlations with the spindle density, were conducted. In all analyses brain regions that differentiated between conditions were identified using a statistical criterion of 48 or more contiguous voxels at a voxel-wise threshold of $p < 0.005$. These height and extent thresholds were selected on the basis of a Monte Carlo simulation using 1000 iterations implemented in MATLAB, to correspond with an overall false-positive rate of $p < 0.05$ (Slotnick et al., 2003).
4.6 Supplemental material

Methods

1. Stimuli

A schematic illustration of schema A and schema B is shown in Figure 4.5. Both schemas were highly parallel in structure and contained information at each hierarchical level. For schema A participants learned general information about arthropods and the two families of arthropods: ants and crabs. Each family was divided into three sub-families, each containing two individual species. Detailed information (15 - 25 facts) about anatomy, habitat, food preferences and behavioural characteristics for each of the 12 species comprised the main part of the schema. Schema B was organised in the same way and contained information about different cells, including different cell types and cell organelles. New names were created for all 12 individual category members of each schema.

For each of the 12 category members, we also created six additional facts (schema-related facts), which were not part of the schema but were used for the encoding. These facts were new but related to information in the schema. Examples are provided in Table 4.1. This
Chapter 4. Spindles mark hippocampal to neocortical consolidation of schema-related memories

gave 72 schema-related facts in total for each schema. Each fact existed in two, equally likely, versions. One version, which was randomly chosen for each participant, was used for the encoding, the other one served as false choice for the recall. This design ensured that participants could not guess the correct answer based on their schema knowledge. The schema-related facts for schema A served as non-schema facts for schema B and vice versa. Facts were kept relatively vague to prevent participants from knowing what the non-schema facts were about. For the same reason we re-named the 12 category members. The facts for schema A and schema B were counterbalanced for the number of words, number of syllables, and numerical values. None of the facts were longer than eight words or fourteen syllables so that all facts could easily be read within the presentation time.

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Oatii is a very colourful crab, which changes its colour when the temperature changes.</td>
<td>Oatii turns blue in heat.</td>
<td>Oatii turns brown in heat.</td>
</tr>
<tr>
<td>Pontu has a very long lifespan.</td>
<td>Pontu has a lifespan of 5 years</td>
<td>Pontu has a lifespan of 7 years.</td>
</tr>
<tr>
<td>Gulosa has a hard exoskeleton due to a high amount of metal particles in its chitin.</td>
<td>Gulosa contains potassium in its shell.</td>
<td>Gulosa contains magnesium in its shell.</td>
</tr>
</tbody>
</table>

2. Procedure

All participants were pre-screened via email to exclude those who had too much prior knowledge in the two schema categories. Participants were required to have no post-GSCE knowledge and no particular interest in biology, medicine, chemistry and zoology. Participants were randomly assigned to one of the two schemas and performed a test on their prior knowledge in that category. The pre-test involved general questions about the main category (arthropods or cells), more detailed questions about the 12 category members, and a picture naming task. All questions were multiple choice questions and presented without a time limit. Participants who achieved a performance above 20% could not take part in the experiment. Three participants were excluded based on this criterion. The actual experiment consisted of two parts. Part one comprised the schema-learning and part two the learning of new schema-related and non-schema facts.

Part I: Schema-Learning

The schema-learning involved six sessions, which were spaced on average across $13 \pm 0.7$ (SE) days (minimum: 11 days, maximum 17 days). Three participants completed one additional session, as they had to leave early during a scheduled session and did not finish with the planned material. Sessions were on average spaced by $2.5 \pm 0.16$ (SE) days (minimum: 1 day, maximum: 6 days). Sessions were about $1.5 \text{ h} \pm 30 \text{ min}$ long, but this could vary as participants were allowed to work through the material at a self-determined
pace. The schema-learning comprised a range of different tasks, which are summarised below. The procedure is presented in Table 4.2. However, depending on the participants’ performances the procedure could vary slightly to assure that all category members were learned equally well. Which sub-family was introduced first (PP3 or PP4) was randomly chosen for each participant.

Schema-learning tasks:

1. Reading Tasks: The reading tasks formed the main part of schema learning. All information was presented in power-point presentations as texts or bullet points intermixed with pictures. Participants could read and work through the slides at a self-determined pace. Five power point presentations were used: one (PP1) contained very general information about the category and the sub-families, one (PP2) which briefly introduced the 12 individual category members, two (PP3, PP4) with very detailed information about the six category members of the two sub-families and one (PP5) with detailed information about all 12 category members. Each power point also contained slides in which participants were asked to recall some of the information and write the answers down.

2. Open Questions: Participants completed three sets of paper-based open questions (OQ1, OQ2, OQ3), in which they were asked to recall and explain information from the reading tasks. The first set involved 15 questions related to the general category (Schema A: characteristics of ants and crabs; Schema B: structure and function of cells and cell organelles). The other two sets comprised ~35 questions regarding the 12 category members. After completion the experimenter worked with the participant through each question to assure that the learned material was comprehended.

3. Multiple Choice Questions: Participants completed three different sets of multiple choice questions (MCQ1, MCQ2, MCQ3). The first set (~20 questions) were true/false statements regarding the general category (Example: Ants have heart: True or False?). In the second and third set (~40 questions each) questions were presented together with four possible answers related to the 12 category members (Example: Pontu.. A) lives in pitcher plants B) can have a green back C) has a very short lifespan D) builds large nests). Feedback was given in all three tasks.

4. Picture naming (PN): In this task four new pictures for each of the 12 category members were presented in randomised order and participants selected the name of the category member that was shown. Feedback was given together with a brief explanation.

5. Free recall (FR): Participants were asked to write down the names of the 12 category members and their main characteristics.

6. Monitoring Test (MT): This test comprised six questions for each of the 12 category members (72 questions in total). For each question participants selected the correct answer out of six choices (Example: Which ant lives deep under the ground? 1) Texana 2) Styga 3) Gulosa 4) Pontu 5) Caphy 6) Avati). No feedback was given, apart from the overall performance at the end of the test. This test served to monitor the schema learning and was repeated at the end of sessions three to six. Participants were only allowed to continue
with the experiment when they reached a threshold of 85% in session six to assure that the schema was established. One participant did not reach this threshold and was excluded from the experiment. The average proportion correct from the remaining participants in the final test at the end of session six was $0.93 \pm 0.01$ (SE).

7. **Word-learning (WL):** All facts of part II started with the name of a category member followed by a new fact, such as ‘Oatii turns brown in heat’. Therefore it was important that participants also learned the names of the category members of the other schema to avoid distraction due to unfamiliar words in the non-schema condition. In each session participants were exposed to and asked to memorise the names of the category members of the other schema. The names were introduced as nonsense words. Different tasks, such as free recall, multiple choice questions (Example 1: Pick the correct spelling A) Maksa B) Maska C) Makso D) Macksa; Example 2: Find one of the non-sense words: A K H H O I Y M P H Q L L I S O U A) and phonological tasks (Example: Which words have 5 letters?, Which word contains two ’As’?) were used to introduce some variety in the learning.

**Table 4.2: Procedure and tasks involved in the schema-learning.**

<table>
<thead>
<tr>
<th>Task</th>
<th>Session 1</th>
<th>Session 2</th>
<th>Session 3</th>
<th>Session 4</th>
<th>Session 5</th>
<th>Session 6</th>
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<tbody>
<tr>
<td>PP 1</td>
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<td>PP 2</td>
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<td>PP 3</td>
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<td>PP 5</td>
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<td>x</td>
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<td>OQ 1</td>
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<td>OQ 2</td>
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<td>OQ 3</td>
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<td>MCQ 1</td>
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<td>MCQ 3</td>
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<td>PN</td>
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<td>FR</td>
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<td>MT</td>
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<td>WL</td>
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</table>

**PP:** Reading tasks; **OQ:** Open questions; **MCQ:** Multiple choice questions; **PN:** Picture naming task; **FR:** Free recall task; **MT:** Monitoring task; **WL:** Word learning task. A cross indicates that a task was undertaken in the corresponding session.

**Part II: Learning of new facts**

The second part of the experiment involved two encoding sessions (E1 and E2) and a recall session. The two encoding sessions were separated by 24h $\pm 1.5h$ (mean starting time for E1: 13:36, SD: 28 min; mean starting time for E2 12:52, SD: 18 min). E1 took place on the day following schema-learning session six. Before each encoding session participants were measured on the Stanford Sleepiness Scale (SSS) and the Karolinska Sleepiness Scale (KSS).
to assess differences in alertness. In each encoding session participants were exposed to 36 schema-related and 36 non-schema facts. Facts were presented in pseudo-random order (consecutive facts were from different category members), in four presentation rounds. Each fact was presented for 6 s in the first round and for 4 s in the remaining three rounds. Each trial started with the presentation of a fact and was followed by a blank screen for 500 ms before the next stimulus appeared. Every 18 facts participants had a 10 s break. After two presentation rounds participants had a 30 s break. Each encoding session lasted approximately 40 min. Participants were instructed to memorise each fact carefully, to focus only at the fact that was presented at the time and to try equally hard to memorise each fact. Participants were also informed about how they would be tested in the recall task. One encoding session involved facts associated with one family of the schema (for example ants) and one family of the unlearned schema (for example cells). The other encoding session involved facts associated with the other family of the schema (for example crabs) and the unlearned schema (for example organelles). This was done to minimise interference between the two encoding sessions. The order was counter-balanced between participants. On the day of E1 participants were invited to sleep overnight from 11 p.m. to 7 a.m. in a bedroom in the Sleep Research Laboratory at the University of Manchester, where they were monitored with PSG while they slept. The recall took place directly after the second encoding session inside a 3T MRI scanner. All 144 facts were tested in a two-alternative task. Each trial started with the presentation of a fixation cross in the middle of the screen for 500 ms. This was followed by the presentation of a fact together with its false choice for 6000 ms. Participants selected the correct answer by pressing the corresponding button on a button box with the right hand within the 6 s interval. Participants were instructed not to guess, but to press a 'Don’t know' button in case they were unsure. Reaction times were recorded as a secondary measure. 72 rest trials lasting 6000 ms each in which a fixation cross was presented in the middle of the screen were included in order to facilitate estimation of baseline activity in fMRI. Participants conducted five test trials before they started with the actual recall task.

3. Equipment

This experiment was realised with custom-written scripts using Cogent 2000 developed by the Cogent 2000 team at the Functional Imaging Laboratory and the Institute for Cognitive Neuroscience (University College, London). It was written and executed using MATLAB® 7.5 running on a PC equipped with a dual-core processor. Responses were recorded using a serial multibutton box attached to a Domino 2 microcontroller from Micromint®, with a time resolution of approximately 1 ms.

4. Results

4.1. Alertness at encoding

Tiredness at encoding was assessed using the alertness measures of the KSS (E1: mean: 3.8, SE:0.32; E2: mean: 3.4, SE: 0.32) and the SSS (E1: mean: 2.95, SE: 0.28; E2: mean:
2.7, SE: 0.23). Both measures showed no differences in alertness between the two encoding sessions (KSS: \( t(19) = 1.00, p = 0.330 \); SSS: \( t(19) = 0.773, p = 0.449 \)).

### 4.2. Reaction time results

A 2x2 repeated measures ANOVA (Factors: schema and time) was conducted on the reaction times. Only correct answers were included into this analysis. There was a significant main effect of schema (\( F(19) = 37.451, p < 0.001 \)), with quicker reaction times for the schema-related than non-schema items (schema-related mean: 2.839 s, SE: 0.054, non-schema mean: 2.998 s, SE: 0.056), a significant main effect of time (\( F(19) = 14.292, p = 0.001 \)) with quicker reaction times for the recent than the remote condition (remote mean: 3.026 s, E: 0.050, recent mean: 2.996, SE: 0.058), but no significant interaction (\( F(19) = 0.276, p = 0.606 \)).

### 4.3. Polysomnography results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (in min)</td>
<td>432 ± 10.53</td>
</tr>
<tr>
<td>Stage 1 (% of TST)</td>
<td>7 ± 0.94</td>
</tr>
<tr>
<td>Stage 2 (% of TST)</td>
<td>53 ± 1.42</td>
</tr>
<tr>
<td>SWS (% of TST)</td>
<td>22 ± 1.16</td>
</tr>
<tr>
<td>REM (% of TST)</td>
<td>17 ± 0.94</td>
</tr>
<tr>
<td>SWS Spindle Density</td>
<td>0.31 ± 0.04</td>
</tr>
<tr>
<td>S2 Spindle Density</td>
<td>0.74 ± 0.06</td>
</tr>
<tr>
<td>nonREM Spindle Density</td>
<td>0.71 ± 0.06</td>
</tr>
</tbody>
</table>

TST: Total sleep time, SWS: Slow wave sleep, REM: Rapid-eye-movement sleep, nonREM: non-rapid-eye-movement sleep (including SWS and stage 2). Stage 1, Stage 2, SWS and REM are presented as percentage of the total sleep time. Spindles density is the number of spindles per minute of sleep.

### 4.4. Regression analysis

Stage 2 sleep (in % of TST) was significantly correlated with SWS (in % of TST), \( r(19) = -0.623, p = 0.004 \), and REM (in % of TST), \( r(19) = -0.535, p = 0.018 \), and was therefore not included in the regression model. The remaining sleep parameters did not show any significant correlations, \( r(19) \leq 0.337, p \geq 0.16 \). Including stage 2 sleep violated the multicollinearity assumption, but did not affect the significant contribution of spindle density in the model.

### 4.5. Spindle Analyses

Correlations between spindle activity (12 Hz - 15 Hz) and the interaction score were calculated separately for central (C3, C4), frontal (F3, F4) and occipital (O1, O2) channels to see whether the effect was carried by specific sites. Central and occipital channels
showed significant correlations, frontal channels revealed a trend (central: $r(19) = 0.672$, $p = 0.002$, frontal: $r(19) = 0.407$, $p = 0.083$, occipital: $r(19) = 0.635$, $p = 0.004$). We also inspected the change in the schema effect for slow (11 Hz - 13 Hz) and fast (13 Hz - 15 Hz) spindles separately. We observed significant and comparable correlations for both spindle types (fast: $r(19) = 0.555$, $p = 0.014$; slow: $r(19) = 0.544$, $p = 0.016$).

### 4.6. Median Split Analysis

The median value was randomly assigned to the low spindle group. Assigning this value to the high spindle group did not change the results: The 2x2x2 ANOVA revealed a significant main effect of schema ($F(17) = 46.767$, $p < 0.001$), main effect of time ($F(17) = 28.822$, $p < 0.001$) and importantly a significant 3-way interaction ($F(17) = 15.767$, $p = 0.001$). In addition to the median split analysis we also explored whether the stage 2 spindle density predicted the difference between the recent and remote condition for the schema-related items only, which was not significant but revealed a trend, $r(19) = -0.431$, $p = 0.065$. The spindle density did not predict the schema effect for the remote condition only, $r(19) = 0.031$, $p = 0.900$. 
## 5. Functional analysis

Table 4.4: Significant activation clusters for the contrast recent > remote.

<table>
<thead>
<tr>
<th>Region of activation</th>
<th>Cluster extent (voxels)</th>
<th>Max z value</th>
<th>P value (unc.)</th>
<th>Peak Region</th>
<th>Peak MNI coordinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precuneus (R/L)</td>
<td>29764</td>
<td>5.74</td>
<td>&lt;0.001</td>
<td>R precuneus</td>
<td>-2 -70 38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.73</td>
<td>&lt;0.001</td>
<td>R BA 7</td>
<td>14 -64 52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.66</td>
<td>&lt;0.001</td>
<td>R precuneus</td>
<td>-44 2 18</td>
</tr>
<tr>
<td>Precentral gyrus (L)</td>
<td>418</td>
<td>4.33</td>
<td>&lt;0.001</td>
<td>sub-gyral</td>
<td>-44 2 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.60</td>
<td>&lt;0.001</td>
<td>L precentral</td>
<td>-54 -12 28</td>
</tr>
<tr>
<td>Lentiform nucleus (R)</td>
<td>661</td>
<td>4.00</td>
<td>&lt;0.001</td>
<td>R pallidus</td>
<td>24 -10 -4</td>
</tr>
<tr>
<td>Middle frontal gyrus (L)</td>
<td>405</td>
<td>4.00</td>
<td>&lt;0.001</td>
<td>L middle frontal</td>
<td>-36 40 32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.93</td>
<td>&lt;0.001</td>
<td>L middle frontal</td>
<td>-30 28 44</td>
</tr>
<tr>
<td>Medial frontal gyrus (R)</td>
<td>347</td>
<td>3.99</td>
<td>&lt;0.001</td>
<td>R medial frontal</td>
<td>18 54 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.74</td>
<td>&lt;0.001</td>
<td>R medial frontal</td>
<td>22 44 14</td>
</tr>
<tr>
<td>Hippocampus (R)</td>
<td>93</td>
<td>3.81</td>
<td>&lt;0.001</td>
<td>R hippocampus</td>
<td>34 -18 -12</td>
</tr>
<tr>
<td>Brainstem (R)</td>
<td>53</td>
<td>3.77</td>
<td>&lt;0.001</td>
<td>R Pons</td>
<td>16 -28 -40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>R parahippocampus</td>
<td>26 -22 -30</td>
</tr>
<tr>
<td>Medial frontal gyrus (L)</td>
<td>479</td>
<td>3.63</td>
<td>&lt;0.001</td>
<td>L medial frontal</td>
<td>-12 54 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.39</td>
<td>&lt;0.001</td>
<td>L medial frontal</td>
<td>6 54 -6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.37</td>
<td>&lt;0.001</td>
<td>L anterior cingulate</td>
<td>10 32 -8</td>
</tr>
<tr>
<td>Middle temporal gyrus (R)</td>
<td>57</td>
<td>3.50</td>
<td>&lt;0.001</td>
<td>R middle temporal</td>
<td>60 2 14</td>
</tr>
<tr>
<td>Middle frontal gyrus (R)</td>
<td>219</td>
<td>3.44</td>
<td>&lt;0.001</td>
<td>R middle frontal</td>
<td>38 38 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.33</td>
<td>&lt;0.001</td>
<td>R BA 9</td>
<td>34 34 42</td>
</tr>
<tr>
<td>Midbrain (R)</td>
<td>132</td>
<td>3.41</td>
<td>&lt;0.001</td>
<td>R brainstem</td>
<td>6 -26 -4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.32</td>
<td>&lt;0.001</td>
<td>L midbrain</td>
<td>-10 -24 -2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.24</td>
<td>0.002</td>
<td>R thalamus</td>
<td>14 -30 -2</td>
</tr>
<tr>
<td>Superior frontal gyrus (L)</td>
<td>58</td>
<td>3.36</td>
<td>0.001</td>
<td>L superior frontal</td>
<td>-12 56 24</td>
</tr>
<tr>
<td>Insula (L)</td>
<td>169</td>
<td>3.17</td>
<td>0.001</td>
<td>L insula</td>
<td>-46 4 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.00</td>
<td>0.001</td>
<td>L superior temporal</td>
<td>-54 -4 2</td>
</tr>
<tr>
<td>Superior temporal gyrus (L)</td>
<td>58</td>
<td>3.14</td>
<td>0.001</td>
<td>L superior temporal</td>
<td>-54 -18 6</td>
</tr>
</tbody>
</table>

Voxel-wise threshold of p = 0.005 and extent threshold of k > 48 voxels, which corresponds with an overall false-positive rate of less than 5%, corrected for multiple comparisons (Slotnick et al., 2003). Up to 3 largest peaks listed per cluster that did not fell in sub-gyral or extra-nuclear regions. L: left. R: right. BA: Brodman area.
Table 4.5: Significant activation clusters for the interaction contrast, which describes the differences in the overnight activation change between the schema-related and the non-schema condition.

<table>
<thead>
<tr>
<th>Region of activation</th>
<th>Cluster extent (voxels)</th>
<th>Max z value</th>
<th>P value (unc.)</th>
<th>Peak Region</th>
<th>Peak MNI coordinate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NS(recent &gt; remote) &gt; S(recent &gt; remote)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus (L/R)</td>
<td>690</td>
<td>4.65</td>
<td>&lt;0.001</td>
<td>L BA 7</td>
<td>-4 -68 44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.14</td>
<td>&lt;0.001</td>
<td>L BA 7</td>
<td>8 -64 42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.29</td>
<td>&lt;0.001</td>
<td>cingulate</td>
<td>0 -48 36</td>
</tr>
<tr>
<td>Superior frontal gyrus (L)</td>
<td>278</td>
<td>3.70</td>
<td>&lt;0.001</td>
<td>L BA 9</td>
<td>-14 38 22</td>
</tr>
<tr>
<td>Cingulate gyrus (R)</td>
<td>246</td>
<td>3.75</td>
<td>&lt;0.001</td>
<td>R cingulate</td>
<td>12 8 46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.72</td>
<td>&lt;0.001</td>
<td>R middle frontal</td>
<td>22 18 42</td>
</tr>
<tr>
<td>Medial frontal gyrus (L)</td>
<td>56</td>
<td>3.73</td>
<td>&lt;0.001</td>
<td>L medial frontal</td>
<td>-12 -18 52</td>
</tr>
<tr>
<td>Middle temporal gyrus (R)</td>
<td>313</td>
<td>3.70</td>
<td>&lt;0.001</td>
<td>R middle temporal</td>
<td>52 -18 -6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.51</td>
<td>&lt;0.001</td>
<td>R superior temporal</td>
<td>45 -28 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.13</td>
<td>&lt;0.001</td>
<td>R BA 21</td>
<td>60 -22 -14</td>
</tr>
<tr>
<td>Supramarginal gyrus (R)</td>
<td>3.68</td>
<td></td>
<td></td>
<td>R inferior parietal</td>
<td>50 -36 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.15</td>
<td>0.001</td>
<td>R BA 40</td>
<td>60 -48 26</td>
</tr>
<tr>
<td>Precentral gyrus (L)</td>
<td>76</td>
<td>3.61</td>
<td>&lt;0.001</td>
<td>L BA 4</td>
<td>40 -18 52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.26</td>
<td>0.001</td>
<td>L precentral</td>
<td>48 -16 52</td>
</tr>
<tr>
<td>Middle frontal gyrus (L)</td>
<td>146</td>
<td>3.39</td>
<td>&lt;0.001</td>
<td>L middle frontal</td>
<td>30 50 22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.16</td>
<td>&lt;0.001</td>
<td>L BA 10</td>
<td>22 56 26</td>
</tr>
<tr>
<td>Inferior parietal (L)</td>
<td>50</td>
<td>3.01</td>
<td>0.001</td>
<td>L inferior frontal</td>
<td>-46 -34 26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.94</td>
<td>0.002</td>
<td>L BA 13</td>
<td>-38 -32 18</td>
</tr>
<tr>
<td><strong>S(recent &gt; remote) &gt; NS(recent &gt; remote)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum (R)</td>
<td>82</td>
<td>3.89</td>
<td>&lt;0.001</td>
<td>R pyramis</td>
<td>18 -64 -38</td>
</tr>
<tr>
<td>Thalamus (L)</td>
<td>64</td>
<td>3.50</td>
<td>&lt;0.001</td>
<td>L thalamus</td>
<td>-10 -32 12</td>
</tr>
</tbody>
</table>

Voxel-wise threshold of $p = 0.005$ and extent threshold of $k > 48$ voxels, which corresponds with an overall false-positive rate of less than 5%, corrected for multiple comparisons (Slotnick et al., 2003). Up to 3 largest peaks listed per cluster that did not fall in sub-gyral or extra-nuclear regions. S: Schema-related, NS: Non-Schema, L: left. R: right. BA: Brodman area.
### 5.1. Left hippocampal cluster

To investigate whether the significant correlation between the interaction contrast and the stage 2 spindle density in the left hippocampus was driven by the schema-related or the non-schema condition, we first masked this cluster by the hippocampus and extracted the beta estimates, separately for the S\[recent-remote\] and the NS\[recent-remote\] contrasts. Subsequently correlations between the parameter estimates and the stage two spindle densities were computed. The spindle density was (at a Bonferroni-corrected $\alpha$-level of 0.025) significantly correlated with the overnight change in hippocampal activation for the schema-related condition, $r(19)= 0.579$, $p = 0.009$, but was not significantly correlated for the non-schema condition, $r(19) = 0.483$, $p = 0.036$.

### 5.2. Right hippocampal cluster
6. Control Group

6.1. Participants

Twenty four native English students (mean age: 21.9, SD: 2.99, 8 males) were recruited for the control group. The same recruitment criteria as for the schema group were applied. Our aim was to mimic in the control group the memory performance from the recent condition of the schema group (i.e. the high performance in the schema-related condition and the difference between the schema-related and the non-schema condition). This allowed us to assess how memory performance changed in the remote condition in terms of encoding strength. For this reason, we excluded participants who performed worse than three standard deviations from the mean of the schema-related recently encoded condition of the schema group. Four participants were excluded based on this criterion.

6.2. Procedure

The control study involved two encoding sessions (times were matched to the schema study), which were separated by 24 h and a recall session, which took place directly after the second encoding. In the encoding sessions participants memorised the same 144 facts (72 facts per session) that were used in the schema study, but without any prior schema knowledge (i.e. in the non-schema condition). To mimic the performance differences that we observed in the schema group between the schema-related and the non-schema condition for the recently encoded facts, half of the facts were presented nine times (strongly encoded facts), while the other half was presented four times (weakly encoded facts). As participants in the schema group could easily distinguish between schema-related and non-schema facts based on their prior knowledge, we used visual cues in the control group, which enabled participants to distinguish between the two groups of facts: strongly encoded facts were presented in purple and weakly encoded facts were presented in yellow. The structure of each encoding trial was equivalent to the schema group (the presentation time of each fact was 4 s). Facts were presented in five rounds. In the first round only the strongly encoded facts were shown, in the other four rounds the strongly encoded
encoded facts were shown twice and the weakly encoded facts once, in pseudo-randomised order. Which facts were shown in which encoding session and in which condition was carefully matched to the schema study. In the night between the two encoding sessions participants slept in the sleep laboratory and sleep was monitored with PSG. The recall task and the procedure was equivalent to the schema group.

6.3. Statistical analyses

PSG data acquisition and analyses was equivalent to those of the schema group. The regression analysis was conducted with the same variables as for the schema group. As S2 sleep was strongly correlated with SWS ($r(20)=-0.870$, $p < 0.001$), S2 sleep was removed from the regression model, leaving TST (in min), REM sleep (% of TST), Stage 1 sleep (% of TST), SWS (% of TST), Stage 2 spindle density (number per min) as explanatory variables. Tolerance statistics indicated no problems regarding multicollinearity of the remaining explanatory variables.

6.4. Polysomnography results

The PSG results of the control group are shown in Table 4.8. There was no significant difference between the control and the schema group in any of the sleep parameters, $t(38) \leq 1.641$, $p \geq 0.11$.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (in min)</td>
<td>459.60 ± 12.69</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>6.31 ± 0.71</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>55.15 ± 1.67</td>
</tr>
<tr>
<td>SWS (%)</td>
<td>19.52 ± 1.80</td>
</tr>
<tr>
<td>REM (%)</td>
<td>19.02 ± 0.91</td>
</tr>
<tr>
<td>Spindle Density</td>
<td>0.67 ± 0.30</td>
</tr>
</tbody>
</table>

TST: Total sleep time, SWS: Slow wave sleep, REM: Rapid-eye-movement sleep. Data are presented as Mean ± SE. Stage 1, Stage 2, SWS and REM are presented as percentage of the total sleep time. Spindles density is the number of spindles per minute of stage 2 sleep.

7. Results of SWS Spindles and nonREM Spindles (12Hz - 15Hz)

Both SWS and nonREM spindles correlated significantly with the interaction score (SWS: $r(19) = 0.627$, $p = 0.004$; nonREM: $r(19) = 0.665$, $p = 0.002$). We also analysed differences between SWS spindles and Stage 2 spindles. As expected SWS spindle densities were lower than stage 2 spindle densities ($t(18) = 10.103$, $p < 0.001$). Stage 2 and SWS spindles also differed in mean frequency (Stage 2: $13.70 ± 0.08$ Hz, SWS: $13.85 ± 0.07$ Hz, $t(18) = -3.421$, $p = 0.003$) and duration (Stage 2: $1.10 ± 0.05$ SWS: $0.90 ± 0.04$, $t(18) = 7.363$, $p < 0.001$). Functionally, SWS spindle densities modulated for the interaction contrast a network including posterior cingulate, putamen and middle temporal gyrus (details in Table 4.9). NonREM spindles results were largely overlapping.
Table 4.9: Significant activation clusters for the interaction contrast modulated by the SWS spindle density.

<table>
<thead>
<tr>
<th>Region of activation</th>
<th>Cluster extent (voxels)</th>
<th>Max z value</th>
<th>P value (unc.)</th>
<th>Peak Region</th>
<th>Peak MNI coordinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior parietal lobule (L)</td>
<td>257</td>
<td>4.82</td>
<td>&lt;0.001</td>
<td>L inferior parietal</td>
<td>-48 -48 44</td>
</tr>
<tr>
<td>Superior frontal (L/R)</td>
<td>534</td>
<td>4.62</td>
<td>&lt;0.001</td>
<td>R superior frontal</td>
<td>10 -4 76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>L BA 6</td>
<td>-4 -6 66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>L superior frontal</td>
<td>-4 -4 74</td>
</tr>
<tr>
<td>Posterior cingulate (R)</td>
<td>223</td>
<td>4.24</td>
<td>&lt;0.001</td>
<td>R BA 30</td>
<td>16 -58 4</td>
</tr>
<tr>
<td>Inferior parietal lobule (R)</td>
<td>392</td>
<td>4.10</td>
<td>&lt;0.001</td>
<td>R BA 40</td>
<td>44 -46 44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.43</td>
<td>&lt;0.001</td>
<td>R precuneus</td>
<td>20 -56 40</td>
</tr>
<tr>
<td>Middle frontal gyrus (R)</td>
<td>634</td>
<td>3.57</td>
<td>&lt;0.001</td>
<td>R middle frontal</td>
<td>38 -2 56</td>
</tr>
<tr>
<td>Middle temporal gyrus (R)</td>
<td>90</td>
<td>3.92</td>
<td>&lt;0.001</td>
<td>R middle temporal</td>
<td>52 -50 -4</td>
</tr>
<tr>
<td>Posterior cingulate (L)</td>
<td>236</td>
<td>3.66</td>
<td>&lt;0.001</td>
<td>L posterior cingulate</td>
<td>-18 -66 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.18</td>
<td>&lt;0.001</td>
<td>L posterior cingulate</td>
<td>-22 -62 4</td>
</tr>
<tr>
<td>Putamen (R)</td>
<td>362</td>
<td>3.63</td>
<td>&lt;0.001</td>
<td>R putamen</td>
<td>18 8 6</td>
</tr>
<tr>
<td>Cuneus (R)</td>
<td>61</td>
<td>3.43</td>
<td>&lt;0.001</td>
<td>R cuneus</td>
<td>26 -78 28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.74</td>
<td>0.003</td>
<td>R precuneus</td>
<td>22 -74 26</td>
</tr>
<tr>
<td>BA 9 (R)</td>
<td>112</td>
<td>3.22</td>
<td>0.001</td>
<td>R BA 9</td>
<td>44 22 38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.95</td>
<td>0.002</td>
<td>R BA 9</td>
<td>40 28 42</td>
</tr>
<tr>
<td>BA 7 (L)</td>
<td>91</td>
<td>3.21</td>
<td>0.001</td>
<td>L cuneus</td>
<td>-10 -80 38</td>
</tr>
</tbody>
</table>

The \([S(\text{recent} > \text{remote}) > S(\text{recent} > \text{remote}) \times \text{Spindle density})]\)-contrast did not reveal any significant activation. Voxel-wise threshold of \(p=0.005\) and extent threshold of \(k > 48\) voxels, which corresponds with an overall false-positive rate of less than 5%, corrected for multiple comparisons (Slotnick et al., 2003). Up to 3 largest peaks listed per cluster that did not fell in sub-gyrual or extra-nuclear regions. L: left. R: right. BA: Brodman area.
Chapter 5

A weak schema link is sufficient to trigger the schema benefit and the association with sleep spindles

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This chapter is based on a manuscript that is being prepared for submission for peer review
5.1 Abstract

Newly learned information that is congruent with a pre-existing schema is memorised better than information that does not relate to prior knowledge. This beneficial effect of schemas on memory has previously been associated with a more efficient consolidation process that seems to be indexed by sleep spindles. How strongly information must be related to the schema to trigger the schema benefit and the association with sleep spindles is unknown. To examine this question participants memorised in the current study new information that was closely-related, distantly-related or completely unrelated to a pre-existing schema. Memory performance was tested in two recall sessions, which were separated by 24 h, including a night of sleep. Results showed a clear schema benefit that was modulated by the degree of relatedness. Closely-related information was memorised better than distantly-related information, which was memorised better than unrelated information. Importantly, the rate of sleep spindles predicted how the schema effect changed across consolidation for both closely-related and distantly-related information. These findings suggest that even a weak link to a pre-existing schema triggers the accelerated consolidation process, which is indexed by sleep spindles and results in a behavioural memory benefit.

Keywords: Schema, prior knowledge, sleep, spindles, and memory consolidation

5.2 Introduction

It has long been known that information that is congruent with a pre-existing schema is remembered better than information that does not relate to prior knowledge (Bartlett, 1932; Bransford & Johnson, 1972). The term schema refers to frameworks of acquired knowledge, which have four key features: i) schemas have an associative network structure, ii) they are acquired across multiple episodes and lack context details iii) schemas can be updated with new information and iv) schema knowledge can generalise (Ghosh & Gilboa, 2014). The positive effect of schemas on memory is known as the schema effect (van Kesteren et al., 2013b). Recent research has started to unravel the underlying neural mechanisms of the schema effect. This research suggests that schemas accelerate memory consolidation (McClelland, 2013; Tse et al., 2007, 2011; van Kesteren et al., 2012). Tse et al. (2007) demonstrated in rodents that in the presence of an associative schema information was remembered better and became independent of the hippocampus more quickly. They further showed that this rapid hippocampal disengagement was accompanied by an increasing involvement of the medial prefrontal cortex, which is thought to take over the binding role of the hippocampus (Tse et al., 2011). Using computational modelling McClelland et al. (2013) demonstrated that new information consistent with existing knowledge structures can be incorporated quickly and without interference into putatively neocortex-like neural networks. Together these findings suggest that memories that link well into a cortically based schema consolidate more quickly as they are assimilated into neocortical networks more efficiently. The beneficial effect of schemas on memory is thought to result from this
accelerated integration of newly acquired memories into long-term memory (van Kesteren et al., 2012; Wang et al., 2012). In line with these findings, we found in Chapter 4 that the schema effect increased across a 24 h consolidation interval, driven by an enhanced retention of memories that linked well into a pre-existing schema. We further showed that this increase in the schema effect was predicted by the rate of sleep spindles that occurred during nocturnal sleep within the consolidation interval. Sleep spindles are brief (0.5 - 3 s) oscillatory events that are generated by thalamo-cortical neuronal circuits (Lüthi, 2013). Sleep spindles are a hallmark of non-rapid eye movement (nonREM) sleep and have been implicated in sleep-dependent memory consolidation in a range of studies (reviewed in Rasch & Born 2013). Specifically, spindle activity has been shown to correlate with memory recall after sleep (Gais et al., 2002; Schabus et al., 2004; Schmidt et al., 2006), spindle activity could be modulated by learning that happened before sleep (Gais et al., 2002; Schabus et al., 2004; Tamminen et al., 2013) and pharmacologically induced increases in spindle density enhanced declarative memory performance (Mednick et al., 2013). Importantly, findings of two studies suggested that spindles index or even mediate the integration of new information with existing knowledge (Tamminen et al., 2010, 2013). The results of Chapter 4 were in line with these findings as they suggested that sleep spindle density marks the process of assimilating new information into existing long-term memory structures. What remains unknown, however, is how closely information must be related to the schema to trigger the schema benefit and to induce the spindle-related consolidation process. In the current study we aimed to explore how the degree of relatedness between new facts and a pre-existing schema influenced the schema effect and the association with spindles. Specifically, we were interested in whether the degree of relatedness modulates: i) the size of the schema effect, ii) the increase in the schema effect across consolidation and iii) the association with sleep spindles. To assess these questions we applied a very similar paradigm as in Chapter 4, but the schema-related facts varied across two levels in how well they linked into the pre-existing schema.

5.3 Methods

5.3.1 Participants

Twenty two native English students (mean age: 22.34, SD: 2.61, 10 males, randomly assigned to one of the two schemas) participated in this study. Participants kept a regular sleep-wake cycle for at least four weeks preceding the study. They had normal or corrected-to-normal vision, no hearing problems, and no history of neurological, psychiatric or sleep disorders. Participants were required to have no post-GCSC knowledge and no particular interest in biology, medicine, chemistry and zoology. Informed consent was obtained from all participants prior to the study, approved by the University of Manchester Research Ethics Committee. One participant was excluded from the study due to a technical failure during the encoding. Two more participants were excluded from the polysomnography (PSG) analysis due to technical difficulties during the sleep recording.
5.3.2 Stimuli

Two artificial schemas (Schema A: ants, Schema B: cell types), which were based on the schemas from Chapter 4, were used. Changes were applied to accommodate the requirements for the current study. A schematic illustration of schemas A and B is shown in Figure 5.1. Each schema contained general information about the category (ants or cells) and detailed characteristics of six individual category members (~20 facts each). For each of the six category members we created 12 additional facts (schema-related facts), which were not part of the schema but were used for the encoding. All 12 facts were new and differed in how closely they related to the schema. Half of the 12 facts were closely related to information in the schema (closely-related facts), while the other half did not relate to information in the schema but was plausible (distantly-related facts). Examples are given in Table 5.1. Each of the 72 facts existed in two, equally likely, versions. One version, which was randomly chosen for each participant, was used for the encoding, the other one served as false choice for the recall (see Table 5.1 for examples). This design prevented participants from guessing the correct answer based on their schema knowledge. The schema-related facts (closely-related and distantly-related facts combined) of schema A served as facts that were completely unrelated (non-schema facts) for schema B and vice versa. We created new names for of all species and facts were kept relatively vague to prevent participants from knowing what the non-schema facts were about. Each fact pair from schema A was matched with one fact pair from schema B within the same congruency condition, in terms of number of words, number of syllables and numerical values. None of the facts were longer than eight words or fourteen syllables so that all facts could easily be read within the 4 s presentation time.

Table 5.1: Examples of schema-related facts. Facts that were closely-related to the schema were directly related to information that was provided in the schema, while distantly-related facts did not have such a direct link but were plausible. Each fact existed in two versions, one was used for the encoding and the other one served as false choice for the recall.

<table>
<thead>
<tr>
<th>Relatedness</th>
<th>Schema information</th>
<th>Fact (version 1)</th>
<th>Fact (version 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>closely-related</td>
<td>Avati is usually completely green, but the colour of its back can change occasionally</td>
<td>Avati sometimes has a blue back</td>
<td>Avati sometimes has a brown back</td>
</tr>
<tr>
<td>closely-related</td>
<td>Pontu lives for very long</td>
<td>Pontu has a lifespan of 5 years</td>
<td>Pontu has a lifespan of 7 years</td>
</tr>
<tr>
<td>closely-related</td>
<td>Gulosa has a hard exoskeleton due to a high amount of metal particles in its chitin</td>
<td>Gulosa contains zinc in its shell</td>
<td>Gulosa contains copper in its shell</td>
</tr>
<tr>
<td>distantly-related</td>
<td>No information in the schema about Avati’s shell</td>
<td>Avati possesses a very soft shell</td>
<td>Avati possesses a very stiff shell</td>
</tr>
<tr>
<td>distantly-related</td>
<td>No information in the schema about the habitat of Pontu</td>
<td>Pontu is found in North America</td>
<td>Pontu is found in South America</td>
</tr>
<tr>
<td>distantly-related</td>
<td>No information in the schema about Gulosa’s food preferences</td>
<td>Gulosa is attracted by pungent odours</td>
<td>Gulosa is repelled by pungent odours</td>
</tr>
</tbody>
</table>
5.3.3 Pilot study

A pilot study was conducted in a group of 40 first year psychology students, to ascertain whether the facts for the encoding were easy to understand and whether the degree of relatedness of the facts fitted the intended conditions (closely-related or distantly-related). As subjectivity plays a crucial role in the perception of relatedness, we used these predefined categories only to assure that facts differed in their relatedness and fell on average into the correct category. For the actual experiment, however, participants rated all facts themselves and analyses were conducted on these individual ratings.

5.3.4 Procedure

Participants were randomly assigned to schema A or schema B and performed a test on their prior knowledge in the related category. This pre-test involved general questions about the category (ants or cells), more detailed questions about the six category members and a picture naming task. All questions were multiple choice questions and presented without a time limit. Only participants whose overall performance was below 15 % could take part in the experiment. The experiment itself consisted of two parts: Part one comprised the schema-learning and part two the learning of new facts that were either related to the schema (distantly-related or closely-related facts) or unrelated (non-schema facts). A schematic illustration of the procedure is shown in Figure 5.2.
Chapter 5. A weak schema link is sufficient to trigger the schema benefit

5.3.4.1 Part I: Schema-learning

The schema-learning involved five sessions, which were spaced on average across 11 ± 0.3 (SE) days. Sessions were approximately 1.5 h ± 30 min long, but this could vary as participants were allowed to work through the material at a self-determined pace. The schema-learning comprised a range of different tasks:

1. Reading Tasks: The reading tasks presented the main part of the schema learning. All information was presented in power-point presentations as texts or bullet points intermixed with pictures. Participants could read and work through the slides at a self-determined pace. Four different power point presentations were used which contained very general information about the category (PP1), briefly introduced the six category members (PP2), and contained very detailed information about the six category members (PP3a, PP3b). The latter presentation existed in two versions containing the same information, but differed in wording and images to avoid exact repetition. Each power-point presentation also contained slides in which participants were asked to recall some of the information and write the answers down.

2. Open Questions: Participants completed three sets of paper-based open questions (OQ1, OQ2, OQ3), in which they were asked to recall and explain information from the reading tasks. The first set involved ∼15 questions related to the general category. The other two sets comprised ∼20 questions regarding the six category members. After completion the experimenter worked through each question with the participant to assure that the learned material was comprehended.

3. Multiple Choice Questions: Participants completed three different sets of multiple choice questions (MCQ1, MCQ2, MCQ3). The first set (∼20 questions) consisted of true/false statements regarding the general category (Example: Ants have a heart: True or False?). In the second and third set (∼30 questions each) questions were presented together with four possible answers, related to the six category members (Example: Pontu.. A)
lives in pitcher plants B) can have a green back C) has a very short lifespan D) builds large nests). Feedback was given in all tasks.

4. **Picture naming (PN):** In this task 18 new pictures for the category members (3 new pictures each) were presented in randomised order and participants selected the name of the category member that was shown. Feedback was given together with a brief explanation.

5. **Free recall (FR):** Participants were asked to write-down the names of the six category members and their main characteristics.

6. **Monitoring Test (MT):** This test comprised six questions for each of the six category members (36 questions in total). In each question participants selected the correct answer out of six choices (Example: Which ant lives deep under the ground? 1) Texana 2) Styga 3) Gulosa 4) Pontu 5) Caphy 6) Avati). No feedback was given apart from the overall performance at the end of the test. This test served to monitor the schema learning and was repeated at the end of sessions two to five. Participants were only allowed to continue with the experiment when they reached a threshold of 85 % in session five.

7. **Word-learning (WL):** As all new facts of the encoding phase started with the name of the respective category member, participants also learned the names of the category members of the other schema to avoid distraction due to unfamiliar words in the Non-Schema condition. In each session participants were exposed to and asked to memorise the names of the six category members of the other schema. The names were introduced as nonsense words. Different tasks, such as free recall, multiple choice questions (Example 1: Pick the correct spelling A) Maksa B) Maska C) Makso D) Macksa; Example 2: Find one of the non-sense words: A K H H O I Y M P H Q L L I S O U A) and phonological tasks (Example: Which words have 5 letters?, Which word contains two ’As’?) were used to allow for some variety in the learning.

Each schema-learning session involved several of the above described tasks. The procedure is summarised in Table 5.2. The procedure could vary slightly depending on the participants’ performance, to assure that all category members were learned equally well.

### 5.3.4.2 Part II: Learning of schema-related and non-schema facts

The second part of the experiment involved an encoding session, which took place on the day after the last schema learning session, and two recall sessions: one immediately after the encoding (immediate recall, mean starting time: 10:05 a.m., SD: 46 min) and one 23 h ± 1 h later (delayed recall, mean starting time: 09:36 a.m., SD: 55 min). In the encoding session, participants were exposed to all 144 facts four times. The first encoding round involved a subjective congruency rating for each fact, in which participants indicated how closely a fact related to the schema. Schema-related and non-schema facts were presented in two separate blocks, to prevent ratings from the schema-related and non-schema condition from influencing each other. The order of the blocks was counterbalanced between participants. A schematic illustration of the trial structure is shown in Figure 5.3(A). Each trial started with a fixation cross in the middle of the screen for 1000 ms.
Table 5.2: Procedure and tasks involved in the schema-learning.

<table>
<thead>
<tr>
<th>Task</th>
<th>Session 1</th>
<th>Session 2</th>
<th>Session 3</th>
<th>Session 4</th>
<th>Session 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP1</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP2</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP3a</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP3b</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>OQ1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>OQ2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>OQ3</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>MCQ1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>MCQ2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>MCQ3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PN</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FR</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>MT</td>
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<td></td>
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</tr>
<tr>
<td>WL</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

PP: Reading tasks; OQ: Open questions; MCQ: Multiple choice questions; PN: Picture naming task; FR: Free recall task; MT: Monitoring task; WL: Word learning task. A cross indicates that a task was conducted in the corresponding session.

followed by the presentation of a fact for 6000 ms. Subsequently, a slider appeared on the screen and participants were asked to rate the fact in terms of how well it related to the category member. Especially for the non-schema condition, it was emphasised that the rating was very subjective and there was no correct answer. The scale ranged from 'Neutral' to 'Fits very well'. Positions of the slider, not visible for participants, ranged from 1 (Neutral) to 6 (Fits very well), with a 0.001 step width. The slider always started in the middle of the scale. Participants were instructed to use the whole range of the slider. The maximum time for each rating was 6000 ms, after which the positioning of the slider was recorded and the presentation of the next fact was initiated. Participants could finish each rating earlier by pressing a 'Done' button. Reaction times for the ratings were recorded. Four breaks with a maximum length of 10 s were included. Participants had five practice trials before the actual rating started. After completion of this first encoding round, three encoding rounds followed in which all facts were presented, once per round, in pseudo-randomised order (facts of the same species were separated by at least four other facts). Each trial started with a fixation cross in the middle of the screen for 500 ms, followed by the presentation of a fact for 4000 ms. Participants were instructed to memorise each fact carefully and to always focus on the currently presented fact only. Participants were also informed on how they would be tested in the recall task.

In two recall sessions participants were tested on how well they remembered all 144 facts. The schema-related facts were divided into closely- and distantly-related facts based on the congruency ratings. For each category member the six facts with the lowest ratings were assigned into the category distantly-related and the remaining ones into the category closely-related. In each recall session facts related to three category members and their
36 matched non-schema facts were tested. This gave 10 possible combinations into how the six category members could be divided across the two recall sessions (e.g. Immediate recall: Texana, Styga, Gulosa and delayed recall: Avati, Caphy, Pontu). Always the combination with the highest similarity in the ratings was chosen, to ensure that the two recall sessions were comparable. Therefore we determined for each combination the difference in the average rating and in the standard deviation of the ratings between the two recall lists, separately for the two categories closely-linked and distantly-related. The combination with the lowest difference in mean ratings was chosen as long as the difference in the standard deviation was below 0.3 (this value was chosen based on pilot data). When there were several combinations with an equivalent difference in the mean ratings, the one with the lowest difference in the standard deviation was chosen. Each trial in the recall task started with the presentation of a fixation cross in the middle of the screen for 500 ms. This was followed by the presentation of a fact together with its false choice. The order in which the correct fact and the false choice were presented was counterbalanced. Participants selected the correct answer by pressing the corresponding key on the computer keyboard. Participants were instructed not to guess, but to press the 'Don’t know’ button in cases where they were unsure, to minimise the number of false responses. Each trial was response terminated. Reaction times were recorded as a secondary measure. A schematic illustration of the trial structure is shown in Figure 5.3B. On the day of recall session one, participants were invited to sleep overnight from 11:00 p.m. to 8:00 a.m. in a bedroom in the Sleep Research Laboratory at the University of Manchester, where they were monitored with PSG while they slept.
This design allowed us to approximate the change in memory performance across time by comparing the immediate versus the delayed condition, which gave us a measure of consolidation. Overall, we could compare memory performance across six conditions: Schema closely-related immediate (18 facts), schema distantly-related immediate (18 facts), schema closely-related delayed (18 facts), schema distantly-related delayed (18 facts), non-schema immediate (36 facts: 18 matched to the schema closely-related condition and 18 matched to the schema distantly-related condition), non-schema delayed (36 facts: 18 matched to the schema closely-related condition and 18 matched to the schema distantly-related condition). Our main interest concerned whether the schema effect was modulated by the degree of relatedness and consolidation. The difference in the number of correctly remembered schema-related facts and their matched non-schema facts served as a measure for the strength of the schema effect. We refer to this measure as 'schema effect' from now on.

5.3.5 Equipment

This experiment was realised with custom-written scripts using Cogent 2000 developed by the Cogent 2000 team at the Functional Imaging Laboratory and the Institute for Cognitive Neuroscience (University College, London). It was written and executed using MATLAB® 7.5 running on a PC equipped with a dual-core processor.

5.3.6 PSG data acquisition and analysis

Polysomnographic monitoring was carried out using an Embla® N7000 sleep monitoring system, with Ag-AgCl electrodes attached using EC2® electrogel after the scalp was first prepared with NuPrep® exfoliating agent. Scalp electrodes were attached according to the 10-20 system at 10 standard locations, C3, C4, F3, F4, O1, O2, P3, P4, T5, T6, each referenced to the contralateral mastoid (M1 and M2). Left and right electrooculogram, left, right, and upper electromyogram, and a forehead ground electrode were also attached. Impedance of less than 5 kΩ was verified at each electrode. The digital sampling rate was 200 Hz. Sleep structure was analysed using RemLogic® 1.1 software, in 30 s epochs, bandpass filtered between 0.3 and 35 Hz, by two trained sleep researchers according to the AASM Manual (American Academy of Sleep Medicine, Westchester, IL, 2012). The proportion of time spent in each sleep stage and the overall sleep duration were calculated. For spindle detection raw EEG data for nonREM sleep (including stage 2 and slow wave sleep) were cleaned of artefacts and band-pass filtered (12-15 Hz) using a linear finite impulse response filter. An automated detection algorithm (Ferrarelli et al., 2007), which identified spindles as amplitude fluctuations in the filtered time series that exceed a predetermined threshold, was used to determine the number of spindle events at each electrode (excluding O1 and O2). Reported results are averaged across channels if not stated otherwise. Additional spindle analyses were conducted for stage 2 and slow wave sleep (SWS), separately, and for fast (13-15 Hz) and slow (11-13 Hz) spindles.
5.3.7 Statistical analyses

Participants’ ratings on the relatedness between the newly learned facts and the schema were assessed using paired t-tests, separately for the schema-related and non-schema condition. The behavioural performance was assessed by calculating the proportion of trials in which the newly learned facts were correctly identified. Reaction times were recorded as a secondary measure. In a first step a 2x2x2 repeated measures ANOVA with factors schema, degree of relatedness and recall (levels: immediate, delayed) was conducted on the number of correctly remembered facts. The same analysis was also conducted on the reaction times of correctly remembered facts. Significant effects were further explored using secondary ANOVAs and t-tests. As our main interest concerned how the schema effect (the difference in the number of correctly remembered schema-related and non-schema facts) was modulated by consolidation and degree of relatedness, this was explored in a second step, using a 2x2 repeated-measures ANOVA with factors relatedness and recall, on the schema effects. The number of false responses was compared between all conditions via paired t-tests, to confirm that false responses did not play a role for the analyses.

In Chapter 4 we found that sleep spindle rates were related to the schema-dependent consolidation process. Therefore we focused the current PSG analysis on sleep spindles.

In order to investigate the role of spindles in the current study, the correlation with the schema-dependent change in memory performance across sessions, i.e. the interaction score [delayed(schema-related - non-schema) - immediate(schema-related - non-schema)], was measured. Data were analysed in SPSS 20. Normality assumptions were not violated as assessed by the Shapiro-Wilk test. In all our results we considered p < 0.05 as significant and all tests were two-tailed.

5.4 Results

5.4.1 Subjective ratings

Schema-related facts were divided into the categories closely-related and distantly-related based on subjective relatedness ratings. Implied by this division, schema closely-related facts (mean: 4.700, SE: 0.132) were rated significantly higher than schema distantly-related facts (mean: 1.780, SE: 0.153), t(20) = 23.121, p < 0.001. The high numerical difference between the means on this scale suggests that some facts were clearly perceived as more strongly related to the schema than others. Importantly, the ratings of the matched non-schema facts did not differ between the two conditions, t(20) = 0.173, p = 0.864 (closely-related mean: 3.066, SE: 0.105; distantly-related mean: 3.085, SE: 0.129). Schema-related and non-schema facts did not differ in terms of their ratings, t(20) = 0.978, p = 0.340, or in terms of the reaction times for the ratings, t(20) = 0.833, p = 0.415, suggesting that participants focused equally on both types of facts.

5.4.2 Behavioural memory performance

Accuracy results of the immediate and delayed recall task are displayed in Figure 5.4. A 2x2x2 repeated measures ANOVA with factors schema, relatedness and recall revealed
significant main effects for recall, $F(20) = 48.188$, $p < 0.001$, schema, $F(20) = 51.037$, $p < 0.001$, and relatedness, $F(20) = 30.155$, $p < 0.001$, and a significant schema $\times$ relatedness interaction, $F(20) = 13.789$, $p = 0.001$. All other interactions were not significant, $F(20) \leq 1.875$, $p \geq 0.186$. The significant schema $\times$ relatedness interaction was further investigated using a pair of 2x2 repeated measures ANOVAs with factors relatedness and recall, separately for schema-related and non-schema facts. For the schema-related facts this analysis revealed a significant main effect of relatedness, $F(20) = 45.459$, $p < 0.001$, with better memory performance for closely-related (mean: 13.881, SE: 0.614) than for distantly-related (mean: 11.810, SE: 0.611) facts. The relatedness $\times$ recall interaction was not significant, $F(20) = 0.793$, $p = 0.384$. For the non-schema condition, the ANOVA displayed no differences in memory performance between closely-related facts (mean: 9.929, SE: 0.562) and distantly-related facts (mean: 9.405, SE: 0.448), $F(20) = 2.635$, $p = 0.120$. The relatedness $\times$ recall interaction was again not significant, $F(20) = 0.269$, $p = 0.610$. These results suggest that the strength of the schema benefit was modulated by the degree of relatedness between the newly learned facts and the schema. No schema-dependent change across consolidation was observed. The average number of false responses was as expected very low; it varied between 0.57 $\pm$ 0.16 and 1.19 $\pm$ 0.28 for all conditions. Conditions did not differ in the number of false responses, $t(21) \leq 1.446$, $p \geq 0.164$.

The 2x2x2 ANOVA did not reveal a significant schema $\times$ recall or schema $\times$ relatedness $\times$ recall interaction. While in this analysis the effect of relatedness on schema-related and non-schema facts was explored separately, our main interest was whether the schema effect itself was modulated by the degree of relatedness and changed across time. Therefore a 2x2 repeated-measures ANOVA with factors relatedness and recall was conducted on the schema effects for the four conditions. The schema effect was significantly greater for the closely-related (mean: 3.952, SE: 0.483) than the distantly-related (mean: 2.405, SE: 0.500) facts, $F(20) = 13.789$, $p = 0.001$. The overall schema effect did not differ between the immediate and the delayed recall, $F(20) = 0.099$, $p = 0.757$, and there was no significant recall $\times$ relatedness interaction, $F(20) = 0.037$, $p = 0.849$. Planned post-hoc tests comparing the schema effect between immediate and delayed recall separately for closely- and distantly-related facts also revealed no difference, $t(20) \leq 0.416$, $p \geq 0.682$. These results suggest that the strength of the schema effect was modulated by the level of relatedness between the newly learned facts and the schema. However, this effect did not change across consolidation.

### 5.4.3 Reaction time results

Reaction time results are presented in Figure 5.5. A 2x2x2 repeated measures ANOVA with factors schema, relatedness and recall was used to investigate schema-dependent differences in the reaction times. This revealed a significant main effect of relatedness, $F(20) = 15.689$, $p = 0.001$, and a significant relatedness $\times$ schema interaction, $F(20) = 7.800$, $p = 0.012$. Post-hoc t-tests showed that while there was no significant difference in the reaction times between closely- and distantly-related facts for the non-schema condition, $F(20) = 0.161$, $p = 0.693$; this difference was significant for the schema-related condition,
Chapter 5. A weak schema link is sufficient to trigger the schema benefit

Figure 5.4: Response accuracy. (A) Proportion of correctly remembered facts, separately for closely- and distantly-related facts. (B) Proportion of correctly remembered facts for all schema-related facts combined. There was a clear schema effect, as shown by better recall of schema-related facts than non-schema facts. The degree of relatedness influenced the size of the schema effect, such that schema closely-related facts were remembered better than distantly-related facts. No schema-related change across consolidation was observed. Data are presented as Mean ± SE. ***p < 0.001, *p < 0.05, †p < 0.1, not sig. p > 0.1.

F(20) = 20.625, p < 0.001, with quicker reaction times for closely-related facts (mean (in ms): 3634.5, SE: 293.8) than for distantly-related facts (mean (in ms): 4608.7, SE: 416.1). All other main effects and interactions were not significant, F(20) ≤ 2.748, p ≥ 0.115. These results were in line with the observed accuracy results and suggest that the level of relatedness between the newly learned facts and the schema modulated difficulty. However, there was no schema-dependent effect on the consolidation.

5.4.4 Polysomnography results

Results of the PSG analysis are presented in Table 5.3. In order to investigate whether spindles predicted a change in the overall schema effect (closely- and distantly-related facts combined) across consolidation, the correlation between the nonREM spindle density and
the interaction score \([\text{delayed}(\text{schema-related}) - \text{non-schema}) - \text{immediate}(\text{schema-related}) - \text{non-schema})\] was measured. This revealed a significant correlation, \(r(19) = 0.614, p = 0.005\) (Figure 5.6A). Participants with higher spindle densities showed a greater schema effect for the delayed than the immediate condition, while participants with lower spindle densities showed the opposite pattern, suggesting that high spindle densities predicted an increase in the size of the schema effect across consolidation. We also explored whether spindles predicted the change in memory performance for schema-related items only. However, this correlation was not significant, \(r(19) = 0.336, p = 0.123\). Equivalent analyses were conducted separately for the closely-related and the distantly-related condition, in order to investigate whether the degree of relatedness had an effect on the association with spindles (Figure 5.6B). The interaction score for the closely-related condition was significantly correlated with spindle density, \(r(19) = 0.545, p = 0.016\). For the distantly-related condition we observed a strong trend, \(r(19) = 0.440, p = 0.059\), suggesting that a weak link to the schema was sufficient to trigger the association with spindles. Again these correlations were specific to the interaction score and were not present for the decay of schema-related memories only, \(r(19) \leq 0.373, p \geq 0.116\).

In a secondary analysis we explored whether the association between spindle density and the overall interaction score was driven by a specific type of spindles. Correlations between spindle activity and the overall interaction score were calculated separately for central (C3, C4), frontal (F3, F4) and parietal (P3, P4 and T5, T6) channels to see whether the effect was carried by specific sites. But all channel pairs showed significant correlations, \(r(19) \geq 0.46, p \leq 0.05\). A division into fast (13-15 Hz) and slow (11-13 Hz) spindles was conducted to assess whether the effect was driven by one of these two types of spindles, but both spindle types showed significant correlations with the interaction score, \(r(19) \geq 0.513, p \leq 0.019\). A division of all nonREM spindles into SWS and Stage 2 spindles, revealed that only SWS spindles showed a significant correlation with the interaction score (SWS spindle density: \(r(19) = 0.546, p = 0.015\); Stage 2 spindle density: \(r(19) = 0.355, p =

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**Figure 5.5. Reaction time (RT) results.** Reaction times were quicker for schema closely-related facts than for schema distantly-related facts, but did not differ in the non-schema condition. No differences were observed between recall sessions. Data are presented as Mean ± SE. ***p<0.001, **p<0.01.
0.136). As expected, no association between the interaction score and any other sleep stage was observed, $r(19) \geq 0.149$, $p \leq 0.542$.

**Figure 5.6:** Association between spindle density and change of the schema effect across consolidation. Participants with higher spindle densities showed a greater schema effect for the delayed than the immediate recall, while participants with lower spindle densities showed the opposite. (A) Correlation between spindle density and the interaction score of the overall schema effect. (B) Correlation between spindle density and the interaction score for the closely-related and distantly-related condition, separately. NS: Non-Schema, S: Schema-related, S-C: Schema closely-related, S-D: Schema distantly-related, NS-C: Non-Schema facts that match S-C facts, NS-D: Non-Schema facts that match S-D facts.
Table 5.3: Polysomnography results.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (in min)</td>
<td>440.08 ± 9.32</td>
</tr>
<tr>
<td>Stage 1 (% of TST)</td>
<td>440.08 ± 9.32</td>
</tr>
<tr>
<td>Stage 2 (% of TST)</td>
<td>5.73 ± 0.92</td>
</tr>
<tr>
<td>SWS (% of TST)</td>
<td>17.26 ± 1.56</td>
</tr>
<tr>
<td>REM (% of TST)</td>
<td>16.82 ± 0.94</td>
</tr>
<tr>
<td>Spindle density</td>
<td>0.60 ± 0.05</td>
</tr>
</tbody>
</table>

TST: Total sleep time, SWS: Slow wave sleep, REM: Rapid-eye-movement sleep. Data are presented as Mean ± SE. Stage 1, Stage 2, SWS and REM are presented as percentage of the total sleep time. Spindles density describes the number of spindles per minute of non-rapid-eye-movement sleep.

5.5 Discussion

The current study explored whether the degree of relatedness between new information and pre-existing knowledge influenced the schema effect and its association with sleep spindles. We found that the degree of relatedness indeed modulated the size of the schema effect. Closely-related facts showed a greater schema benefit than distantly-related facts. Consistent with the results of Chapter 4, sleep spindles predicted how the schema effect changed across consolidation. Participants with higher spindle densities showed an overnight increase in the schema effect, while participants with lower spindle densities showed a decrease. This association was also evident for the closely-related and the distantly-related conditions separately: while the closely-related condition showed a clear association, the distantly-related condition revealed a strong trend. These results suggest that the schema benefit on memory is modulated by the degree of relatedness, but even facts that are only weakly related seem to trigger the spindle-related assimilation process.

In line with the results of Chapter 4 and previous research (Tse et al., 2011; van Kesteren et al., 2010a, 2013a, 2014), we observed an immediate schema benefit, which suggests that schema-dependent differences are already present during memory acquisition. Van Kesteren and colleagues (van Kesteren et al., 2010a, 2013a, 2014) showed that in the presence of an associative schema the encoding of new information relies stronger on the medial prefrontal cortex (mPFC) and less strongly on the medial temporal lobe (MTL) than in the absence of a schema. These differences in the contribution of neocortex and hippocampus are thought to lead to an immediate memory benefit and to initiate differences in subsequent consolidation mechanisms (van Kesteren et al., 2012). In the current study we observed a greater schema effect for the closely-related facts than the distantly-related facts. This was expected as the closely-related facts were more strongly interrelated with the pre-existing schema, which is assumed to facilitate the assimilation into neocortical knowledge structures (McClelland, 2013; van Kesteren et al., 2013a; Wang et al., 2012). Van Kesteren et al. (2013) assessed in a similar study the effect of congruency on the schema advantage using an associative memory task in which participants memorised images of object pairs, such as 'kitchen - plate' or 'tennis court - umbrella'. Memory per-
formance was investigated across three categories: consistent, neutral, and inconsistent, and was shown to increase linearly with congruency. Our results are consistent with these findings. In contrast to the strongly episodic task applied by van Kesteren et al. (2013) we showed that the effect of relatedness is also present when new information is learned and integrated into an experimentally controlled schema.

Surprisingly, and in contrast to the findings of Chapter 4 we did not observe an increase in the schema effect across consolidation. In Chapter 4 schema-related memories were preferentially retained, possibly mediated by more efficient assimilation into the schema. In the current study, however, schema-related memories showed the same approximated decay rate as non-schema memories. Several components of the experimental design of Chapter 4 were changed in the current study, which may explain these findings. Firstly, as one recall session took place before the consolidation interval, this might have changed the consolidation process and maybe influenced what was consolidated. Having two recall sessions could have also introduced some interference, especially for the schema-related category. By recollecting schema-related information in recall session one, newly acquired memories of other category members might have been reactivated through the overlapping schema. Memory reactivation during wakefulness is thought to destabilise memory traces (Nader & Hardt, 2009) and makes them prone to interference (Diekelmann et al., 2011), which could explain the observed results. Secondly, rating the relatedness at the beginning of the encoding round might have led to a deeper encoding, preferentially benefiting non-schema memories, whose retention is more difficult and requires more active processing (van Kesteren et al., 2012). As differences in the consolidation process are more subtle than the general schema benefit, all these factors could explain the comparable persistence of schema-related and non-schema memories, while preserving the overall schema benefit.

In Chapter 4 we found that the rate of spindles predicted the overnight increase in the schema effect. Consistent with these results we observed in the current study that spindle densities correlated with the overnight change in the overall schema effect. Importantly, this association was also reflected in the closely- and distantly-related conditions. These findings suggest that even information that is only weakly related to a pre-existing schema triggers this spindle-related consolidation process and therefore leads to a behavioural memory benefit. Whether the association with spindles is stronger for closely-related facts than for distantly-related facts cannot be concluded from the current results, as the difference might simply be due to very low statistical power. That spindles play a role in the integration of newly learned information with existing knowledge has already been suggested in two recent studies (Tamminen et al., 2010, 2013), in which a lexical competition task was applied for measuring integration. Tamminen et al. (2010) for example demonstrated that participants with higher spindle densities showed larger overnight increases in the lexical competition effect, reflecting increased integration, than participants with lower spindle densities. Spindles are assumed to provide brief windows of enhanced plasticity in the neocortex (Rosanova & Ulrich, 2005). Due to the synchronising property of slow oscillations, spindles occur in temporal alignment with hippocampal sharp wave...
ripples (SWR), which have been causally implicated in memory consolidation by connecting hippocampal and neocortical cell assemblies (Mölle et al., 2006; Siapas & Wilson, 1998; Sirota et al., 2003; Steriade & Timofeev, 2003). In close temporal association with SWR, memory traces that were active during wakefulness are reactivated during sleep, which is proposed to be a key mechanism for sleep-dependent memory consolidation (Buzsáki, 1996; Diekelmann & Born, 2010; Kudrimoti et al., 1999). The temporal alignment between periods of increased neocortical plasticity, induced by spindles, memory reactivation and the enhanced neocortical-hippocampal information exchange during SWR might provide the neural basis for integrating new memory traces into existing neocortical networks (Rasch & Born, 2013). Thus, spindle activity might mark hippocampal-to-neocortical consolidation in general and thus the rate of spindles will be highest for the information that is more readily assimilated into existing knowledge (i.e., schema-consistent).

In summary, the current study supports the hypothesis that the rate of sleep spindles marks the integration of new information into existing neocortical knowledge structures. A weak link to a pre-existing schema seems sufficient to trigger the schema benefit, which is reflected in enhanced memory retention and in an association with sleep spindle densities.

Acknowledgements
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Chapter 6

General Discussion

This thesis investigated the role of sleep in memory reorganisation with a focus on processes that are thought to be involved in the formation of semantic memory. Over the past years research has shown that memories can be reorganised during sleep. However, this does neither occur under all circumstances nor for all memories equally. Hence, many open questions regarding the processes that are supported by sleep and the mechanisms underlying memory reorganisation remain. By using polysomnography (PSG), behavioural memory testing, functional magnetic resonance imaging (fMRI) and cued memory reactivation, our work has raised important questions for future research and extended the current understanding of the role of sleep in memory reorganisation. This discussion is divided into two parts. First, it addresses the underlying mechanisms of sleep-related memory reorganisation and factors that influence this process, with respect to Chapters 2 and 3. Secondly, it is discusses the role of sleep in the assimilation of new information into semantic networks, based on Chapters 4 and 5. For each of the two parts, the key results are summarised and then related to findings in the literature. Finally, the relation between the two parts and resulting future research questions are discussed.

6.1 The impact of sleep on processes of abstraction and integration

6.1.1 Summary of findings (Chapters 2 and 3)

In Chapter 2 we aimed to mimic the formation of abstract semantic representations by reducing this process to two of its key computational challenges, the integration of cross-modal information and the extraction of statistical regularities. Therefore we used a cross-modal category learning task and investigated the emergence of category knowledge over an offline retention period, containing wakefulness and sleep. In line with prior findings, which showed a beneficial effect of time on probabilistic category learning (Djonlagic et al., 2009; Durrant et al., 2011) and the formation of generalisable and integrated memory representations (Ellenbogen et al., 2007; Sweegers et al., 2014; Tamminen et al., 2012), we found that an offline retention period facilitated the emergence of category knowledge. We also observed a dissociation between day-time and sleep-related processes, but surprisingly the beneficial effect of time was restricted to wakefulness. This was unexpected as sleep is thought to promote the extraction of statistical regularities and the integra-
tion of distinct elements into more coherent, gist-like representations (Lewis & Durrant, 2011; Rasch & Born, 2013; Stickgold & Walker, 2013). However, our study was the first to address the impact of sleep on the integration of information from different sensory modalities. Hence, our results suggest that this particular process preferentially occurs during wakefulness. Our findings highlight the important question, of what determines whether memories are processed during sleep. As we did not observe a sleep benefit in Chapter 2, the goal of Chapter 3 was to further explore the underlying mechanisms in a task, in which the positive effect of sleep on statistical learning mechanisms was already established. In Chapter 3 we investigated whether cued memory reactivation during slow wave sleep (SWS) could enhance the beneficial effect of sleep on abstraction and generalisation. Cued memory reactivation during sleep has been applied in a range of previous studies to strengthen memory (Rudoy et al., 2009; Rihm et al., 2013; Schreiner & Rasch, 2014). Whether processes that contribute to semanticisation can also be promoted by this manipulation is largely unknown. Participants conducted an auditory statistical learning task, in which the abstraction of the underlying statistical structure is thought to be facilitated by SWS (Durrant et al., 2011, 2013, submitted). Surprisingly, participants, who received cued reactivation during SWS performed significantly worse the next morning and the association between SWS and performance, that was evident in the control group, was abolished. Participants who received the replay directly before sleep during wakefulness showed no impairment across sleep, suggesting that the negative effect of replay on abstraction performance was specific to replay during sleep. These results suggest that the replay during SWS disrupted the mechanisms, which support abstraction during sleep. One possible explanation for these unexpected findings is that the memory cue interfered with spontaneously occurring reactivations, due it is probabilistic nature. These results raise important questions about the scope of cued memory reactivation and the underlying mechanisms of abstraction.

### 6.1.2 Relation to semantic memory

Chapters 2 and 3 addressed the impact of sleep on abstraction and cross-modal information integration, processes involved in the semanticisation of memories. This view that semantic representations emerge as a product of statistical learning mechanisms is strongly based on one specific theoretical framework for semantic memory, the hub-and-spoke model (Lambon Ralph et al., 2010; Rogers et al., 2004; Rogers & McClelland, 2004). According to the hub-and-spoke model the formation of modality-invariant multi-dimensional representations that code the higher-order statistical structure of conceptual relationships results from interactions between a transmodal hub and modality-specific spokes (Lambon Ralph, 2014; Rogers & McClelland, 2004). The hub is thought to conduct the crucial computations, such as the integration of information across multiple modalities and experiences, and the coding of statistical regularities and conceptual relationships (Lambon Ralph et al., 2010). Important to note is that we did not try in Chapters 2 and 3 to look at semantic memory per se, but at the basic computational mechanisms that are assumed to underlie the formation of abstract semantic representations. An obvious limitation of this approach is that it is very abstract and strongly based on the hub-and-spoke model.
We do not know if we really tackled the formation of semantic representations in these studies and further research is needed to answer this question. The advantage of this approach is that it provides a bridge between theories on semantic memory and findings from sleep research. Supporting evidence that the basic mechanisms, investigated in our studies, directly relate to semantic knowledge comes from a recent study by Hoffman et al. (2014). In this study semantic dementia patients, who had cortical damage of the ATL, conducted a family resemblance category learning task. Similar to the cross-modal category learning task of Chapter 2, correct categorisation in a family resemblance task is based on the integration of multiple information into a single concept. Hoffman et al. (2014) showed that patients were unable to integrate multiple features but instead based their category judgements on a single dimension. These findings provide first evidence that the formation of new, abstract category representations and the organisation of well-established conceptual knowledge might rely on the same system, the anterior temporal lobe (ATL). A possible future direction to address whether we tapped into the formation of semantic representations could be to investigate whether the ATL becomes active when category knowledge emerges. This could be done using distortion-corrected (Binney et al., 2010) or dual gradient echo (Halai et al., 2014) functional magnetic resonance imaging (fMRI) or transcranial magnetic stimulation (TMS, Pobric et al., 2007).

6.1.3 Benefit of consolidation on the formation of semantic memory

Systems memory consolidation is thought to represent a main route towards creating semantic memory (Battaglia et al., 2011; Cermak, 1984; McClelland et al., 1995; Meeter & Murre, 2004; Moscovitch et al., 2005; Rosenbaum et al., 2001; Stickgold, 2009). This is usually assumed to be a very slow and gradual process, in which the neocortex learns to discover the structure in ensembles of experiences and gradually incorporates this without causing interference with existing knowledge structures (McClelland et al., 1995). The Complementary Learning Systems theory (CLS) suggests that repeated reactivation of initially hippocampal-dependent memory traces supports reinstatement of recent memories in the neocortex (McClelland et al., 1995). With each reinstatement neocortical connections are thought to alter slightly, such that commonalities across different memories can be gradually extracted into neocortical (semantic) representations. Importantly, reinstatement also occurs during post-learning periods, suggesting that systems consolidation requires offline intervals (Frankland & Bontempi, 2005; McClelland et al., 1995). However, experimental evidence that the formation of semantic memory relies on offline consolidation is still very sparse. Most studies, which showed that memories semantically over time, did not separate the effects of offline consolidation and additional learning (Conway et al., 1997; Conway, 2009; Nelson, 1974). Support for the hypothesis comes from studies, which show that mechanisms that contribute to semanticisation, such as the integration of information into unified representations (Ellenbogen et al., 2007), the extraction of regularities (Durrant et al., 2011; Sweegers & Talamini, 2014), generalisation (Tamminen et al., 2012) and the decontextualisation of information (Talamini & Gorree, 2012) benefit from offline consolidation. The beneficial effect of time on category learning that we observed in Chapter 2 is in line with these findings. Our study extends previous
work by including a cross-modal component. Furthermore our results suggests that the very early phase of concept formation is facilitated by offline consolidation. Many open questions remain regarding the underlying mechanisms and the role of offline consolidation for later phases in concept acquisition. Important to note is also, that additional routes towards creating semantic memory seem to exist, which can be independent of the hippocampus (Gardiner et al., 2008; Knowlton & Squire, 1993; Ryan et al., 2013; Smith & Grossman, 2008) or rely on accelerated memory consolidation (McClelland, 2013; Tse et al., 2007). Further research is needed to get a better understanding of how these different processes relate to each other.

Research over the last three decades has provided strong evidence that sleep plays a crucial role for memory consolidation. During sleep, memories are repeatedly reactivated, which is assumed to cause a reorganisation, such that memories can be integrated into long-term memory and qualitatively altered to become decontextualised, schema-like representations (Inostroza & Born, 2013; Lewis & Durrant, 2011; Rasch & Born, 2013). Sleep has been shown to benefit different processes that contribute to semanticisation such as the extraction of regularities (Djonlagic et al., 2009; Durrant et al., 2011, 2013; Fischer et al., 2006), and the integration of information across multiple memories (Ellenbogen et al., 2007; Lau et al., 2011a,b). The category learning task of Chapter 2 involved both aspects, but we observed a daytime and no sleep-related consolidation benefit. These findings highlight the very timely question of what determines whether memories are processed during sleep.

6.1.4 What determines which memories are processed during sleep?

By now it is beyond dispute that sleep can benefit memory strengthening and reorganisation. However, it does not do this under all circumstances and for all memories equally. An initial selection during or shortly after encoding seems to determine which memories are 'tagged' for sleep-dependent processing and which are not (Wilhelm et al., 2011; Stickgold & Walker, 2013). Stickgold and Walker (2013) suggested that this selective gating of relevant and irrelevant information plays a crucial role in filtering out evolutionary important information that are of future relevance. Experimental support for this hypothesis came from Saletin et al. (2011). In their study explicit cues were presented during learning, which indicated whether specific information would be tested after sleep. They found that sleep, relative to wakefulness, selectively ignored the facilitation of items previously cued to be forgotten, yet preferentially enhanced recall for items cued to be remembered. These results suggest that sleep can selectively strengthen memories that are relevant for future behaviour. In line with this hypothesis, memories that seem to be preferentially processed during sleep are emotional memories (Hu et al., 2006) or memories linked to reward (Abe et al., 2011; Fischer & Born, 2009). Importantly, also individual components of a single episodic memory can be selectively tagged if they are of particular importance (Payne & Kensinger, 2011). In both of our studies participants completed an immediate test session before sleep and were informed that there was a delayed test session after sleep, which is thought to be sufficient to induce future relevance (Wilhelm et al., 2011). The lack of a sleep effect in Chapter 2 suggests that in our case, however, this did not
initiate sleep-related processing, possibly due to the complex nature of our task.

Apart from specific types of memories that seem to be preferentially consolidated across sleep, several factors regarding memory acquisition also influence whether memories benefit from sleep. One important factor, which could also explain the lack of a sleep benefit in our data, is awareness (Robertson et al., 2004). Evidence is for example provided by Song et al. (2007) who used a probabilistic variant of the serial reaction time task (SRTT), in which awareness could be carefully manipulated. The authors demonstrated that when learning occurred implicitly wakefulness but not sleep had a beneficial effect. Our results of Chapter 2 are in line with these findings as we observed a daytime but no sleep-related consolidation benefit for the CMCL task, in which learning was largely implicit. Some studies, however, also reported positive effects of sleep on implicit tasks, such as the statistical learning task used in Chapter 3 (Cousins et al., 2014; Durrant et al., 2011). This makes awareness as only factor mediating sleep-related processes unlikely. In fact, a range of other factors such as attention (Song, 2009) or the type of learning (Djonlagic et al., 2009) also seem to modulate sleep benefits (Djonlagic et al., 2009; Song, 2009). Overall, these studies show that sleep benefits are susceptible to even small changes in the experimental design and no factor on its own can adequately explain all existing data (Diekelmann et al., 2009; Stickgold & Walker, 2013). More complex interactions between several factors mentioned above might determine which memories are ‘tagged’ for sleep-related processing and which are not. The question of what determines whether memories are processed during sleep remains a topic of active investigation and further research is needed to get a better understanding of the underlying processes (Stickgold & Walker, 2013).

### 6.1.5 What determines how memories are processed during sleep?

Once memories are ‘tagged’ for sleep-dependent consolidation, they can undergo different processing routes. Memory stabilisation, which represents a quantitative memory change, is one possible form of offline memory processing that occurs during sleep. This thesis focuses on another process, memory reorganisation, during which memories are integrated into long-term memory and qualitatively altered to become decontextualised, schema-like representations. Whether processes of memory stabilisation and reorganisation occur subsequently or independently from each other is not yet known, but most evidence argues for the former (Diekelmann & Born, 2010; Rasch & Born, 2013; Stickgold & Walker, 2013). A growing body of research has shown that sleep can facilitate a variety of different mechanisms that contribute to the semanticisation of memories (see Rasch & Born, 2013). While at the outset of this thesis the assumption prevailed that these processes are generally promoted by sleep (Diekelmann & Born, 2010; Lewis & Durrant, 2011; Walker & Stickgold, 2010), this view subtly started to change and it seems to become evident that they occur in a very selective way only. In skill learning that requires the abstraction of often complex rules it is known that a sleep benefit is not consistently observed (Nemeth et al., 2010; Song et al., 2007). For declarative tasks, however, negative reports are barely published, although they seem to be accumulating. Here are a few examples. Cox et al. (2014b) inves-
tigated the impact of sleep- and time-dependent consolidation on the de-contextualisation of information and observed that whereas contextual cues lost their potency with time, sleep did not modulate this process. That sleep can promote insight into a hidden rule was shown by Wagner et al. (2004). A follow-up study from the same group, however, did not replicate this behavioural effect (Darsaud et al., 2011). Similarly, in a study that I conducted during my PhD but have not included here, I failed to replicate, a sleep-benefit on abstraction, originally shown by Lau et al. (2011). Sweegers & Talamini (2014) demonstrated in a study, which explored the role of sleep on the abstraction of regularities, that sleep had no beneficial effect on this process compared to wakefulness. Comparable results were presented on a poster at the 21st European Sleep Research Society Congress by Schönauer et al. (2012), which summarised several episodic category learning studies in which no beneficial effect of sleep on the extraction of statistical regularities was observed. Together, these studies demonstrate that even under very similar conditions sleep does not always facilitate processes that contribute to a change in memory quality. Just as with the selective memory tagging described above, gist extraction and integrative processing during sleep seem to be selectively applied and not universal sleep-related mechanisms (Stickgold & Walker, 2013).

Which factors determine how memories are processed during sleep is largely unknown and presents another important knowledge gap in this field that needs to be solved. One hypothesis suggested by Stickgold & Walker (2013) is that the tag labelling a memory to undergo sleep-related processing also contains information about the nature of this processing. Future relevance might again play a crucial role as sleep-related processing often seems to reflect an optimisation for future behaviour (Saletin et al., 2011; Stickgold & Walker, 2013; Wilhelm et al., 2011). The weather prediction task for example can be solved by abstracting underlying regularities. Sleep has been shown to facilitate this process (Djonlagic et al., 2009) and not individual item memory, which would not benefit this task. In word-pair learning on the other side, sleep facilitates the retention of individual words (Gais et al., 2002), which optimises task performance. In false memory paradigms like the Deese-Roediger-McDermott paradigm, in which it is less clear which mechanisms benefit performance, both processes, abstraction of common themes and protected item memory, have been observed to be facilitated by sleep (Diekelmann & Born, 2010; Fenn et al., 2009). Overall, these findings suggest that task relevance plays a role in the selection of the processing type that occurs during sleep. Whether this aspect contributed to the lack of a sleep effect in Chapter 2 can only be speculated. Another factor that additionally complicates the investigation of sleep-related processes is that behavioural measures are often not sensitive enough to pick up changes in the memory quality. In Chapter 3 we did not observe an overnight improvement in task performance, as reported in previous studies (Durrant et al., 2011, 2013), but the association between SWS and an overnight change in performance was still present. Similarly, Darsaud et al. (2011) who failed to replicate the finding that sleep promoted insight into a hidden rule by Wagner et al. (2004) still showed differences in sleep-related processes for participants who gained insight and those who did not. In these studies it appears that although not reflected
in the behavioural measure, specific processing occurred during sleep. This suggests that sleep-related behavioural benefits might be very subtle and susceptible to environmental factors, making them a not very sensitive measure.

### 6.1.6 Underlying mechanisms of memory reorganisation during sleep

Memory reorganisation represents one form of sleep-related memory processing. The goal of Chapter 3 was to further explore the underlying mechanisms using cued memory reactivation. A general assumption made by studies using cued reactivation (or replay) is that external cues influence the occurrence of natural reactivations, and thereby manipulate the consolidation process. Evidence for this hypothesis comes from animal studies in which cued reactivation was shown to trigger (Dave & Margoliash, 2000) and bias (Bendor & Wilson, 2012) the occurrence of natural reactivations. Chapter 3 provided no direct evidence that cued reactivation during SWS influenced memory consolidation, but as the replay was reflected in a behavioural effect, this suggests that it manipulated sleep-related consolidation processes. The prevailing hypothesis based on the Active Systems Consolidation theory (ASC) is that memory reorganisation during sleep relies on the repeated reactivation of recently acquired memory traces. During sleep memory reactivations are thought to be tied into complex wave-sequences, which enable enhanced interactions between hippocampus and neocortex. Slow oscillations orchestrate in their depolarising up-phase the occurrence of thalamo-cortical spindles and sharp wave ripples (SWR, e.g. Sirota et al., 2003). This temporal synchrony is thought to ensure that hippocampal memory reactivation coincides with periods of enhanced neocortical plasticity, which is assumed to facilitate the information transfer from hippocampus to neocortex that underlies systems memory consolidation (Born et al., 2006; Diekelmann & Born, 2010). In the neocortex information is assumed to be stored in context-independent, generalisable semantic representations, implying that a transformation in the memory quality takes place when memories become independent of the hippocampus. Recently, Lewis and Durrant (2011) proposed a mechanism, called 'Information Overlap to Abstract' (iOtA), by which memory reactivation could actively underpin both the semanticisation of memories and the addition of new knowledge to existing semantic networks. According to this model, the sequential reactivation of experience-specific memories results in a selective strengthening of the elements that are shared across these memories, due to accumulating reinstatement. The model suggests that repeated reactivation of memories in different contexts and with slightly varying features progressively builds schematic representations, which reflect the shared elements across different memories. For the auditory statistical learning task of Chapter 3 this model predicts that the beneficial effect of sleep, that was observed in several studies (Durrant et al., 2011, 2013, submitted), results from the reactivation-induced selective enhancement of the highly likely transitions. Based on this theory, our hypothesis for Chapter 3 was that cued reactivation would, by manipulating the occurrence of spontaneous reactivations, further promote the abstraction process. Our negative findings seem to suggest that, against our predictions, some sort of interference occurred, which blocked the abstraction process during SWS. Several studies have used 'fixed' (not probabilistically determined) auditory sequences as memory cues during sleep and have
reported beneficial effects of the replay on implicit (Antony et al., 2012; Schönauer et al., 2014) and explicit (Cousins et al., 2014) sequence knowledge. Therefore, one explanation for our unexpected finding might be the probabilistic nature of the memory cue that we used for the replay. Assuming, according to the theoretical framework, that the memory representation of the auditory sequence that was formed during the encoding phase was spontaneously reactivated during sleep, then the replay stream did only partly overlap with this existing memory trace, due to its probabilistic structure. This partial overlap might have disrupted the natural replay and therefore inhibited the benefit of sleep on this task. Even though this explanation is speculative, it raises important questions about the nature of cued memory reactivation.

A clear limitation of Chapter 3 is the between-subject design. We tried to rule out the possibility that the auditory cues disrupted SWS, which could have caused the observed impairments, but we cannot fully exclude it. This problem was overcome in another study, which I conducted during my PhD (not included in this thesis). In this study we investigated whether cued memory reactivation promoted the linkage of elements that were not experienced together. We used a relational memory task, which has been shown to benefit from sleep (Lau et al., 2011a). In this task participants first learned to associate specific faces with specific scenes, e.g. a Buddhist temple, (Face A - Scene1). Subsequently, participants learned to associate another set of faces with the same scenes (Scene1 - Face B). Thus, each scene was associated with two different faces. The faces were not shown as being explicitly related, but they were indirectly related via the overlapping association with the same scene. Each scene was paired with a typical sound (e.g. Buddhist temple - monks singing) that was always presented together with the scene and served as memory cue for cued reactivation during sleep. Before sleep all face-scene pairs were learned to a certain threshold. During SWS half of the sounds (corresponding to half of the scenes) were replayed, while the other half was not replayed. In the morning participants conducted two tasks. One task tested their memory on the direct association between faces and scenes. The other task tested whether they had formed associations between indirectly related faces. Based on previous research, which showed that cued reactivation can strengthen associations (Rudoy et al., 2009) and that memories for face-scene pairs are spontaneously reactivated during sleep (Bergmann et al., 2012), we hypothesised that cued reactivation would promote a strengthening of the direct associations between those faces and scenes that were replayed during SWS. Based on iOtA we further expected that through the overlap with the same scene the indirect association between two faces would also be enhanced. According to our prediction we found that participants were significantly quicker in identifying those matching face-scene pairs, which were replayed, compared to those that were not replayed. This suggests that cued reactivation promoted a strengthening of the direct association between faces and scenes. Surprisingly, however, participants were less accurate in identifying those indirectly related face-face pairs that were replayed during sleep. This suggests that the indirect link was weakened by the cued reactivation. Similarly to the results of Chapter 3, cued reactivation impaired performance in the task that measured memory reorganisation. Extending the findings of Chapter 3 this study suggests that cued reactivation can influence quantitative and qualitative mem-
ory processes in different manners. Further studies are needed to determine whether these results reflect differences in the underlying mechanisms between memory strengthening and memory reorganisation or whether they are related to the specific memory cues or the cueing process itself.

Cued memory reactivation as a technique to manipulate consolidation during sleep, is still relatively new and many open questions remain regarding the underlying mechanisms and the boundary conditions. Cued reactivation has been shown to benefit memory stabilisation in several declarative and skill learning tasks (Antony et al., 2012; Rihm et al., 2013; Rudoy et al., 2009; Schönauer et al., 2014). It is largely unknown, however, whether cued reactivation can promote memory reorganisation and a transformation in memory quality. So far only one study has started to address this issue (Cousins et al., 2014). In this study replay of an auditory sequence during SWS promoted the emergence of explicit sequence knowledge in a SRTT. As the statistical learning task, the relational memory task and the SRTT all vary in many aspects from each other, no conclusion can be drawn in terms of when cued memory reactivation benefits and when it impairs processes involved in memory transformation. But, importantly, by demonstrating that cued reactivation can selectively impair memory, our studies suggest a whole new application for cued memory reactivation to investigate the underlying processes of memory reorganisation.

### 6.1.7 Function of sleep versus wakefulness

Chapters 2 and 3 were conducted under the hypothesis that sleep generally promotes processes involved in the formation of abstract semantic representations. Based on our results and findings in the literature it seems to become important to distinguish between different processes: those that benefit specifically from sleep, those that benefit equally from wakefulness and sleep, and those that benefit specifically from wakefulness. How processes that contribute to memory reorganisation could benefit from sleep was discussed in detail in the section above. Several studies, however, reported that some processes involved in semanticisation showed an equal benefit from offline intervals containing wakefulness and sleep. These studies included the abstraction of statistical regularities (Durrant et al., 2011), the integration of distinct elements (Ellenbogen et al., 2007), decontextualisation (Cox et al., 2014a) and generalisation of information (Sweegers & Talamini, 2014). The fact that in some of these studies the positive effect of sleep correlated with slow wave activity (Durrant et al., 2011; Sweegers & Talamini, 2014) suggests that the comparable benefits of wakefulness and sleep result from different underlying mechanisms. In line with this hypothesis, Ellenbogen et al. (2007) reported slight differences in memory quality after offline intervals containing sleep and wakefulness. This study showed that sleep facilitated the connection between elements as a function of distance. Connections between distantly related elements were preferentially enhanced. Wakefulness on the other side equally enhanced connections between distantly and closely related elements. Memory reactivation is generally assumed to underlie memory reorganisation (Frankland & Bontempi, 2005; Inostroza & Born, 2013; McClelland et al., 1995). While detailed models exist for how reactivation could induce memory reorganisation during sleep (Born et al., 2006), very
little is known about memory reactivation during wakefulness and how it could contribute to this process. A recent study by Gupta et al. (2010) showed in rodents not only that memory traces that were formed during prior experience were replayed during wakefulness, but they observed the construction of never-experienced novel-path sequences from experience-dependent hippocampal traces. These findings suggest that during wakefulness a reactivation-induced memory reorganisation within hippocampal circuits may promote processes of abstraction and generalisation. However, further research is needed to investigate this question. The observation in Chapter 2 that category knowledge only emerged across wakefulness but not sleep could be explained by a positive effect of wakefulness but also by a negative effect of sleep on the abstraction process. Werchan & Gómez (2013) who observed a similar benefit of wakefulness on the generalisation ability in children proposed that by strengthening irrelevant details in certain circumstances sleep can impair processes of gist extraction. This hypothesis relates back to the question of which factors determine how memories are processed during sleep. How processing in wake and sleep are related is still largely unknown. Some aspects of wake processing may be totally independent of subsequent sleep-dependent processing, others may be related. The formation of semantic memory includes a variety of different processes and while some of these seem to benefit from sleep others, maybe cross-modal integration, may not.

6.2 The role of sleep in the integration of new information with semantic memory

So far the role of sleep in memory reorganisation was discussed with a focus on the extraction of regularities and integrative processing. This section of the discussion will concern the role of sleep in the assimilation of new information into existing semantic networks.

6.2.1 Summary of findings (Chapters 4 & 5)

Chapter 4 was the first of two studies investigating the role of sleep in the integration of new information into existing knowledge structures (also called ‘schemas’). The existence of prior knowledge to which new information can be related generally improves memory for that information (Bartlett, 1932; Brewer & Nakamura, 1984; Tse et al., 2007; van Kesteren et al., 2014). Only recently research has started to unravel the underlying neural mechanisms of this beneficial effect of schemas on memory retention, or in short the ‘schema effect’. This research suggests that memories that link well into existing neocortical knowledge structures can become assimilated and independent of the hippocampus more rapidly than arbitrary or inconsistent information (McClelland, 2013; Tse et al., 2007). Another line of research showed that the integration of new information with existing knowledge benefits from sleep (Tamminen et al., 2010, 2013). In Chapters 4 and 5 we attempted to combine these two lines of research and we explored whether sleep was associated with the accelerated assimilation of congruent information into existing semantic networks. In Chapter 4 we investigated sleep-dependent differences in the consolidation of information that either related to a pre-existing schema or was completely unrelated. We observed an increase in the schema effect over time, driven by a protection
Chapter 6. General Discussion

of schema-related memories against decay. Importantly, this increase in the schema effect was predicted by sleep spindle density. Functionally, we found that higher spindle densities were associated with decreased hippocampal engagement across time, for schema-related memories only. These findings suggest that the rate of sleep spindles is associated with the hippocampal-to-neocortical consolidation of information that relates to prior knowledge. In Chapter 5 we investigated how strongly information must be related to a schema to trigger the schema benefit and the association with sleep spindles. We observed that a weak link to prior knowledge was sufficient in triggering the schema benefit and the association with spindles. Overall, these findings suggest that the rate of sleep spindle marks the assimilation of new information into long-term memory, a process, which is facilitated when the information relates to existing knowledge structures.

6.2.2 Schema benefit on memory

Based on research in rodents Tse et al. (2007, 2011) proposed the idea that in the presence of an associative schema, systems memory consolidation of newly acquired memories is accelerated. Tse et al. (2007) demonstrated, using a flavour-place associations task, that rats learned information that related to prior knowledge much quicker than unrelated or inconsistent information. The schema seemed to engage a rapid consolidation process such that after only 48 hours the integrity of the hippocampus was already unnecessary for the retrieval of the newly learned information. In two subsequent studies it was shown that such rapid, schema-dependent hippocampal disengagement was accompanied by increasing involvement of the neocortex (Tse et al., 2011; Wang et al., 2012). These findings challenged the long-standing view, based on the CLS, that the assimilation of new information into the neocortex is a slow and gradual process (McClelland et al., 1995). By running new simulations, extending those reported in McClelland et al. (1995), McClelland (2013) demonstrated that new information that is consistent with existing neocortical knowledge structures can indeed be learned rapidly and without interference, confirming the hypothesis by Tse et al. (2007, 2011). Overall, these studies provide strong evidence that schemas act as catalysts for memory consolidation by accelerating the shift in the representational division of labour in favour of neocortical over hippocampal regions (McClelland, 2013; Tse et al., 2007; van Kesteren et al., 2012). The accelerated assimilation into long-term memory is thought to drive the beneficial effect of schemas on memory, which was present in both of our studies. Our results extend this hypothesis by suggesting that sleep spindles play a role in this process.

6.2.3 Association between sleep and the schema benefit

The results of our studies suggest that the rate of sleep spindle marks the assimilation of new information into long-term memory. This is in line with the findings by Tamminen et al. (2010, 2013), who showed that more spindles were associated with enhanced integration of new information with prior knowledge. Whether spindles play a causal role in this process is unknown. The overarching framework of the ASC suggests they do by providing brief time windows of enhanced neocortical plasticity (Diekelmann & Born, 2010). Slow
oscillation are thought to coordinate memory reactivation with periods of increased neocortical receptivity, induced by sleep spindles (Mölle et al., 2006; Sirota et al., 2003). The coupling of these network events is an effective way to link neocortical and hippocampal cell assemblies and to enhance hippocampal-neocortical information exchange, which in turn could mediate the integration of new information into existing neocortical networks (Siapas & Wilson, 1998; Sirota et al., 2003). These proposed mechanisms could explain the association between the rate of spindles and the schema effect that was present in our studies. The iOtA model provides a more explicit mechanism by which sleep-related memory reactivation could facilitate the assimilation of new information into existing neocortical networks (Lewis & Durrant, 2011). iOtA suggests that the reactivation of newly acquired memories can trigger responses in existing neocortical knowledge structures, if they share overlapping elements. iOtA claims that this additional neocortical activity subsequently leads to an amplification of responses in the neocortical nodes that are involved in the new memory, which allows a more efficient incorporation. This implies that the greater the overlap between a new information and prior knowledge, the quicker the assimilation process. Our finding that the beneficial effect of prior knowledge on memory was modulated by the degree of relatedness is in line with this hypothesis. So far there is no direct evidence linking hippocampal memory reactivation during sleep to the integration of information into neocortical networks. Future studies could address this issue by using cued memory reactivation to differentially manipulate the consolidation of schema-related and unrelated memories.

A limitation of our studies is that we only show an association but no causal role for spindles in the schema-related consolidation process. Our findings support the idea that spindles mediate the assimilation of new information with existing knowledge as proposed by the ASC, and thereby modulate the behavioural schema benefit, but they do not provide conclusive evidence. Further research is needed to address whether spindles are causally involved or only a marker of this process. Another important, but missing component in our studies, is a measure of integration. The behavioural benefit and the association between spindle density and hippocampal independence strongly suggest that memories became integrated into neocortical networks, but our results do not provide direct evidence that assimilation occurred. Integration of information into neocortical networks could for example be reflected in semanticisation, such as de-contextualisation or enhanced generalisability of information. We made an attempt to measure integration by testing if a newly learned fact had generalised overnight to a higher level in the hierarchical structure i.e. the category family. Therefore, true/false statements were presented (e.g. Some hermit crabs live longer than humans), which were related to the newly learned facts (Latro can reach an age of 120 years). However, this test failed to show any effect and is therefore not included in this thesis. Another possibility to address integration would be to use neuroimaging techniques to assess whether the same neocortical circuits that support information of the schema mediate the newly learned information. Further insights could also be gained from incongruent information, as the degree of interference with prior knowledge might provide information about the level of integration.
6.2.4 Schema-related differences during memory acquisition

While our studies focused on how prior knowledge affects memory consolidation, a series of studies by van Kesteren and colleagues (2010, 2013, 2014) showed that differences in the underlying neural mechanisms that are observed during consolidation emerge already during memory acquisition. Based on these studies and research in rodents (Tse et al., 2007, 2011) van Kesteren et al. (2012) provided a theoretical framework called SLIMM ('Schema-Linked Interactions between Medial prefrontal and Medial temporal regions'), which offers a mechanism by which prior knowledge influences new incoming information. This model presents an extension to the standard two-stage model for systems memory consolidation, and introduces a third component: the medial prefrontal cortex (mPFC). SLIMM proposes that the main function of the mPFC is to detect congruency between new information and existing knowledge during memory acquisition. SLIMM further claims that when information links well to prior knowledge the mPFC inhibits activity in the hippocampus, such that the information is directly assimilated into neocortical networks. Even though SLIMM and iOtA propose different mechanisms for the beneficial effect of prior knowledge on memory retention, they are not mutually exclusive, but seem to complement each other. SLIMM proposes that, enabled by mPFC, congruent information is directly assimilated into the neocortex and therefore memorised better. iOtA on the other side suggests that the schema benefit results from accelerated memory consolidation due to a greater overlap between the newly acquired memory and existing neocortical structures during sleep-related memory reactivation. Both models agree in the assumption that the memory advantage results from facilitated assimilation of congruent information into the neocortex. While the mPFC might play a crucial role to initiate this process during memory acquisition, sleep-related memory reactivation might further contribute to accelerate the subsequent consolidation process. In our study we did not observe schema-related activation in the mPFC, possibly because we scanned during memory retrieval. So far only one study reported mPFC activity during memory retrieval (van Kesteren et al., 2010b) and according to SLIMM the mPFC only plays a dominant role during memory encoding. This suggests that the mPFC is not crucially involved in memory retrieval and might only be activated under certain conditions.

In summary, the findings of Chapters 4 and 5 are the first to show an association between sleep and the schema benefit on memory. Our results suggest that spindles mark the assimilation of new information into exiting neocortical knowledge structures, which is enhanced for information that relates to prior knowledge.

6.3 Future directions

By now, it is generally accepted that memories can be processed during sleep and that different types of memory processing can occur. Memories can be strengthened, they can be transformed towards more abstract and generalised representations or they can be integrated into existing semantic networks. All these processes are assumed to underlie the same reactivation-induced mechanism. Slow oscillations are thought to drive hippocam-
pal memory reactivation, in synchrony with thalamo-cortical spindles. This is thought to enable an information exchange between hippocampus and neocortex and to induce long-term changes within neocortical networks. Even though this theoretical model is supported by numerous studies, evidence for several critical assumptions is still missing. While many studies support the view that memory reactivation induces the beneficial effect of sleep on memory stabilisation (see e.g. Rasch & Born, 2013), direct evidence that reactivation also underlies sleep-related changes in memory quality and the integration of new information with prior knowledge is still lacking. Future research is needed to gain further insights into the underlying processes of sleep-related memory reorganisation. A major constrain in contemporary sleep-research, which could explain some of the inconsistent findings in the field, might be that the majority of studies, including ours, still focus on individual frequency oscillations or even sleep stages as a whole. According to the theoretical framework the specific wave-sequence of slow oscillations, spindles and SWR is of particular importance for sleep-related memory processing. However, this key feature of sleep is only sporadically addressed in human studies at the moment. Closely related to this topic, Genzel et al. (2014) suggest that the effect of slow oscillations, which they equate to K-complexes, is more global (i.e. recruits more distant brain regions such as the hippocampus) and hence more important for memory consolidation during light sleep than during deep sleep. Genzel et al. (2014) argue that during deep sleep delta activity prevails, which has been linked to synaptic downscaling, while during light sleep global brain interactions are most optimal, providing ideal conditions for memory consolidation. In line with this theory, our functional results of Chapter 4 were specific to stage 2 spindles. It could be addressed in future studies whether spindles that occur linked to slow oscillations (or K-complexes) during stage 2 sleep are even better predictors of the behavioural schema effect. Sleep is a highly complex state, in which different oscillatory patterns interact in complicated ways. To get a better understanding of how memory processing occurs during sleep it seems crucial that research activity focusses more strongly on the interactions between individual oscillatory events.

6.4 Conclusions

This thesis investigated the impact of sleep on processes that are assumed to underlie the formation of abstract semantic representations. These included the integration of information across different sensory modalities, the abstraction of statistical patterns, and the assimilation of new information into existing knowledge structures. While cross-modal category learning did not benefit from sleep, the assimilation of new information into semantic networks showed a clear association with the rate of sleep spindles. We further showed that cued reactivation during sleep influenced the extraction of statistical regularities, providing indirect support that memory reactivation underlies abstraction during sleep. Sleep and memory research is a highly complex field and numerous factors seem to influence whether memories are processed during sleep and what type of processing occurs. While sleep might support some of the computations involved in the formation of semantic memory, it only does this in a very selective way. Other processes of semanticisation are
not facilitated by sleep. In conclusion, this thesis provides new insights into the role of sleep in memory reorganisation and raised important questions for future research.
Bibliography


Bibliography


Bibliography


