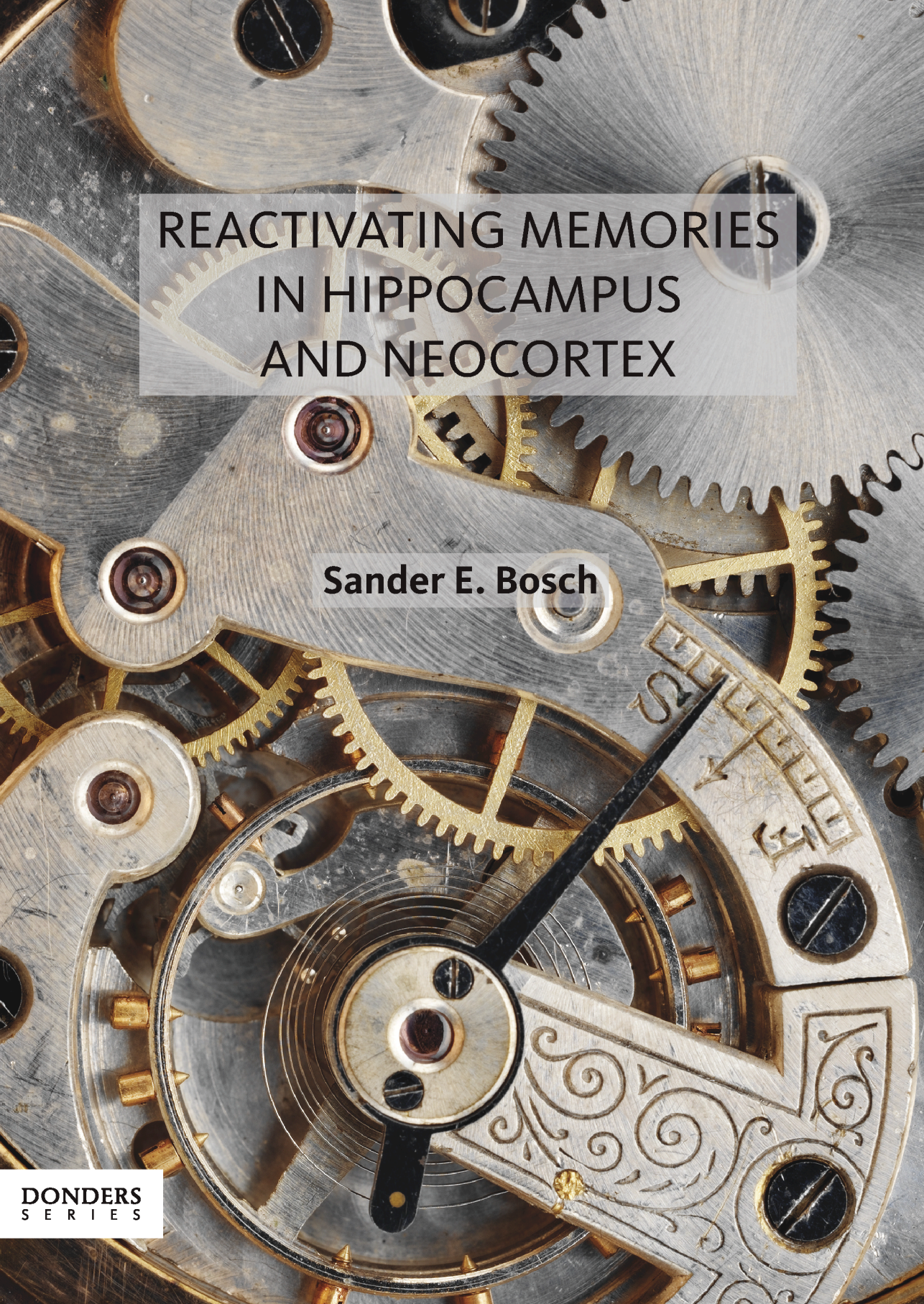

# REACTIVATING MEMORIES IN HIPPOCAMPUS AND NEOCORTEX

Sander E. Bosch

DONDERS SERIES

# REACTIVATING MEMORIES IN HIPPOCAMPUS AND NEOCORTEX

**Sander E. Bosch**

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# REACTIVATING MEMORIES IN HIPPOCAMPUS AND NEOCORTEX

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# Propositions

accompanying the dissertation

**Reactivating memories in hippocampus and neocortex**

by

**Sander E. Bosch**

1. The hippocampus represents conjunctive information about learned associations. *(this thesis)*
2. Memory retrieval is associated with reinstatement of representations in early visual cortex. These reinstated representations resemble those during passive perception. *(this thesis)*
3. During retrieval, the hippocampus is involved in supporting reinstatement of cortical representations and guiding memory performance. *(this thesis)*
4. The purpose of memories is not only to travel back in time to relive old experiences, but to predict and create the future. "It's a poor sort of memory that only works backwards." *(Lewis Carroll)*
5. Every act of perception, is to some degree an act of creation, and every act of memory is to some degree an act of imagination. *(Oliver Sacks)*
6. "In order to properly understand the big picture, everyone should fear becoming mentally clouded and obsessed with one small section of truth." *(Xun Kuang)* Every scientist should at all times maintain a connection to the bigger picture by regularly sharing their work with a layman audience.
7. The success of a research project is proportional to the quality of its six-letter acronym.

*The Time Traveller: "Well, I do not mind telling you I have been at work upon this geometry of Four Dimensions for some time. Some of my results are curious. For instance, here is a portrait of a man at eight years old, another at fifteen, another at seventeen, another at twenty-three, and so on. All these are evidently sections, as it were, Three-Dimensional representations of his Four-Dimensioned being, which is a fixed and unalterable thing (…)"*

*The Medical Man: 'But (…) if Time is really only a fourth dimension of Space, why is it, and why has it always been, regarded as something different? And why cannot we move in Time as we move about in the other dimensions of Space? (…) you cannot move at all in Time, you cannot get away from the present moment."*

*The Time Traveller: "(…) you are wrong to say that we cannot move about in Time. For instance, if I am recalling an incident very vividly I go back to the instant of its occurrence: I become absent-minded, as you say. I jump back for a moment."*

The Time Machine, H.G. Wells, pp. 33-37

# Contents

# 1

# General introduction

## 1.1. Introduction

In The Time Machine by Herbert George Wells (1895), a man, the Time Traveller, explains to his friends that there are four dimensions in our world. Three of those we refer to as Space, the fourth as Time. He discusses how three-dimensional snapshots of a life can be viewed along the fourth dimension of Time. This fourth dimension, Time, is often seen as separate from the other three, because we cannot move as freely in Time as we can do in Space. However, the Time Traveller discusses an exception when he compares memory retrieval to time travel: upon retrieval of a vivid memory, your mind is transported back to the original experience. In other words, you move back along the Time dimension to an earlier snapshot. This phenomenon of mental time travel while vividly remembering a past event is something everyone has experienced. Memory retrieval lies at the heart of adaptive behaviour: we learn from past experiences to adapt and guide future behaviour. Many psychologists and philosophers have studied memory retrieval, but up until recently the mechanisms underlying mental time travel could not be directly studied. Approximately 80 years after the Time Traveller told his friends the anecdote about the fourth dimension and how we can traverse it, Endel Tulving proposed a theory on how the brain might support mental time travel (Tulving, 1983): cortical brain regions that were involved during the original experience should become active again when one actively remembers that experience (i.e. these regions reinstate the original experience). The hippocampus, a phylogenetically old brain structure present in all vertebrates (West, 1990), is thought to be crucial in this process. Interestingly, the hippocampus has been shown to represent both spatial and temporal relations, making it an excellent candidate for the representation of all four dimensions the Time Traveller mentioned.

In this thesis, I set out to answer outstanding questions on how the hippocampus and regions in the neocortex support the reinstatement of previous experiences to guide behaviour. To answer these questions, I have investigated retrieval from both the cortical and from the hippocampal perspective: in the first two experimental chapters, I studied the reinstatement of memory representations in sensory cortex (Chapter 2) and its relation to memory performance (Chapter 3). In the two remaining chapters, I looked at the role of the hippocampus as an index for conjunctive information between associated events as a function of associational strength (Chapter 4) and time delay between learning and retrieval (Chapter 5). To answer these research questions, I combined memory tasks with analysis approaches from visual psychophysics (Chapter 2 and Chapter 3), and used

pattern analysis techniques to look at conjunctive representations in hippocampus (Chapter 4 and Chapter 5). In this introductory chapter, I will set the stage for these experimental chapters by introducing important concepts in memory that are central to this thesis, briefly defining a selection of memory concepts and describing the hippocampus and previous work on its role in the three stages of memory: encoding, consolidation and retrieval. Next, I will specify the research questions that were investigated in the four experimental chapters and will briefly introduce the methods and analyses described in the experimental chapters.

## 1.2. A taxonomy of memory

Memory can be broadly defined as the capacity of the nervous system to change as a result of experience and is often divided into three stages encoding, consolidation and retrieval (Tulving and Craik, 2000). Memory is pervasive in every aspect of life, from perception to action and prediction. Memory is not a single entity but consists of several separate components that depend on different brain mechanisms (Cohen and Squire, 1980). The primary division is made between declarative (or explicit) forms of memory, which are conscious and can be articulated, and non-declarative (or implicit) forms of memory, which are unconscious and thus cannot be articulated (Squire and Zola, 1996). Declarative memories can be further subdivided into episodic memory and semantic memory (Tulving, 1972). Episodic memory is generally defined as memory for an experienced event, which can be vividly recollected in detail, both in time and space (Tulving, 2002). Semantic memories are more factual and concept-based, and less related to any specific contextual details: they represent general knowledge and understanding about the world (Martin, 2007). Much of what we know about the differences between the described types of memory comes from case studies on human patients. The most famous example is Mr. Henry Molaison, better known under his initials H.M., who suffered from temporal lobe epilepsy. After a surgery, in which large parts of his medial temporal lobes (MTL), including bilateral hippocampus, were removed to treat his epilepsy, H.M. exhibited very specific memory deficits (Scoville and Milner, 1957). For instance, he completely lost his ability to store new memories, a deficit known as anterograde amnesia. Furthermore, he was unable to retrieve recently learned information, but could remember more remote memories such as his self-knowledge and childhood memories (temporarily graded retrograde amnesia). However, these deficits seemed to be specific to declarative memory: H.M. was still able to acquire new

motor skills, such as mirror drawing. This dissociation prompted the primary division, declarative versus non-declarative, in the memory taxonomy. Further patient studies provided evidence for the distinction between episodic (Scoville and Milner, 1957; Tramoni et al., 2011) and semantic (Rosenbaum et al., 2005; Patterson et al., 2007) amnesia. The arrival of functional neuroimaging techniques provided researchers with the tools to investigate healthy brains non-invasively (see section 1.8). Neuroimaging studies have both challenged and supported the taxonomy of memory (see Gaffan, 2002; Henke, 2010): episodic and semantic memory seem to rely on different brain structures (Rugg et al., 2002; Martin, 2007; Binder et al., 2009; Binder and Desai, 2011), warranting their taxonomic distinction, but the boundaries between other types of memory are vague. This probably has to do with the fact that memory is ubiquitous, and therefore intricately linked to other processes in the brain, like perception and attention (Peelen and Kastner, 2014). Interactions between these processes make it difficult to draw clear boundaries between different types of memory. Alternative taxonomies therefore base the distinction between memory types on processing modes, dependent on the type of information that is encoded, instead of the subjective boundaries between declarative and non-declarative memories (Henke, 2010). In this thesis, I have studied the mechanisms behind episodic memory retrieval. Specifically, I have investigated associative learning and retrieval, in which participants learn to associate different pieces of information and are later asked to retrieve them. This type of memory is crucially dependent on the hippocampus, will I will describe next.

## 1.3. The hippocampus

Patient H.M. suffered from anterograde and temporally graded retrograde amnesia following the removal of large parts of both hippocampi, indicating an important role for the hippocampus in memory formation and retrieval (Squire, 1992). The hippocampus is a brain structure resembling a seahorse (in Latin: hippocampus), located deep within the brain, in the medial temporal lobe (see Figure 1.1A). The neurons in the hippocampus are very sensitive to long-term potentiation (LTP), defined as the adaptive strengthening of synaptic connections between neurons after firing together (Hebb, 1949; Bliss and Gardner-Medwin, 1973). This flexible strengthening of connections between neurons might be how the brain represents memories (Dudai, 2004). Next to the sensitivity of its neurons to LTP, there is also adult neurogenesis in the hippocampus: new cells can

be integrated into existing neuronal networks (Deng et al., 2010). These properties render the hippocampus very plastic, making it an excellent candidate structure to support dynamic memory functions (Teyler and DiScenna, 1985).

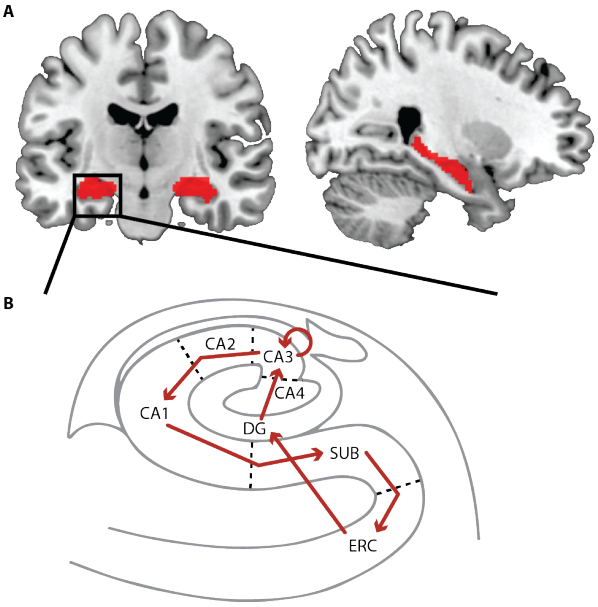


**Figure 1.1: The hippocampus**
A) The hippocampus, shown in red, superimposed on a structural MRI image. The left panel shows a coronal slice, the right panel a sagittal slice.
B) A coronal cross-section of the hippocampus, showing its subfields. The entorhinal cortex (ERC) receives multimodal input from sensory cortices, and projects these to the dentate gyrus (DG). DG transfers orthogonalized patterns to to cornu ammonis 3 (CA3), which acts as an autoassociative network due to its abundant recurrent connections. CA3 projects to CA1, which in turn transfers to the subiculum, which routes back to entorhinal cortex.

Furthermore, the neuronal architecture of the hippocampus is excellently suited for memory processes: its specialized subfields are connected in a way that allows for incoming information to be compared to internal representations (see Figure 1.1B). When new information is processed by the brain, it is transferred from sensory cortices to the entorhinal cortex (ERC), which is the connectivity relay between many cortical association areas and the hippocampus (van Strien et al., 2009). ERC forwards incoming information to dentate gyrus (DG). In the dentate gyrus, this information is processed in such a way that the information patterns are made as dissimilar from each other as possible in process called pattern separation (Mc-

Naughton and Morris, 1987; Treves and Rolls, 1994). Pattern separation renders patterns less vulnerable to interference (O'Reilly and Rudy, 2001). Dentate gyrus projects these orthogonalized representations to the cornu ammonis (CA), named after the horns of the Egyptian god Ammon due to its shape. CA3 is well suited to create conjunctive representations from separate incoming pieces of information, due to its dense recurrent connections (Kesner et al., 2008), which allow autoassociative coding (Grossberg, 1971). This architectural property allows CA3 to quickly auto-complete an incomplete input pattern (O'Reilly and McClelland, 1994; Norman and O'Reilly, 2003), a process called pattern completion (McNaughton et al., 1986). However, CA3 is also able to perform pattern separation (Guzowski et al., 2004). Hippocampal region CA1 might function as a comparator between perceptual input it receives from ERC and the processed, pattern-separated or -completed projections from CA3 (Jensen and Lisman, 1996; Colgin et al., 2009). Finally, CA1 projects to subiculum (SUB), which routs information back to ERC. The hippocampal subregions together form a system that is capable of associating pieces of information (Henke et al., 1999), both temporal (Staresina and Davachi, 2009) and spatial (Moscovitch et al., 2006), and of retrieving them based on partial input. The hippocampus is thus well-equipped to bind new information together and serve as an index for stored memory representations (Marr, 1971). The actual storage of memories may not be in the hippocampus itself, but in neocortical networks (see section 1.5, Marr, 1970). Below, the role of the hippocampus in the different stages of memory is discussed.

## 1.4. Memory encoding

New information about the world enters the brain via the sensory cortices. If this information is represented in the brain for longer-term storage, it is assumed to have been encoded. Encoding consists of at least two stages (Paller and Wagner, 2002). In the first stage, the sensory input is transformed into an internal representation that is interpreted. For this interpretation, it is often necessary to retrieve associated stored knowledge that is relevant to the current goals. In the second stage, internal representations are bound into a lasting memory trace that can be stored and retrieved at a later point in time. This memory trace can include perceptual and contextual details, but also associated knowledge or self-generated thoughts. The first component of encoding may occur outside the hippocampus, although the interpretation may rely on hippocampal-dependent retrieval of prior knowledge. The second component is thought to be dependent upon the

hippocampus (Paller and Wagner, 2002). Encoding processes in the medial temporal lobes have not only been observed during encoding of long-term declarative memories (Kirchhoff et al., 2000; Davachi et al., 2001; Otten et al., 2001), but also during perceptual learning (Graham et al., 2010) and working memory (Jeneson and Squire, 2012). How do the medial temporal lobe structures detect the events worth storing from the continuous flow of incoming sensory input? The MTL (specifically, hippocampal subregion CA1, see above) is thought to serve as a novelty detector: information that has not been encountered before is more likely to be useful, whereas familiar information does not have to be stored again (Tulving and Kroll, 1995; Nyberg, 2005; Kumaran and Maguire, 2009). For this novelty detection to work, the incoming information must be compared with stored representations to determine its novelty (Tulving and Kroll, 1995; Jensen and Lisman, 1996). This notion is consistent with the predictive coding theory, which posits that the brain continuously tries to predict incoming and future input on the basis of experiences, and thereby to minimise the difference between input and prediction (Friston, 2005). When new information is very different from the brain's generated prediction, this leads to a large prediction error, which signals novel or surprising information that is worthwhile to encode and store to be used for later predictions (Nyberg, 2005; Bar, 2009; Kumaran and Maguire, 2009). The role of the hippocampus in the representation of predictable event sequences will be discussed in Chapter 4.

## 1.5. Memory consolidation

After rapid initial storage and binding, memory traces are stored in the brain by a process that is called memory consolidation: over time, newly constructed memory traces are stabilised in distributed neural networks (Sutherland and McNaughton, 2000; Frankland and Bontempi, 2005; Stickgold, 2005; Diekelmann and Born, 2010; Wang and Morris, 2010; Lewis and Durrant, 2011; McKenzie and Eichenbaum, 2011). A more detailed account is provided by systems consolidation theory, which posits that over time, the binding role of the hippocampus gradually diminishes (Marr, 1971), while the role of neocortical networks becomes more important (Marr, 1970; Frankland and Bontempi, 2005; Wang and Morris, 2010). Specifically the medial prefrontal cortex (mPFC) is thought to take over the linking function of the hippocampus with time (Frankland and Bontempi, 2006; Takashima et al., 2006; Euston et al., 2007; Gais et al., 2007; Sterpenich et al., 2007). Consolidation is hypothesized to occur when the

brain is not encoding or retrieving, such as during sleep (Stickgold, 2005; Rasch and Born, 2007; Diekelmann and Born, 2010). Indeed, sleep has been shown to be beneficial for memory performance (Fischer et al., 2002; Wagner et al., 2004; Marshall and Born, 2007). A possible neuronal mechanism for this consolidation-related shift from hippocampal-dependent to cortical memories during sleep was discovered in rodents. Wilson and McNaughton (1994) let rats run along a fixed, narrow track and recorded hippocampal place cell ensembles (which code the animal's location in an environment) during exploration and subsequent sleep. Interestingly, they showed that the same place cells that were active in a sequence during exploration, became active again in the same temporal sequence during subsequent sleep: the hippocampus was 'replaying' the learned routes. During short, highly synchronous bouts of coordinated neuronal firing, called sharp-wave ripples, this replayed information is transferred to the neocortex (Skaggs and McNaughton, 1996; Ribeiro et al., 2004; Takehara-Nishiuchi et al., 2006; Euston et al., 2007; Ji and Wilson, 2007; Takehara-Nishiuchi and McNaughton, 2008). Awake rest may also support processes related to memory consolidation (Foster and Wilson, 2006; O'Neill et al., 2006; Axmacher et al., 2008; Tambini et al., 2010), suggesting that consolidation processes might occur anytime the brain is not focused on acquiring new memories or retrieving old ones (Buckner et al., 2008; Carr et al., 2011). In Chapter 5, the transfer from hippocampal to medial prefrontal memory representations as a function of consolidation is discussed.

## 1.6. Memory retrieval

Memories are stored to be retrieved. Endel Tulving, much like the Time Traveller, describes memory retrieval as 'mental time travel': when recalling an event, it is as if one was 'transported' back to the situation in which that event took place. The theory of cortical reinstatement posits that during retrieval, cortical representations that were involved during initial encoding are reactivated (Tulving, 1983). Indeed, reactivation of regions involved during encoding has been found throughout the sensory hierarchy with associative memory paradigms (Nyberg et al., 2000; Wheeler et al., 2000; Rugg et al., 2008; Danker and Anderson, 2010).

Several neurocomputational models hypothesize that the hippocampus plays a pivotal role in orchestrating the reactivation of past events in neocortex by pattern-completing the partially overlapping neural patterns that are activated through a retrieval cue, thereby reinstating stored represen-

tations in neocortex (Alvarez and Squire, 1994; McClelland et al., 1995; Rolls, 2000; Shastri, 2002; Norman and O'Reilly, 2003). In Chapter 2 and Chapter 3, cued cortical reinstatement is discussed. Apart from the hippocampus and sensory regions involved in initial encoding, there are a number of regions that show consistent involvement during memory retrieval (Rugg and Vilberg, 2013): these regions include parahippocampal, retrosplenial/posterior cingulate, lateral parietal, and medial prefrontal cortices (Schott et al., 2005; Duarte et al., 2011; Hayama et al., 2012). This recollection network partially overlaps with the default mode network, which is characterised by greater activity during rest than during task-related activity (Schacter et al., 2008), perhaps pointing to a link between retrieval and consolidation (see section 1.5, Carr et al., 2011) mediated by these regions during rest periods. Furthermore, the recollection network also overlaps with regions active during mental simulation or imagination (Addis et al., 2007), suggesting a link between retrieval and imagination (Miyashita and Hayashi, 2000; Mechelli et al., 2004; Eger et al., 2007; Johnson et al., 2007). In Chapter 3, a functional role of this recollection network is discussed.

Episodic memory retrieval in humans is typically investigated using a limited number of memory paradigms. In so-called old/new item recognition tests, participants are shown previously seen (encoded) and unseen (most often visual) stimuli, and decide whether or not the stimuli are 'old' or 'new' for them. Recognition memory decisions rely on recollection and familiarity processes. Recollection is defined as an effortful process in which the context of studied items is retrieved, whereas familiarity is viewed as an automatic process involving less specific knowledge about the item (Yonelinas and Levy, 2002). Participants are expected to respond 'old' to an item if they can recollect qualitative information about the moment of encoding of that item, or if they deem it sufficiently familiar. In remember/know (RK) tests participants are specifically asked to indicate whether their recognition responses are based on recollection of qualitative details ('remember') or on the basis of familiarity without recollection ('know', Tulving, 1985). Other paradigms that are used are source and associative memory tasks, in which participants are cued with an item and must indicate the source (the context in which it was studied) or associate of that cue. In these tasks, recollection is much more important than familiarity, since the participant is asked for the specific context, unlike in item recognition (Yonelinas et al., 2010). Recollection- and familiarity-based memory judgments have been studied with neuroimaging, most often with the remember/know test (Eldridge et al., 2000; Wheeler and Buckner, 2004; Vilberg

and Rugg, 2007), but also with source retrieval tasks (Cansino et al., 2002; Dobbins et al., 2002; Ranganath et al., 2003). In Chapter 2, Chapter 3 and Chapter 5, I used associative memory tasks to investigate recollection of previously learned associations.

## 1.7. Outline of this thesis

The aim of the work described in this thesis was to gain more insight into the mechanisms of human memory. Specifically, the overarching question for the chapters in this thesis was: "How do the hippocampus and neocortex support memory retrieval?" In four experimental chapters, we investigated this main questions from two perspectives: from the sensory cortex, in which memory representation are thought to be reinstated; and from the hippocampus, which is assumed to bind and represent conjunctive information about associated events.

In Chapter 2, we were interested in the mechanism by which the hippocampus interacts with sensory cortex during retrieval. The cortical reinstatement theory (see section 1.6) posits that activity in sensory cortex at encoding is reinstated at retrieval (Tulving, 1983), a process thought to be mediated by the hippocampus . This theory puts forth testable research questions:

1. Can we observe reactivation of sensory cortex upon retrieval?
2. Does this reactivation reflect content-specific information or general retrieval-related activation?
3. Does the reactivation represent qualitatively similar information as during encoding?
4. Can reinstatement happen at all levels of the sensory hierarchy?
5. Does the hippocampus mediate cortical reinstatement?

Previous studies have shown reactivation of encoding-related areas (Nyberg et al., 2000; Wheeler et al., 2000), and some have reported that the reactivation reflected content-specificity on a category-level (Polyn et al., 2005; Johnson et al., 2009; Gordon et al., 2014). However, previous work has focused on reinstatement of complex object-based information in higher-level sensory cortex, begging the question whether reinstatement of detailed sensory, feature-based information is supported by early sensory

cortex. To answer the above questions, we combined basic visual and auditory stimuli (see section 1.8), functional neuroimaging, multivoxel pattern analysis and a well-controlled cued recall paradigm. Participants learned two audio-visual associations and performed a cued retrieval task, in which they were cued with a tone and retrieved the associated visual stimulus. The findings in Chapter 2 provide evidence for reinstatement of unique associative memories in early visual cortex and suggest that the hippocampus modulates the mnemonic strength of this reinstatement.

In Chapter 3, we expanded upon the work from Chapter 2, from which we learned that early visual cortex can support stimulus-specific memory reinstatement. However, it remained unclear how these reinstated memory representations contribute to variability in memory-based decisions. Therefore, we asked the following questions:

1. Can early visual cortex support reinstated representations for multiple associations?
2. Does the strength of these representations predict the precision of memory-based decisions?
3. Are the regions in the recollection network sensitive to memory precision?
4. Does the hippocampus connect differentially to these other nodes in the recollection network as a function of memory precision?

Previous studies reported higher hippocampal (Davachi et al., 2003; Staresina et al., 2013) and sensory cortical (Kahn et al., 2004; Kuhl et al., 2011) activity for correctly than incorrectly retrieved memories. However, the memory paradigms used in these studies yielded a dichotomous (or discrete) classification of remembered and forgotten items, making it difficult to make claims about whether cortical reinstatement during retrieval varies parametrically and how this relates to trial-by-trial variations in mnemonic decision-making. In Chapter 3, we combined rapid functional magnetic resonance imaging and generative multivariate analysis with a parametric memory task to address this issue. The results from Chapter 3 provide evidence for a continuously varying recollection signal in early sensory cortex that predicts the accuracy of memory-based decisions, mediated by coordinated activity in key nodes of the recollection network.

In Chapter 4, we investigated retrieval from the perspective of the hippocampus. From Chapter 2 and Chapter 3 we learnt that the hippocampus is involved in the reinstatement of cued memories in cortex, but how does the hippocampus represent associations between stimuli? In this Chapter, we were interested in the build-up of hippocampal representations for predictable and unpredictable stimulus associations. We asked:

1. Can participants learn regularities between stimuli to facilitate behaviour?

2. Which brain regions are sensitive to the predictability of associations between stimuli?

3. Does the hippocampus represent predictable stimulus associations differently from unpredictable stimulus associations as a function of regularity learning?

4. Does a representational change reflect temporal proximity of associated stimuli or the relevance of these stimuli for the sequence?

Previous work showed that the hippocampus can represent learned temporal regularities (Strange et al., 2005; Kumaran and Maguire, 2006) through increased neural pattern similarity between the associated stimuli (Schapiro et al., 2012). However, it is unclear whether this increase reflects temporal proximity or the relevance of the stimuli for the sequence representation. In this Chapter, we combined a sequence-learning task with functional magnetic resonance imaging and representational similarity analysis to investigate what properties of new regularities are represented in the hippocampus and how they can guide behaviour. We presented participants with pictures, which were related to each other through statistical regularities. These regularities divided the stimulus set into sequences of three pictures (triplets), of which some were fully predictable, whereas in other sequences, the last picture was unpredictable (transitional probability of 0.5). The findings from Chapter 4 highlight the sensitivity of the hippocampal system to the strength of learned associations and its importance in the representation of conjunctive information between relevant stimulus associations in a sequence.

In Chapter 5, we investigated the shift of hippocampal to neocortical involvement during retrieval as a function of consolidation. In the previous Chapters, we looked at hippocampal involvement during the acquisi-

tion (Chapter 4) or retrieval (Chapter 2 and Chapter 3) of stimulus associations immediately after learning. However, systems-level consolidation theory (Squire, 1992; Alvarez and Squire, 1994) posits that the representational role of the hippocampus diminishes over time (Marr, 1971), while medial prefrontal cortex may take over (Marr, 1970). We asked the following questions:

1. Is there a change in retrieval-related activity in the hippocampus as a result of consolidation?
2. Is behavioural performance different for recent compared to remote retrieval?
3. Does the hippocampus represent conjunctive information at both a general categorical and an episode-specific level?
4. Is there a shift in the locus of conjunctive information from hippocampus to medial prefrontal cortex?

Some human neuroimaging studies have reported a decrease in hippocampal activity for retrieval of remote versus recent memories, while the medial prefrontal cortex showed more activity after consolidation (Takashima et al., 2006; Sterpenich et al., 2007) , whereas others reported no difference for retrieval of remote and recent memories (Stark and Squire, 2000; Janzen et al., 2008) or even the opposite effect (Bosshardt et al., 2005a; Gais et al., 2007). It therefore remains unclear what happens to the conjunctive representations in hippocampus during systems-level consolidation. In this Chapter, we combined an associative memory paradigm, functional magnetic resonance imaging and representational similarity analysis to investigate hippocampal and medial prefrontal representations as a function of time. In two separate sessions, participants learned to associate pairs of visual stimuli and performed a cued-recall task in the fMRI scanner, either thirty minutes (recent session) or one week (remote session) after learning. The results from Chapter 5 suggest that consolidation shifts associative memory representations from hippocampus to medial prefrontal cortex.

## 1.8. Methods

To answer our research questions, we used different memory paradigms and analysis techniques. In this section, I will briefly describe the most important methods and techniques.

### 1.8.1. Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging (fMRI) is a technique used to study brain activity in vivo. The signal measured with fMRI is called the Blood Oxygenation Level Dependent (BOLD) signal, which means that we do not measure brain activity directly, but an indirect proxy: as a result of neuronal activity in a brain region, that region will consume more oxygen. The brain responds to this oxygen depletion by increasing the flow of oxygen-rich blood to the active region. Since this blood-flow response takes a few seconds, the temporal resolution of fMRI is in the order of seconds. However, the spatial resolution is quite good, at the scale of several millimetres (Huettel et al., 2004). In all four chapters in this thesis, we used fMRI to investigate brain activity while participants performed a memory task. Participants lay in the scanner horizontally, and viewed a screen through a mirror attached to the head coil. They perform memory task by pressing buttons on a response box.

### 1.8.2. Memory paradigms

In Chapter 2, Chapter 3 and Chapter 5, we used a cued retrieval paradigm. In these paradigms, participants learned to associate pairs of stimuli. Subsequently, they were cued with one element of the pair, and were instructed to recall its associate. In Chapter 4, we used a sequence learning paradigm. In this paradigm, participants viewed a continuous stream of images, which were subject to a specific regularity structure. Participants performed a detection task on each image, but were instructed to learn the associational structure between the stimuli. Depending on the questions that we wanted to answer, we used different stimuli. In Chapter 2 and Chapter 3, we wanted to meticulously investigate the cortical reinstatement hypothesis. We turned to basic visual (oriented gratings) and auditory (pure tones) stimuli, commonly used in psychophysics (Haynes and Rees, 2005; Kamitani and Tong, 2005; Zhang and Luck, 2008; Harrison and Tong, 2009; Jehee et al., 2011, 2012; Kok et al., 2012; Xing et al., 2013), to be able to carefully control for unspecific effects of stimulus features or attention. Furthermore, in Chapter 3 we applied a parametric matching task, previously used to probe working memory (Wilken and Ma, 2004; Zhang and Luck, 2008; Rademaker et al., 2012; Ester et al., 2013), to investigate the putatively continuous nature of the cortical recollection signal. In Chapter 4 and Chapter 5 we used standardized stimuli of faces, houses, bodies and objects. These stimulus categories are commonly used, due to their differential representation in clearly separable ventral visual stream regions, and are easy for participants to learn because of their multitude of features.

### 1.8.3. Multivariate pattern analysis

When acquiring neuroimaging data, the brain signal is sampled repeatedly during experimental conditions. During analysis, condition-specific activations are contrasted against each other and a statistical model is applied to decide if the variance in the measured signal can be related to the contrast of interest. In a conventional univariate analysis, statistical tests are performed for each individual location in the brain. In these analyses, each of these locations is assumed to be independent from the others (Friston et al., 1995). Univariate approaches can reveal local differences in activity between conditions, but ignore the spatial structure of neighbouring locations. In the new millennium, multivariate statistical methods have gained popularity in neuroimaging (Haxby et al., 2001; Haynes and Rees, 2006; Norman et al., 2006). These approaches do not focus on only one location at a time, but are designed to detect statistical regularities across multiple dimensions of the data and later predict the experimental condition from multiple or single data samples (Cox and Savoy, 2003). In this thesis, three types of multivariate analyses were employed to answer our questions: in Chapter 2, we used a linear support vector machine, which is an example of a relatively simple type of classifiers; in Chapter 3, we used a generative model; and in Chapter 4 and Chapter 5 we used representational similarity analysis. Here, I will briefly describe each of these methods.

A classifier learns to distinguish between two conditions on the basis of data features it is presented with. First, the classifier algorithm is trained on the training data (a feature-by-repetition matrix): the repetitions should belong to multiple different classes (or experimental conditions). In the case of fMRI, the data features are spatial locations (voxels). The classifier tries to distinguish the functional relationship between the data features and the class labels based on the training data. Subsequently, it is presented with a new sample of test data. The algorithm now makes a prediction about which class the test data belongs to (Pereira et al., 2009). Training and test data can be designated in a cross-validation procedure. A linear support vector machine is a relatively simple classifier that is used for its robust performance and computational efficiency (see Chapter 2).

Encoding (or generative or forward) models and decoding (classifier) models are complementary operations: encoding uses stimuli to predict activity while decoding uses activity to predict information about the stimuli (Naselaris et al., 2011). A generative model tries to reconstruct stimulus features and matches the new sample against those, allowing it to predict

outcomes that it was not trained on. In Chapter 3, a model with parameters specific for orientation was used: data were mapped onto hypothetical orientation channels (Brouwer and Heeger, 2011). This approach allowed us to predict behavioural memory precision on the basis of neural data (see Chapter 3).

In a representational similarity analysis (RSA, Kriegeskorte et al., 2008), the voxel patterns associated with each presented stimulus or condition are correlated to each other. This yields a similarity matrix, in which stimuli or conditions that show high correlations can be said to be representationally similar. A representational similarity analysis can be performed in a searchlight-procedure, in which a sphere (or searchlight) of voxels is moved through the brain to sample local patterns. A similarity matrix is constructed for each sphere, resulting in a brain map of representational similarity estimates. Often parts of the similarity matrix are contrasted to show which stimuli or conditions are more similarly represented (Kriegeskorte et al., 2008). In Chapter 4, we employed RSA to investigate a change in hippocampal representations of images as a function of sequence learning; in Chapter 5, we used this analysis to show a representational shift from hippocampus to medial prefrontal cortex as a function of consolidation.

In the following Chapters, the answers to the research questions outlined above will be discussed and interpreted. In Chapter 6, I will evaluate the key observations obtained in this thesis and will provide an outlook for future research.

# 2

# Reinstatement of associative memories in early visual cortex is signaled by the hippocampus [correa]

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## 2.1. Introduction

Retrieving memories of past events is central to adaptive behavior. Tulving's episodic memory theory describes memory retrieval as 'mental time travel': when recalling an event, it is as if one was 'transported' back to the situation in which that event happened, thereby reactivating cortical representations during retrieval that were involved during initial encoding (James, 1890; Tulving and Thomson, 1973). Indeed, reactivation of regions involved during encoding has been found throughout the sensory hierarchy with associative memory paradigms (e.g. Nyberg et al., 2000; Wheeler et al., 2000; Duzel et al., 2003; Khader et al., 2005; Ranganath et al., 2005; Woodruff et al., 2005; Slotnick and Schacter, 2006; Diana et al., 2013; Rugg and Vilberg, 2013). Studies employing multivariate methods have shown that the reactivation of higher-order sensory cortical areas carries information about the recalled stimulus category (Polyn et al., 2005; Lewis-Peacock and Postle, 2008; Johnson et al., 2009; Kuhl et al., 2011; Buchsbaum et al., 2012; Gordon et al., 2014). Notably, this content-specific reactivation was only observed for higher-order sensory regions, begging the question whether cortical reinstatement selectively occurs higher up in the sensory hierarchy. Thus, it remains unclear until what level of detail memory reinstatement can occur: what is the mnemonic resolution of neural reinstatement? Is only object-based, higher-order information subject to cortical reinstatement, or are lower-level features reinstated as well?

Here, we investigated the generalizability of the reinstatement phenomenon to early sensory cortex. By using basic visual and auditory stimuli, we carefully controlled our paradigm for potential confounding factors such as unspecific attentional or stimulus differences, and rigorously examined whether activity patterns in early visual cortex during cued memory recall 1) reflect stimulus-specific mnemonic representations, 2) share common representations with stimulus-driven activity patterns, and 3) what the role of the hippocampus is in mnemonic reinstatement in early visual cortex. Participants first learned two audio-visual associations (specific tones paired with the orientation of visual gratings, see Figure 2.1B). Subsequently, they performed a cued recall task, in which they were cued with a tone and covertly recalled the associated grating. After this recall phase, a probe grating was presented, on which participants performed an orientation discrimination task. Crucially, there was no visual information present during the covert recall phase, so any information pertaining to the orientation of the recalled stimulus must have been due to the retrieval of the associated grating. Participants additionally performed a separate task in which they

passively viewed the same visual gratings and performed a rapid serial visual presentation (RSVP) letter task. We used standard retinotopy procedures to delineate visual regions V1, V2 and V3 for each participant. We subsequently extracted the signal time courses from V1-V3 during the different tasks and applied a linear classification algorithm to predict the recalled and perceived gratings from the neural patterns in early visual cortex. To investigate the role of the hippocampus during reinstatement, we examined the relationship between classifier decision values and hippocampal signal strength.

## 2.2. Materials and Methods

### 2.2.1. Participants

Twelve healthy adult volunteers (aged 22–29 years; average 26 years; 4 females) with normal or corrected-to-normal vision gave written informed consent and participated in the experiment. The study was approved by the local ethical review board (CMO region Arnhem-Nijmegen, The Netherlands).

### 2.2.2. Experimental paradigm

Participants completed four experimental tasks in the study (Figure 2.1A). First they learned tone-grating associations, after which they performed six runs of a cued recall task. Between recall run 3 and 4, associations were shown again. Subsequently, participants completed two runs of a rapid serial visual presentation (RSVP) task with unattended gratings and two runs of a visual localizer task. Before and after the experimental sessions, short resting-state scans were obtained. Participants were instructed to maintain fixation on the central bull's eye throughout all tasks. Stimuli The stimuli were generated using Matlab and the Psychophysics Toolbox (Brainard, 1997). Stimuli were displayed on a rear-projection screen using a luminance-calibrated EIKI projector (1,024 x 768 resolution, 60 Hz refresh rate) against a uniform grey background. Pure tones (450 Hz or 1000 Hz) were used as auditory stimuli, presented to both ears over MR-compatible in-ear headphones. Visual stimuli comprised sinusoidal annular gratings (55 or 145°; grating outer radius, 7.5°; inner radius, 1.875°; contrast, 20%; spatial frequency, 0.5 cycles/deg with randomized spatial phase) that were presented around a central fixation point (radius, 0.25°). Contrast decreased linearly to zero over the outer 0.5° radius of the grating.

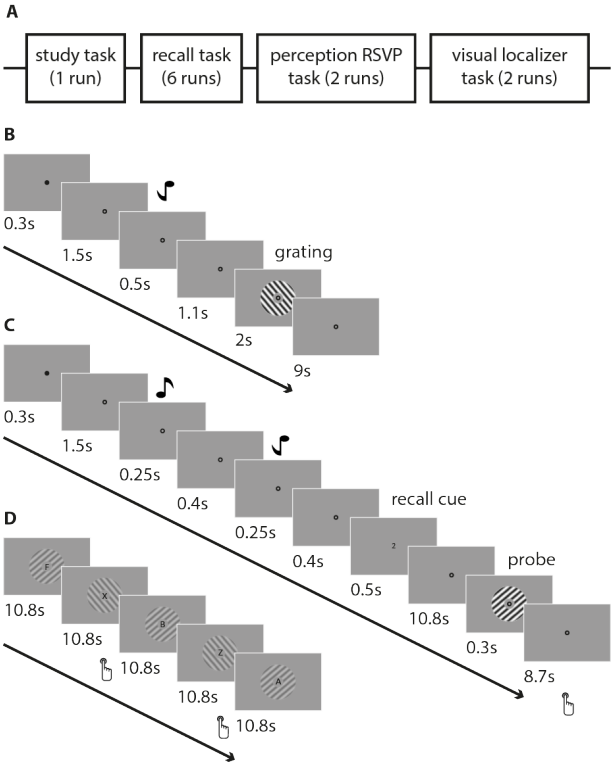



**Figure 2.1: Schematic illustration of session and trial structure**
(A) Participants completed four experimental tasks in the study. First they learned tone-grating associations, after which they performed six runs of a cued recall task. Subsequently, participants completed two runs of a rapid serial visual presentation (RSVP) task with unattended gratings and two runs of a visual localizer task.
(B) Participants learned to associate two tone-grating pairs. During the study task, a tone was presented, after which the associated grating was shown. The grating was presented for 2 seconds (250 ms on, 250 ms off, with randomized phase).
(C) During cued recall, a black cue at fixation indicated the start of the trial. Subsequently, two tones were presented briefly, followed by a recall cue (1 or 2, denoting the first or second tone, respectively) that indicated which tone to recall the associated grating from. The presentation of both tones in each trial reduced the difference between the recall trials to a minimum. After a 10.8s (6 volumes) recall phase, a probe grating (slightly tilted with respect to the recall stimulus) was presented. Participants indicated by button press whether the probe was rotated clockwise or counterclockwise with respect to the recalled stimulus.
(D) In the passive viewing task, participants performed a letter detection task at fixation, with task-irrelevant gratings presented on the background.

### **2.2.3.** Learning task

Participants learned associations between two pairs, with each pair consisting of a tone and an orientation stimulus. Using a counterbalanced design, participants were randomly assigned to the two different combinations of the two tones (450 Hz or 1000Hz) and gratings (55° or 145°). Each trial started with the presentation of a black cue at fixation (300 ms on, 1500 ms off), followed by the tone (500 ms), an interstimulus interval (ISI, 1100 ms), the associated grating (flashed on and off every 250 ms for 2 s), and ended with an intertrial interval (ITI) of 9 s (see Figure 2.1B). Each pair of stimuli was presented 10 times.

### **2.2.4.** Cued recall task

In six separate runs (of 16 trials each), participants performed a cued recall task. In this task, each trial started with a central black cue (300 ms on, 1500 ms off), followed by both tones, presented in counterbalanced order (each 250 ms on, 400 ms off), a recall cue consisting of either a '1' or '2' presented at fixation (500 ms), a 10.8 s recall phase (6 TRs, see below), a probe grating (300 ms, contrast 20%), and an inter-trial interval of 8.7-12.3 s (see Figure 2.1C). On each trial, participants performed a two-alternative forced-choice orientation discrimination task and reported via a button press whether the probe grating was rotated clockwise (middle finger of right hand) or counterclockwise (index finger of right hand) relative to the recalled grating (Harrison and Tong, 2009). The change in orientation between the recalled grating and the probe gratings on each trial, and subsequent orientation discrimination threshold estimates, were determined using an adaptive staircase procedure at 75% accuracy (Watson and Pelli, 1983). The staircase was seeded with an orientation difference of 10° and dynamically adapted based on the participants' accuracy. The maximum orientation difference between the probe and the recalled orientation was set at 20°.

### **2.2.5.** Passive viewing task

Subsequent to the main experimental tasks, participants performed two runs of an unattended gratings task, in which they were required to report whenever a 'Z' or 'X' appeared within a sequence of centrally presented letters (~2 letters per s, performance accuracy 82.0%, SE 4.0%), while task-irrelevant gratings around fixation flashed on and off every 250 ms during each 18-s stimulus block (Figure 2.1D). There were 18 stimulus blocks per run. The gratings were identical to those used in the cued recall task, but presented at lower contrast (4%).

### **2.2.6.** Visual localizer task

Spatially selective visual regions were identified using a visual localizer task, which consisted of blocked presentations of flickering checkerboards (checker size, 0.5°; display rate, 10 Hz; edge, 0.5° linear contrast ramp), presented in the same location as the gratings in the cued recall task, but within a slightly smaller annulus (grating radius, 6.5°). This smaller window was used to minimize selection of retinotopic regions corresponding to the edges of the grating stimuli. The checkerboard stimulus was presented in 10.8 s blocks, interleaved between blocks of fixation (7 blocks of fixation, 6 blocks of stimulation). Participants were instructed to press a button when the contrast of the fixation bull's eye changed (performance accuracy 97.8%, SE 1.9%).

### **2.2.7.** Eyetracking

Eye position was successfully monitored in the MRI scanner for all participants, using an MR-compatible eye-tracking system (SMI systems, 60 Hz). Analysis of the data confirmed that participants maintained stable fixation throughout the recording sessions. Mean eye position deviated by 0.06° (SE 0.02°) of visual angle between stimulus blocks, and the stability of the eye position did not differ between the orientation conditions (all $p > 0.5$).

### **2.2.8.** fMRI acquisition

fMRI data were recorded on a 3T MR scanner (TIM Trio; Siemens Healthcare) with a 3D-EPI (Poser et al., 2010) sequence (64 slices, TR = 1.8 s, voxel size = 2 × 2 × 2 mm, TE = 25 ms, flip angle = 15°, field of view = 224 × 224 mm) and a 32-channel head coil. Using the AutoAlign Head software by Siemens, we ensured that the orientation of our field of view was tilted -25 degrees from the transverse plane for each of our participants, resulting in the same tilt relative to the individual participant's head position. In addition, T1-weighted structural images (MPRAGE, voxel size = 1 × 1 × 1 mm, TR = 2.3 seconds) and a fieldmap (GRE, voxel size = 3.5 × 3.5 × 2 mm, TR = 1.02 seconds) were acquired.

### **2.2.9.** fMRI data preprocessing

The Automatic Analysis Toolbox (Cusack et al., 2015) was used for fMRI data preprocessing, which uses core functions from SPM8 and FreeSurfer, combined with custom scripts. Multivariate analyses were performed using functions of the Donders Machine Learning Toolbox. Functional imaging data were initially motion corrected and coregistered using SPM-functions. No spatial or temporal smoothing was performed. A high-pass filter of 128

seconds was used to remove slow signal drifts. The T1 structural scan was segmented using FreeSurfer functions.

### **2.2.10.** Multivoxel pattern analyses

For the cued recall task, fMRI data samples included averaged activity of individual voxels across time points 5.4-9 seconds (i.e., TRs 4-5) after the recall cue. We selected the start point of this time window to account for the hemodynamic lag of the BOLD response (4-6 s). We adopted a conservative strategy in selecting the end point of the analysis window at 9s. This procedure prevented the possible inclusion of any BOLD activity associated with the presentation of the test grating at time 10.8s (which, in principle, could begin to influence fMRI activity partway through the acquisition of TR 6 and beyond). All trials were included in the classification analyses. For classification analysis of individual fMRI time points, no temporal averaging was performed. For the unattended gratings task, fMRI data samples were created by averaging activity over each 18-s stimulus block, after accounting for a 3-volume (5.4 s) lag in the BOLD response. All fMRI data were transformed from MRI signal intensity to units of percent signal change, calculated relative to the average level of activity for each voxel across all samples within a given run. In addition, the data were z-normalized across voxels. All fMRI data samples for a given experiment were labelled according to the corresponding orientation, and served as input to the orientation classifier. On average, V1 included 396 (SE 33 voxels), V2 236 (SE 23), V3 166 (SE 19) and V1-3 797 voxels (SE 60 voxels).

### **2.2.11.** Linear support vector machine

A linear support vector machine (SVM) classifier was used to obtain a linear discriminant function distinguishing between the two orientations $\theta_1$ and $\theta_2$:

$$g(x_j) = \sum_{i=1}^{n} w_i x_{ij} + w_0$$

where $x_j$ is a vector specifying the BOLD amplitude of all $n$ voxels on block $j$, $x_i$ and $w_i$ are the amplitude of voxel $i$ and its weight, respectively, and $w_0$ is the overall bias. The classifier solved this function so that for a set of training data, the following relationship was satisfied:

$g(x_j) > 0$, when fMRI activity was generated by orientation $\theta_1$, and
$g(x_j) \leq 0$, when fMRI activity was generated by orientation $\theta_2$.

Patterns in the test data were assigned to orientation $\theta_1$ when the decision value $g(x_j)$ was larger than 0 and to orientation $\theta_2$ otherwise. The size of the deviation of the decision value from 0 was taken as an index of classification strength. Cross-validation was performed in a leave-one-run-out procedure for all classification analyses. Performance over test iterations was averaged and tested against chance level with paired-sample T-tests with a threshold of $p < 0.05$.

### **2.2.12.** Univariate parametric recall analysis

The functional data from the recall runs for each participant were also modelled in a general linear model (GLM). Four task regressors were included: one representing the trial cues, one for the audio cues, one for the recall cue and recall phase, and one representing the probe presentations. These regressors were convolved with a canonical hemodynamic response function (HRF), as well as its temporal and dispersion derivatives (Friston et al., 1998). Six movement parameters and the time courses from the white matter and lateral ventricles were modeled as nuisance regressors. In addition, the recall phase regressor was parametrically modulated by an additional regressor. This parametric modulator was constructed from the absolute trial-by-trial decision values of the SVM classifier that was trained on the perception task and tested on the cued recall task, because this generalization classifier was least biased by possible attentional effects during recall. The reported parametric effects were thresholded at $p < 0.05$, cluster-corrected using threshold-free cluster enhancement (Smith and Nichols, 2009).

### **2.2.13.** Regions of interest

Freesurfer was used to delineate the visual areas using standard retinotopic mapping procedures (Sereno et al., 1995; DeYoe et al., 1996; Engel et al., 1997; Wandell et al., 2007). Retinotopy data were obtained during scan sessions on a separate day. These visual regions of interest were defined on the reconstructed cortical surface for V1 and extrastriate areas V2, V3, separately for each hemisphere (Sereno et al., 1995; Engel et al., 1997). Within each retinotopic region of interest (ROI), we identified the stimulus-responsive voxels according to their response to the checkerboard stimulus in the independent functional localizer task. Voxels in the foveal confluences were not selected. For the V1-V3 region of interest, we combined the stimulus-responsive voxels from the separate visual ROIs. The functional data from the localizer runs for each participant were modeled using a block-design approach within a general linear model. A regressor representing the visual checkerboard stimulation blocks was created and convolved with the

HRF. The same filtering kernel and nuisance regressors were used as described above. The contrast 'stimulation' vs 'fixation' was thresholded at $p < 0.05$ (familywise error corrected).



## 2.3. Results

Frst, we asked whether we could predict the recalled orientation from voxel patterns in visual cortex during the recall phase. A linear support vector machine (SVM) classifier was trained and tested on the neural patterns in early visual regions during recall in a leave-one-run-out cross-validation procedure. The time window, ranging between 5.4-9 seconds (volume 3-5), of each recall phase was used for classification. The start of this time window was chosen to allow for peak BOLD activity to fully emerge; a conservative end-point of 9 seconds was used to exclude any potential activity elicited by the probe grating (at 10.8 seconds or 6 volumes after the recall cue). As illustrated in Figure 2.2A (purple bars), we could reliably decode the recalled orientation from activity patterns in retinotopically defined early visual areas V1-3 (decoding accuracy: 67%, chance-level accuracy: 50%, $T(11)= 4.29$, $p < 10e\text{-}3$). Note that these patterns in visual cortex could not have been instated by the auditory cues. No visual stimulus was presented immediately before and during each of the recall phases, thus the information about the decoded stimulus is likely due to reinstatement based on memory retrieval.

The classification of the different recalled orientations revealed that the patterns could be distinguished in early visual cortex. However, this does not necessarily mean that these patterns are similar to those during encoding or perception: reinstatement and perception could be differently represented in early sensory cortex (Nyberg et al., 2000; Wheeler et al., 2000). Cortical reinstatement suggests similarity between activity patterns during encoding and retrieval. However, already during encoding the memory might be represented in an abstracted format and guided by attentional processes, making it difficult to dissociate memory and attention (Vicente-Grabovetsky et al., 2012). Our approach allowed us to test the hypothesis that top-down retrieval-related patterns in early visual cortex resembled bottom-up, passive viewing-related patterns. To probe these bottom-up activity patterns, our participants performed a letter-detection task at fixation, while task-irrelevant low-contrast gratings were presented around the fixation bull's eye. The same grating orientations were used as in the recall task. To test classification on this passive viewing task, a classifier was trained and

tested on the neural patterns for the orientations during the passive viewing experiment in a leave-one-run-out procedure. This classifier performed well in regions V1-V3 ($T(11)= 9.87$, $p = 8.4 \times 10e\text{-}7$, see Figure 2.2A, yellow bars), consistent with earlier work (Kamitani and Tong, 2005; Jehee et al., 2011, 2012). To investigate whether the orientation-selective responses for recalled gratings were similar to stimulus-driven activity, a third classifier was trained on activity patterns generated by passive viewing (P) and tested on the recalled orientation from neural patterns during cued recall (R). Performance for this generalization PR classifier was significantly above chance in regions V1-V3 ($T(11)= 5.01$, $p = 4.0 \times 10e\text{-}4$, Figure 2.2A, red bars). The fact that classification performance generalizes across these two tasks suggests that there are shared neural representations in early visual cortex for stimulus-driven activity and cued recall. Finally, a classifier trained on data from the cued recall task and tested on passive viewing data (generalization RP, Figure 2.2A, brown bars) also performed significantly above chance ($T(11)= 4.57$, $p = 8.1 \times 10e\text{-}4$). Note that this generalization of classification performance across tasks also suggests that our above-chance classification is not due to a verbally-mediated encoding/retrieval strategy, since the generalization PR classifier was trained on unattended gratings. A repeated measures analysis across visual areas and the abovementioned classifiers (PP, RR, PR and RP) yielded a main effect of classifier ($F(3)= 61.73$, $p = 2.6 \times 10e\text{-}27$), but not of visual areas ($F(3)= 2.45$, $p = 0.07$) or their interaction term ($F(3)= 0.5$, $p = 0.87$).

Importantly, the number of visual cortical voxels used for classification did not influence classifier performance, indicating that the performance effects were robust and stable (see Figure 2.3A). To investigate whether global differences in response amplitudes elicited by the two orientations could account for the above-chance classification observed in early visual cortex, we trained and tested four classifiers (perception, cued recall and generalization) on the average response amplitude of the originally selected voxels. None of the three classifiers achieved above-chance performance ($T < 2$, $p > 0.05$) on the averaged response (see Figure 2.3B), indicating that global BOLD differences cannot account for the observed classification performance in our analyses.

We subsequently looked at individual volumes during the recall phase to assess how classification performance unfolds throughout each trial (see Figure 2.2B, red line and left axis). Classification starts at chance level during presentation of the audio cues and the recall cue. From around two to three volumes (3.6-5.4 seconds) after the recall cue, the classifier selects the

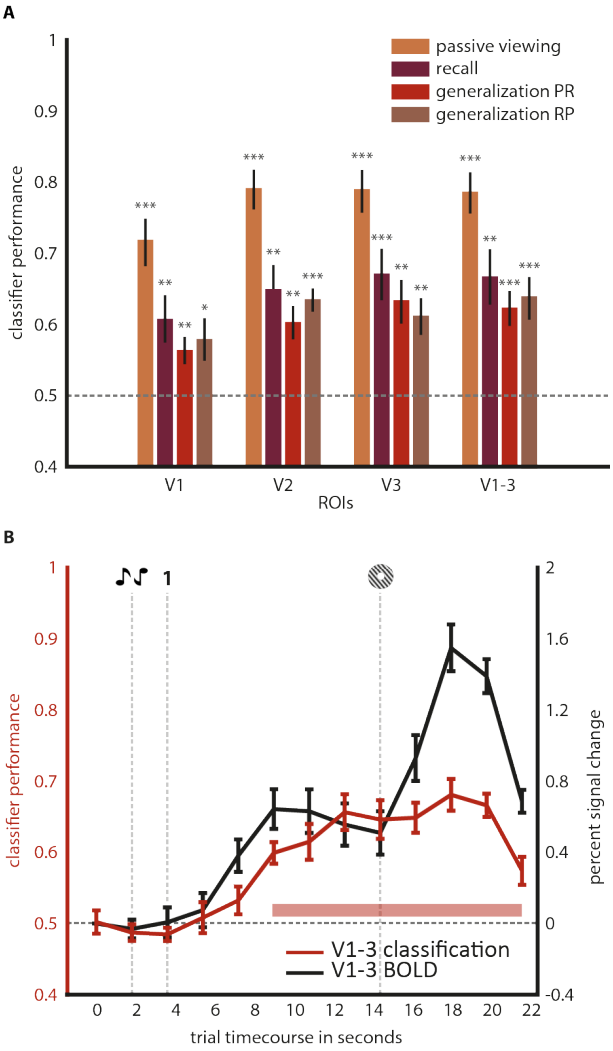



**Figure 2.2: SVM classifier performance for different experimental sessions and visual ROIs**

A) For each of the delineated visual ROIs (V1, V2 and V3), as well as a combined ROI (V1-3), decoding accuracies were calculated over 5.4-9 seconds (TR 3-5) after onset of the recall phase. Performance of the four classifiers was significantly above chance level (50%, grey dotted line, significance levels: $*p < 0.05$; $**p < 0.01$; $***p < 0.001$). The passive viewing classifier was trained and tested on data from the passive viewing task; the cued recall classifier was trained and tested on data from the cued recall task; the generalization PR classifier was trained on passive viewing (P) data and tested on recall (R) data; and the generalization RP classifier was trained on cued recall and tested on passive viewing data. Error bars indicate SE.

B) In red (left axis), performance of the generalization PR classifier is depicted for individual fMRI time points. Data for the combined visual ROI (V1-3) is shown. The pink bar denotes significant decoding performance at $p < 0.001$. In black (right axis), the percent signal change across voxels from V1-V3 during the trial is shown. Chance level was 50% (horizontal grey dotted line). The vertical grey dotted lines indicate trial events. Error bars indicate SE.

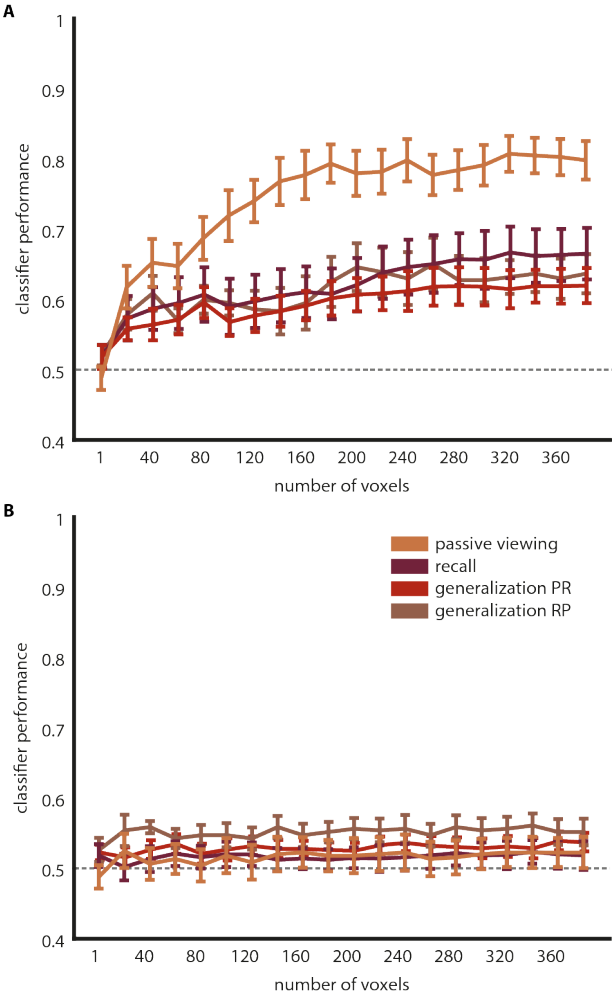



**Figure 2.3: Effect of voxel number on classifier performance**
(A) To investigate the stability of classifier performance, the classifiers (passive viewing, cued recall, and generalization) were applied on different numbers of voxels. The voxels were sorted according to their response to the localizer stimulus. All four classifiers were trained and tested in a leave-one-run-out cross-validation procedure. Classifier performance gradually improved as a function of voxel number for each classifier, reaching near-asymptotic performance at about 200-250 voxels. Error bars indicate SE.
(B) The responses of all originally selected voxels, for different numbers of voxels (sorted according to their response to the localizer stimulus), were averaged to obtain the mean response amplitude of V1-V3. This average response was used as input for the classifiers. All four classifiers were trained and tested in a leave-one-run-out cross-validation procedure. The absence of above-chance classifier performance indicates that global BOLD differences could not account for the classifier performance obtained in V1-V3 (see Figure 2.2A).

recalled grating with above-chance-level accuracy. Classifier performance continues to increase after the presentation of the probe grating. This is due to the fact that for every trial the orientation of the probe grating only slightly deviated from the recalled orientation: in other words, the probe grating, albeit having a slightly different orientation, adds information to the activity pattern that is used for classification. After participants finished the orientation discrimination judgment, classification accuracy dropped back to chance level. The overall BOLD amplitude in early visual cortex followed a similar pattern throughout the trial as the classification performance (see black line and right axis in Figure 2.2B). Note, however, that there was no overall BOLD difference between the two classes of recalled orientations during the phase between recall cue and probe grating.

The cortical reinstatement hypothesis predicts that the hippocampus mediates reinstatement in neocortex (Marr, 1971; Tulving and Thomson, 1973). We therefore repeated the above classification analyses for a hippocampal mask. None of the classifiers reached above-chance level performance. This is not surprising, since the hippocampus is unlikely to represent the associated orientation itself, but rather an index of the mnemonic association in cortex (Marr, 1971). Therefore, we asked whether hippocampal activation was related to the reinstatement we observed in visual cortex. To investigate these putative hippocampal-cortical interactions, we obtained the generalization classifier's decision value for each recall trial. The decision value for a given trial can be taken as an indication of how similar the neural patterns of passive viewing and cued recall were in visual cortex for each recall trial; in other words, it reflects the strength of reinstatement. We performed a GLM-analysis on the cued recall data, with this absolute trial-by-trial decision value of the visual cortex SVM classifier as a parametric modulator of the recall-related regressor. We found that BOLD fluctuations in left hippocampus, extending into left entorhinal cortex, covaried with cortical reinstatement accuracy in early visual cortex. This finding supports the view that hippocampal activity signals, on a trial-by-trial level, stimulus-specific cortical reinstatement accuracy (as indexed by classifier decision estimate) in early visual cortex (see Figure 2.4A, and Table 2.1 for the full list of regions that showed effects for this parametric modulation). To illustrate this effect, the bars in Figure 2.4B show that for the trials with the highest absolute classifier decision estimates in V1-V3, hippocampal activity is higher compared to activity in the trials with lower V1-V3 classifier decision estimates (trials divided in half based on their decision estimate). The observed effects were corrected for multiple comparisons ($p < 0.05$,

using threshold-free cluster enhancement). The observed covariation of hippocampal activity with classifier decision estimates suggests cross-talk between hippocampus and visual cortex during cued memory recall.



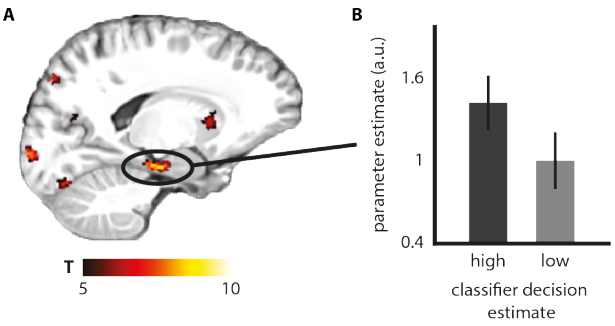



**Figure 2.4: Hippocampal activity correlates with trial-by-trial classifier decision value**
(A) SPM t-map of the parametric modulation of classifier decision value overlaid on a structural template. The map is thresholded at $p < 0.05$, cluster-corrected, cluster size > 50 voxels.
(B) Bar plots show effect size for the hippocampal peak voxel in (A), binned by absolute classifier decision value in visual cortex.

## 2.4. Discussion

In this study, we investigated cortical reinstatement in early visual cortex. We used a multivariate analysis approach to assess whether encoded stimulus-specific patterns are reinstated during cued recall, compared the cortical patterns during stimulus reinstatement with those during passive viewing of the stimuli, and related strength of reinstatement to hippocampal activity. We observed cortical reinstatement of the mnemonic representation of tone-grating associations in early visual cortex. This reinstatement was association- and feature-specific: the orientation of the recalled grating could reliably be predicted from the neural pattern across voxels in visual cortex. In addition, the neural activity patterns during stimulus recall resembled those elicited by physically presented stimuli, indicating shared representations between cued recall and perception. Furthermore, we found that hippocampal activity covaries with the strength of reactivation, consistent with the hypothesis that the hippocampus mediates cortical reinstatement (Marr, 1971; Tulving and Thomson, 1973).

Early neuroimaging work on cortical reinstatement (Nyberg et al., 2000; Wheeler et al., 2000) showed that upon cue word presentation, retrieval of

associated pictures and sounds elicited activity in higher-order visual and auditory regions, and not in primary sensory cortex. The authors interpreted this as evidence for the dissimilarity of encoding and retrieval mechanisms (Nyberg et al., 2000; Wheeler et al., 2000). We argue that depending on the nature of the task, reinstatement involves different sensory regions: if the task requires participants to recall a higher-order sensory representation (like in the earlier work: pictures and words), those areas reinstate the representation during recall; when, however, the participants have to recall more detailed representations (like in our paradigm, an orientation), early sensory cortex supports the reinstatement. Our results suggest that reinstatement generalizes across the entire breadth of the sensory hierarchy and indicate that retrieval can entail detailed sensory aspects of the memory representation. We predicted that the reinstated representations are association- and stimulus-specific: the representation should specifically reflect the recalled stimulus, instead of the stimulus category, for instance. Most studies on cortical reinstatement pooled recall stimuli of one category (e.g. faces or objects) to assess category-specific reinstatement (Polyn et al., 2005; Lewis-Peacock and Postle, 2008; Johnson et al., 2009; Gordon et al., 2014; Liang et al., 2013). Some studies show evidence for memory-specific episodic reinstatement of different videos/pictures in the medial temporal lobe, specifically the hippocampus (Chadwick et al., 2010) and parahippocampal cortex (Staresina et al., 2012). Here, we extend these findings by showing that early visual cortex can also support stimulus-specific reinstatement, providing evidence for the predicted specificity of reinstatement even at the lowest levels of the sensory hierarchy.

The core prediction of the cortical reinstatement hypothesis is that the reinstated representation during recall resembles the representation during encoding. However, similarity between encoding and recall does not necessarily indicate that mnemonic representations built during encoding are reinstated at retrieval: indeed, factors such as attention or executive strategy could interact with memory at encoding (Chun and Turk-Browne, 2007), retrieval (Vicente-Grabovetsky et al., 2012) or both (Summerfield et al., 2006b). With our well-controlled design, we could rigorously test a stringent reinstatement hypothesis, namely whether stimulus recall resembles passive and unattended perception of the stimulus. We show that the reinstated patterns in early visual cortex are indeed similar to patterns driven by unattended stimuli. This indicates a common representation of bottom-up and top-down signals in these cortical areas. Note that this generalization can rule out certain confounds that might cause the above-chance classifi-

cation performance, like attention: because the classifier was trained on a task in which participants were not actively attending the oriented gratings, it is not sensitive to such biases in the cued recall data.

Our findings dovetail with earlier neuroimaging work that showed that voxel patterns in visual cortex are not only predictive of bottom-up visual processes like specific visual stimulus properties (Kamitani and Tong, 2005) and unconscious perception of a stimulus (Haynes and Rees, 2005), but that visual cortex is also involved in complex, top-down visual computations (Mumford, 1991; Lamme and Roelfsema, 2000): several fMRI studies showed that the participants' attentional state (Kamitani and Tong, 2005; Liu et al., 2007; Serences and Boynton, 2007; Jehee et al., 2011) and stimulus expectation (Kok et al., 2012) can be predicted from activity patterns in early visual cortex. Recently, it was shown that activity patterns in early visual cortex during working memory contain stimulus-specific information about the maintained stimulus. The neural representations of this top-down working memory process were shown to be similar to those during bottom-up, passive viewing of the stimuli (Harrison and Tong, 2009; Serences et al., 2009; Xing et al., 2013). Shared neural representations have also been found for perception and imagery, throughout the higher visual hierarchy (Kosslyn et al., 1995; Stokes et al., 2009; Reddy et al., 2010; Cichy et al., 2012; Lee et al., 2012), and recently in early visual cortex (Albers et al., 2013). The converging evidence of shared neural representations between perception and working memory (Harrison and Tong, 2009; Xing et al., 2013), imagery (Reddy et al., 2010; Cichy et al., 2012; Albers et al., 2013) and memory reinstatement suggest that these processes might be implemented in early visual cortex in a very similar fashion (Tong, 2013), and may support conscious retrieval of memories (Slotnick and Schacter, 2006; Thakral et al., 2013).

Although working memory and memory retrieval mechanisms might converge in early sensory cortex, differences between the two processes are expected in the medial temporal lobe: reinstatement is more dependent on hippocampus than working memory maintenance (Ranganath et al., 2004). There is little debate that successful memory reinstatement is mediated by the hippocampus (Marr, 1971; Eichenbaum et al., 1992; Eldridge et al., 2000; Squire et al., 2004). Indeed, stronger hippocampal activity has been observed for correct than for incorrect memory reinstatement trials in several previous studies (Davachi et al., 2003; Duzel et al., 2003; Kuhl et al., 2011; Gordon et al., 2014; Liang et al., 2013; Staresina et al.,

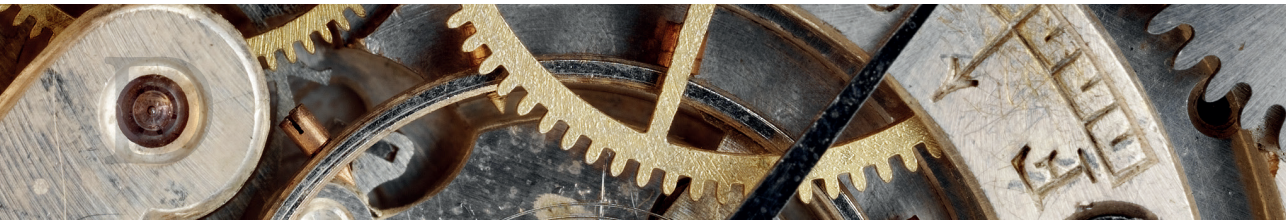
2013). A recent study found correlations between hippocampal activity and encoding-retrieval pattern similarity in parahippocampal cortex (Staresina et al., 2012). In the current study, we show that there are fine-grained, trial-by-trial interactions between the hippocampus, in conjunction with entorhinal cortex (the hippocampal-cortical interface, van Strien et al., 2009), and early visual cortex: hippocampal activity was stronger for recall trials with higher reinstatement strength, i.e. in trials in which the early visual neural patterns during cued recall resembled those during passive perception most. Our findings fit well with human and animal studies that have observed crosstalk between the hippocampus and sensory cortex during post-encoding 'offline' replay (Ji and Wilson, 2007; van Dongen et al., 2012; Deuker et al., 2013; Tambini and Davachi, 2013). Although we cannot infer the directionality of this hippocampo-cortical crosstalk, our results are consistent with two recent studies suggesting that hippocampus might drive reinstatement in higher-order regions (Gordon et al., 2014; Staresina et al., 2013). In conclusion, we observed stimulus-specific reinstatement of neural activity patterns in early visual cortex, which resembled stimulus-driven neural activity patterns. These findings provide evidence for cortical reinstatement on a feature-level at some of the lowest levels of the sensory hierarchy and suggest that the hippocampus modulates the level of mnemonic detail reactivated in early sensory regions.

## 2.5. Supplementary materials



**Table 2.1:** Summary of regions that show a parametric modulation of decision estimate MNI coordinates are shown (from anterior to posterior) for all regions that were significantly modulated by the trial-by-trial classifier decision value ($p < 0.05$, cluster-corrected, cluster size > 50 voxels) during the delay between cue and probe in the cued recall paradigm.

| Region | X | Y | Z | Z-value |
|---|---|---|---|---|
| R lateral frontal cortex | 36 | 28 | 19 | 4.55 |
| R insular cortex | 31 | 18 | 5 | 5.40 |
| L insular cortex | -28 | 26 | 5 | 5.52 |
| Post cingulate cortex | 4 | 8 | 46 | 5.98 |
| R inferior frontal gyrus | 41 | 7 | 28 | 4.73 |
| L caudate nucleus | -13 | 14 | 3 | 5.14 |
| L hippocampus | -12 | -18 | -14 | 4.19 |
| L thalamus | -9 | -18 | 12 | 4.87 |
| L cerebellum | -22 | -41 | -36 | 3.74 |
| Striate cortex | -6 | -94 | -2 | 4.12 |



# 3

# Cortical reinstatement predicts precision of mnemonic decisions [morrea]

**Sander E. Bosch, Christian F. Doeller**

This chapter is in revision as: SE Bosch and CF Doeller. Cortical reinstatement predicts precision of mnemonic decisions

## 3.1. Introduction



To be able to predict and act upon future events, it is crucial to match current perceptual information with expectations derived from previous experiences (Buckner, 2010). Upon retrieval, these mnemonic expectations are instantiated as cortical representations (e.g. Nyberg et al., 2000; Wheeler et al., 2000; Rugg et al., 2008; Danker and Anderson, 2010), thereby reactivating the regions involved during the initial encoding of the previous experience (Morris et al., 1977; Tulving, 1983). Studies employing multivariate pattern analyses observed that reinstated sensory cortical activity reflects category- (Polyn et al., 2005; Lewis-Peacock and Postle, 2008; Johnson et al., 2009; McDuff et al., 2009; Kuhl et al., 2011; Staresina et al., 2012; Gordon et al., 2014) and item-specific (Ritchey et al., 2013; Bosch et al., 2014; Wing et al., 2014) memory representations.

Several neurocomputational models hypothesize that the hippocampus plays a pivotal role in orchestrating the reactivation of past events in neocortex by pattern-completing the partially overlapping neural patterns that are activated through a retrieval cue, thereby reinstating stored representations in neocortex (Alvarez and Squire, 1994; McClelland et al., 1995; Rolls, 2000; Shastri, 2002; Norman and O'Reilly, 2003). From these models, it follows that more complete reinstatement should lead to more accurate memory decisions, mediated by the hippocampus (Marr, 1971; Eichenbaum et al., 1992; Squire et al., 2004), which has indeed been observed in several previous studies (Eldridge et al., 2000; Davachi et al., 2003; Qin et al., 2009; Kuhl et al., 2011; Liang et al., 2013; Staresina et al., 2013; Gordon et al., 2014). Reinstatement effects are also greater for correct than for incorrect memory judgements in content-selective cortical regions (Kahn et al., 2004; Kuhl et al., 2011; Hofstetter et al., 2012; Staresina et al., 2012; Gordon et al., 2014; Kuhl and Chun, 2014) and a number of non-content-selective regions (dubbed the recollection network, see Rugg and Vilberg, 2013), including the hippocampus and parahippocampal, retrosplenial/posterior cingulate, lateral parietal, and medial prefrontal cortices (Duarte et al., 2011; Hayama et al., 2012; Rugg and Vilberg, 2013).

Importantly, studies on cortical reinstatement and its relation to mnemonic decision-making have hitherto employed recognition memory paradigms in which participants make either a recognition judgment (Eldridge et al., 2000; Wheeler and Buckner, 2004; Vilberg and Rugg, 2007), in some cases followed by a source memory judgment (Cansino et al., 2002; Dobbins et al., 2002; Davachi et al., 2003; Ranganath et al., 2003), or cued

recall paradigms in which participants indicate whether a probe stimulus matches a presented cue (Nyberg et al., 2000; Wheeler et al., 2000; Khader et al., 2005; Woodruff et al., 2005; Qin et al., 2009; Johnson et al., 2013). These paradigms yield a dichotomous (or discrete) classification of remembered and forgotten items, making it difficult to make claims about whether cortical reinstatement during retrieval varies parametrically and how this relates to trial-by-trial variations in mnemonic decision-making.

In visual psychophysics, parametric matching tasks have been employed to probe subtle variations in behaviour in a continuous fashion (Wilken and Ma, 2004; Zhang and Luck, 2008; Rademaker et al., 2012; Ester et al., 2013). The continuous nature of the response measure requires an analysis method that can generate estimated responses spanning the entire response space, while only being trained on a subset of these responses. Such generative (or forward) models have been applied to reconstruct participants' representations of colour (Brouwer and Heeger, 2009, 2013) and orientation space (Brouwer and Heeger, 2011; Ester et al., 2013; Kok et al., 2013), as well as complex visual images (Kay et al., 2008), movie clips (Nishimoto et al., 2011) and semantic categories (Huth et al., 2012), but have to our knowledge never been applied to cued associative retrieval.



In this study we employed a parametric matching task and generative multivariate analysis to investigate 1) the influence of neural patterns in visual cortex on mnemonic decision making and 2) the relation of activation in the recollection network to these decisions. Participants learned six associations comprising tones and oriented visual gratings, and subsequently performed a cued recall task (see Figure 3.1A), in which they were cued with a melody and recalled its associated grating. After a short delay, participants rotated a line segment to match the orientation of the recalled grating.

## 3.2. Materials and Methods

### 3.2.1. Participants

Twenty-six healthy adult volunteers (aged 18-30 years; average 24.5 years; 14 females) with normal or corrected-to-normal vision gave written informed consent and participated in the experiment. Three participants had to be excluded from further analyses due to technical difficulties during data acquisition. An additional two participants were excluded because of poor performance on the recall task (average absolute error across trials above 45 degrees from target orientation), thus data from twenty-one par-

ticipants (aged 18-30 years; average 24.4 years; 11 females) were included in the reported analyses. The study was approved by the local ethical review board (CMO region Arnhem-Nijmegen, The Netherlands).

### **3.2.2.** Stimuli

The stimuli were generated using MATLAB (version 2014a) and the Psychophysics Toolbox (Brainard, 1997). Stimuli were displayed on a rear-projection screen using a luminance-calibrated EIKI projector (1,024 x 768 resolution, 60 Hz refresh rate) against a uniform grey background. Pure tones (500 Hz, 800 Hz or 1100 Hz) were used as auditory stimuli, presented to both ears over MR-compatible in-ear headphones. Visual stimuli comprised sinusoidal annular gratings (10°, 35°, 75°, 100°, 125°, and 165°; grating outer radius, 7.5°; inner radius, 1.875°; contrast, 20%; spatial frequency, 0.5 cycles/deg with randomized spatial phase) that were presented around a central fixation point (radius, 0.25°). Contrast decreased linearly to zero over the outer 0.5° radius of the grating.

### **3.2.3.** Procedure

First, participants learned associations between six pairs of three-tone melodies and oriented visual gratings in two runs. After learning, they performed six runs of a cued recall task. At the end of the scanning session, participants were presented with two runs of a visual localizer task (see Figure 3.1A). Participants were instructed to maintain fixation on the central bull's eye throughout all tasks.

### **3.2.4.** Learning task

Participants learned associations between six pairs, each consisting of a three-tone melody and an orientation stimulus. Tone-to-grating mappings were counterbalanced across participants. Each trial started with the presentation of a black cue at fixation (300 ms), followed after 800 ms by the three-tone melody (each tone presented for 200 ms on, with 400 ms in between tones), an inter-stimulus interval (ISI, 400 ms), the associated grating (flashed 400 ms on and 150 ms off for 4.4 s), and ended with an inter-trial interval (ITI) of 5.5 s (see Figure 3.1B). Each pair of stimuli was presented 3 times per run.

### **3.2.5.** Cued recall task

In six separate runs (of 36 trials each), participants performed a cued recall task. In this task, each trial started with a central black cue (300 ms), directly followed by a three-tone melody (each tone presented for 500 ms,

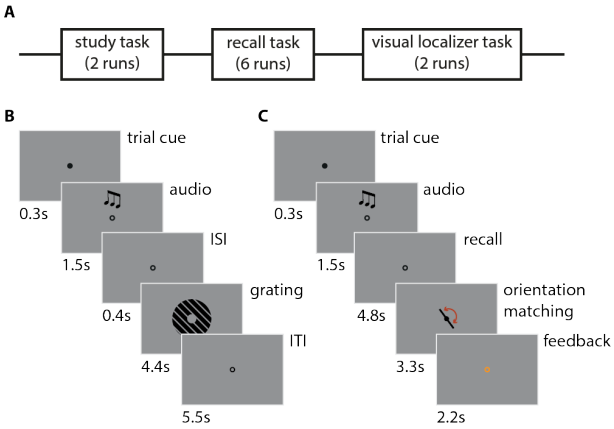



**Figure 3.1: Parametric cued recall paradigm**
A) Participants first learned associations in two runs (see B) and subsequently performed six runs of the cued recall task (see C). At the end of the session, participants performed two runs of a visual localizer task.
B) Participants learned six audio-visual associations, each consisting of a distinct three-tone melody and an oriented grating. Each association was presented 6 times in total. The melody was always presented first, followed by the grating. ISI=Inter-Stimulus Interval, ITI=Inter-Trial Interval.
C) After learning, participants performed a cued recall task, in which they were cued with a melody, they recalled the associated grating and were asked to match a presented line to the remembered orientation. They were presented with feedback (in the form of a coloured fixation dot indicating performance) after each trial.

without pauses). After a recall window of 4.8 s, a line (radius 1.4°) was presented in the centre of the screen. Participants were instructed to use two buttons to rotate the line to match the orientation that was associated to the presented melody. After 2.2 s, the line began to fade, indicating that the response window was drawing to an end; after 3.3 s, the response window was followed by a 2.2 s inter-trial interval (ITI, see Figure 3.1C). On each trial, participants performed the matching task on the remembered grating orientation. During the ITI, the fixation dot changed colour depending on precision of the previous response: red for an absolute error over 40 degrees, orange for an error between 30 and 40 degrees, yellow between 20 and 30 degrees, light green between 10 and 20 and green between 0 and 10.

### **3.2.6.** Visual localizer task

Spatially selective visual regions were identified using a visual localizer task, which consisted of blocked presentations of flickering checkerboards (checker size, 0.5°; display rate, 10 Hz; edge, 0.5° linear contrast ramp),

presented in the same location as the gratings in the cued recall task, but within a slightly smaller annulus (grating radius, 6.5°). This smaller window was used to minimize selection of retinotopic regions corresponding to the edges of the grating stimuli. The checkerboard stimulus was presented in blocks of 11 s, interleaved between blocks of fixation (10 blocks of fixation, 9 blocks of stimulation). Participants were instructed to press a button when the contrast of the fixation bull's eye changed (performance accuracy 93%, SE 3%).

### **3.2.7.** Eyetracking

Eye position was monitored in the MRI scanner for all participants, using an MR-compatible eye-tracking system (SMI systems, 60 Hz). Analysis of the data confirmed that participants maintained stable fixation throughout the recording sessions. Mean eye position deviated by 0.07° (SE 0.02°) of visual angle throughout the recall task, and the stability of the eye position did not differ between recall of the different associations.

### **3.2.8.** Gaussian mixture model on behavioural data

Maximum likelihood estimation (Myung, 2003) was used to decompose the behavioural responses from each subject into two classes of trials (Zhang and Luck, 2008): one represented a mixture of a uniform distribution of errors (trials in which the cued associate was not in memory) and a von Mises distribution (Fisher, 1993) of errors (for trials in which the cued associate was in memory).

### **3.2.9.** fMRI acquisition

fMRI data were recorded on a 3T MR scanner (TIM Trio; Siemens Healthcare) with a rapid 3D-EPI (Poser et al., 2010) sequence (40 slices, TR = 1.1 s, voxel size = 1.9 × 1.9 × 1.9 mm, TE = 25 ms, flip angle = 15°, field of view = 224 × 224 mm) and a 32-channel head coil. Using the AutoAlign Head software by Siemens, we ensured that the orientation of our field of view was tilted +3 degrees from the transverse plane for each of our participants, resulting in the same tilt relative to the individual participant's head position. In addition, T1-weighted structural images (MPRAGE, voxel size = 1 × 1 × 1 mm, TR = 2.3 seconds) and a field map (GRE, voxel size = 3.5 × 3.5 × 2 mm, TR = 1.02 seconds) were acquired.

### **3.2.10.** fMRI data preprocessing

fMRI data were analysed using the Automatic Analysis Toolbox v4 (Cusack et al., 2015). Multivariate analyses were performed using functions of the

Donders Machine Learning Toolbox. Functional imaging data were initially motion corrected and coregistered. No spatial or temporal smoothing was performed. A high-pass filter of 128 seconds was used to remove slow signal drifts. The T1 structural scan was segmented using FreeSurfer v5.1 functions (Fischl et al., 2002). In order to account for inter-subject differences in brain morphology, we constructed a group structural template using the Advanced Normalization Tools (ANTs) toolbox v1.9.



### **3.2.11.** Multivoxel pattern analyses

For the cued recall task, fMRI data samples included averaged activity of individual voxels across time points 4.4-8.8 seconds (i.e., TRs 5-9) after the last tone of the melody. We selected the start point of this time window to account for the hemodynamic lag of the BOLD response (4-6 s). Note that although this shifted time window temporally overlaps with the match response window of the recall task, the voxels that were selected for classification did not overlap with those that were stimulated by the presentation of the match line (see subsection 3.2.15). All trials were included in the classification analyses. For the unattended gratings task, fMRI data samples were created by averaging activity over each 11-s stimulus block, after accounting for a 4-volume (4.4 s) lag in the BOLD response. All fMRI data were transformed from MRI signal intensity to units of percent signal change, calculated relative to the average level of activity for each voxel across all samples within a given run. In addition, the data were z-normalized across voxels. All fMRI data samples for a given run were labelled according to the corresponding orientation, and served as input to the orientation classifier. A naive Bayes classifier (as implemented in the Donders Machine Learning Toolbox, based on Chan et al., 1983) was used to solve the six-class classification problem in a leave-one-run-out cross-validation procedure.

### **3.2.12.** Forward model

To probe remembered stimulus representations in the visual cortex, we applied a forward modelling approach to reconstruct the orientation of the recalled grating from the BOLD signal (Brouwer and Heeger, 2011). We characterized the orientation selectivity of each voxel as a weighted sum of six hypothetical channels, each with an idealized directional tuning curve (or basis function). Each basis function was a half-wave-rectified sinusoid raised to the fifth power, and the six basis functions were spaced evenly within the 180° orientation space, such that a tuning curve with any possible orientation preference could be expressed exactly as a weighted sum of the six basis functions (Brouwer and Heeger, 2009, 2011, 2013). The

shape of the resulting orientation response channels closely approximated observed tuning curves of neurons in early visual cortex (Heeger, 1992). The channels in the forward model were evenly spaced and wrapped around the full circular space, enabling the model to capture each voxel's selectivity for all possible orientations instead of only the ones that the model was trained on. To train the model, we used the data from five of six recall runs to estimate the weights on the six hypothetical channels separately for each voxel, using linear regression. These weights reflected the relative contribution of the six hypothetical channels in the forward model (each with their own orientation selectivity) to the observed response amplitude of each voxel. Using these weights, we reconstructed the channel outputs associated with the pattern of activity across voxels evoked by the stimuli in the left-out recall run, again using linear regression. This step transformed each vector of n voxel responses for each trial into a vector of six (number of basis functions) channel responses. These channel outputs were used to compute a weighted average of the six basis functions, and the orientation at which the resulting curve reached its maximum value constituted the reconstructed orientation for a specific trial (Brouwer and Heeger, 2009, 2011, 2013). We obtained an orientation estimation (reconstruction) for each trial in the test recall run and performed this reconstruction analysis in a leave-one-run out procedure to get a model reconstruction of each trial.

### **3.2.13.** Univariate recall analysis

The functional data from the recall runs for each participant were also modelled in a general linear model (GLM). Four task regressors were included: one representing the trial cues, one for the audio cues, one for the recall phase, and one representing the match response window. These regressors were convolved with a canonical hemodynamic response function (HRF). Six movement parameters were modelled as nuisance regressors. For the parametric analysis, the recall phase regressor was parametrically modulated by an additional regressor. This parametric modulator was constructed by subtracting the absolute deviation from the target orientation for each trial from 90 degrees (the maximal error). This procedure ensured that higher values for this memory precision score corresponded to better performance. The reported parametric effects were thresholded at $p < 0.05$, cluster-corrected using permutation tests (FSL randomise) with threshold-free cluster enhancement (Smith and Nichols, 2009). To illustrate the parametric nature of the effect, we split recall trials into four bins on the basis of their mnemonic precision and ran a new GLM, consisting of

the four resulting recall regressors, supplemented by regressors for trial cues, audio cues and match response. Beta estimates for the four recall regressors from the significant regions in the parametric analysis were extracted and plotted (Figure 3.5).

### **3.2.14.** Psychophysiological interaction analysis

The GLM with four recall regressors (described above) was also used for the psychophysiological interaction (PPI) analysis. As the seed, we used the timecourse from the voxels in left hippocampus that showed the parametric effect with memory performance. PPI regressors were constructed for the four recall regressors. An F-contrast including these four regressors was constructed. The reported PPI effect was tested for significance using small volume correction (SVC). As mask for the SVC, a medial prefrontal cortex mask was constructed by combining the left and right hemisphere cingulate labels from a Freesurfer cortical parcellation (Destrieux et al., 2010), performed on the study-specific ANTS template. Beta estimates for the four PPI regressors (the interaction between the seed-region timecourse and the recall regressors) were extracted from SVC mask and plotted in Figure 3.6.



### **3.2.15.** Regions of interest

Freesurfer reconstructions from early cortical regions (V1 and V2) were used as regions of interest. Within each retinotopic region of interest (ROI), we identified the stimulus-responsive voxels based on their response to the checkerboard stimulus in an independent functional localizer task. Voxels in the foveal confluences were not selected. Note that since the line stimulus presented during the response window in the recall task fell within the annulus of the checkerboard stimulus in the localizer task, the selected voxels did not receive visual stimulation throughout the recall task. The functional data from the localizer runs for each participant were modelled using a block-design approach in a general linear model. A regressor representing the visual checkerboard stimulation blocks was created and convolved with the HRF. The same filtering kernel and nuisance regressors were used as described above. The contrast 'stimulation' vs 'fixation' was thresholded at $p < 0.05$, cluster-corrected using threshold-free cluster enhancement (Smith and Nichols, 2009).

## **3.3.** Results

On each trial of the recall task, participants performed an orientation adjustment. Across trials, these matching responses yielded a distribu-

tion of behavioural responses for each association, centred on the to-be-remembered orientation. Circular orientation space in this task spanned 180 degrees: 90 degrees clockwise and counterclockwise relative to the target orientation, (see schematic in Figure 3.2A, black line). We observed considerable spread in the average absolute error across associations within and between participants, with an average absolute rotation error of 23.33 degree (SE 3.03 degree, Figure 3.2B, grey bar). There was no absolute error difference between the six associations ($F(5,125)=0.163$, $p = 0.976$).

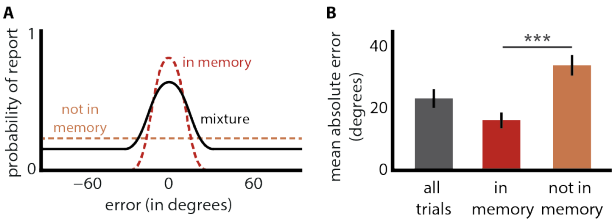



**Figure 3.2: Mixture model of memory precision**
A) Schematic of a mixture model showing the probability of reporting the correct orientation after an auditory cue (the correct orientation is centred at 0 degrees). When the cued grating associate is present in memory, the reported orientation is expected to be near the target orientation (dashed red line). In contrast, the participant is equally likely to report any orientation (dashed yellow line) when the cued associate is not remembered. When collapsed across trials, the data comprise a mixture of these two trial types (black line), weighted by the probability that the cued associate was stored in memory.
B) The grey bar shows the average absolute error in degrees over all trials across participants. The red and yellow bars show average absolute error, separately for trials in memory and trials not in memory. Error bars indicates standard error. *** = $p < 0.001$.

The continuous nature of the response measure poses a challenge to distinguish responses in non-recalled trials from responses in correctly recalled trials: in trials in which the participant recalled the associated orientation correctly, the behavioural response is expected to fall within a Gaussian distribution around the target orientation (see Figure 3.2A, red line). In contrast, trials in which the participant did not recall the associated orientation, the response is expected to fall within a uniform distribution across orientation space (see Figure 3.2A, yellow line). The observed data is likely a mixture of these two types of responses (Zhang and Luck, 2008). To be able to answer our question of continuous variation in recollection, we sought to separate the remembered from the non-remembered trials, and investigate the variations within these groups of trials. A Gaussian mixture model was applied to the association-specific behavioural responses to determine each trial's likelihood of belonging to the 'in memory' or the 'not

in memory' trials (Bishop, 2006; Zhang and Luck, 2008). Average absolute error (as measured in degrees) was higher for the trials in the uniform ('random response') distribution than for trials belonging to the target Gaussian distribution ($T(20)$=-8.06, $p < 0.001$, see Figure 3.2B, red and yellow bar), suggesting that non-remembered trials indeed were further from the target orientation than remembered trials.

Next, we investigated the involvement of different brain regions in the recall task by modelling the data using a general linear model (GLM) with regressors for the trial cue, audio cue, recall and match response (see subsection 3.2.13 for details). Upon presentation of the auditory cue, there was widespread activation in early visual cortex, and strong deactivation in auditory cortex (see Figure 3.3, left panel). During the subsequent recall window, this visual activation spread to more extrastriate areas and persisted well into the match response phase (Figure 3.3, middle and right panel). For a complete list of significantly activated regions during the task, see Table 3.1. Note that during the audio cue and recall phases, the only visual information on screen was the fixation point. The activation observed during these phases therefore reflects recall-related processing in visual cortex.

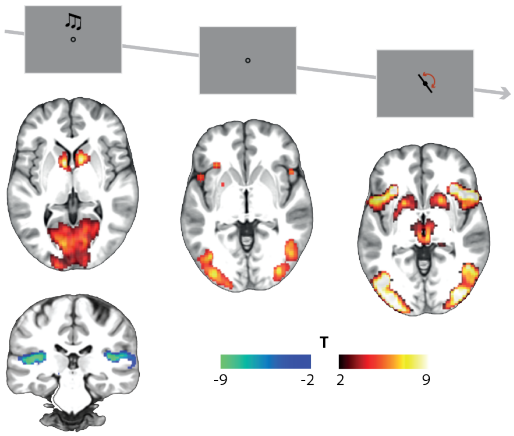



**Figure 3.3: Early visual activation during cued recall**
Statistical maps for three cued recall task regressors (from left to right: auditory cue, recall window and match task). Maps were thresholded at $p < 0.05$ (cluster-corrected). Colours indicate T-values.

To investigate whether neural patterns in early visual cortex during recall were predictive of the remembered orientation, we extracted the BOLD time courses from the recall task for visually responsive voxels (as defined by significant activity in a separate localizer task) from each participant's early visual cortex (see Figure 3.4). Using a leave-one-run-out cross-validation procedure, a naive Bayes classifier (Chan et al., 1983) was trained and tested on the recall data. The classifier could predict which orientation was being remembered in a significantly higher proportion of trials than would be expected by chance ($T(20)=2.43$, $p = 0.025$, see Figure 3.4A, grey bar), indicating that patterns in early visual cortex hold stimulus-specific mnemonic representations of the grating associates during recall (Bosch et al., 2014). When classification performance was split for trials that were 'in memory' and those 'not in memory' based on the Gaussian mixture model, we observed that classification performance was significantly above chance for memory trials ($T(20)=2.70$, $p = 0.014$), but not for non-remembered trials ($T(20)=1.15$, $p = 0.265$). Performance was significantly better for remembered trials than for non-remembered trials ($T(20)=2.11$, $p < 0.048$, see Figure 3.4A, red and yellow bar).

In a next step, we asked whether the strength of cortical reinstatement in these neural patterns was linked to variations in behavioural memory performance on the task. To capture orientation-specific responses in a fine-grained manner, we applied a forward model to the recall task data (see Figure 3.4B, left plot and subsection 3.2.12 for more details), which produced a trial-by-trial model estimation (reconstruction) of the orientation best reflected in the neural pattern. Next, we regressed these orientation estimations against the actual behavioural errors, separately for 'in-memory' and 'not-in-memory' trials (see Figure 3.4B, right plot). For the remembered trials, there was a significant correlation between the model estimation and memory performance ($T(20)=2.97$, $p = 0.008$). In contrast, there was no such relation for the trials that were not remembered ($T(20)=1.04$, $p = 0.310$, see Figure 3.4C). In sum, these data suggest that for remembered trials, the strength of neural pattern reinstatement in early visual cortex during recall can predict the participant's memory-based decision.

Since we found considerable spread across trials within each of our participants, we next asked whether there were brain regions other than early visual cortex specifically signalling the precision of trial-by-trial memory decisions. To this end, we calculated a trial-by-trial memory precision score

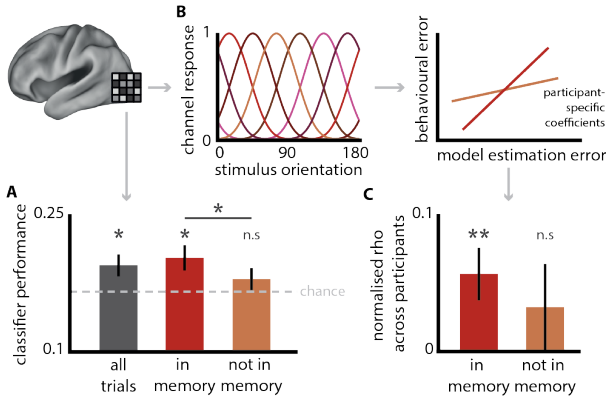



**Figure 3.4: Memory reinstatement in early visual cortex**
A) A pattern classifier was trained and tested on the recall task in a leave-one-run-out cross-validation procedure. The left bar shows that classifier performance on all trials was significantly above chance (16.67%). The middle and right bars show that classifier performance was significantly better for trials in memory than for trials not in memory. Error bars indicate standard error. * = $p < 0.05$.
B) To investigate whether subtle trial-by-trial variations in the neural pattern from visual cortex could predict mnemonic decisions on a continuous parametric task, a forward model was used. In this generative model, six hypothetical voxel tuning curves (or channels) span the 180 degree orientation space (left plot). The model was trained and tested on recall data in a leave-one-run-out procedure (see Methods), and produced trial-by-trial reconstructions or estimates of the recalled orientation. For each participant, these estimates were regressed against the corresponding behavioural responses, separately for the 'memory' and 'not in memory' trials (the right plot shows a schematic of the described regressions).
C) For trials in memory, there was a significant correlation between the forward model estimations of remembered orientation and actual participant memory behaviour. For trials not in memory, we did not find such a correlation. For each participant, model orientation estimations were correlated with behavioural orientation responses (see B), right plot). The resulting coefficients were normalised and tested across participants. Error bars indicate standard error. ** = $p < 0.01$.

for each trial by subtracting the absolute deviation of each response from the target orientation from 90 degrees (the maximal error). We performed another GLM on the data from the recall task, with this precision score as a parametric modulator of the recall-related regressor. We found that BOLD fluctuations in left hippocampus, medial prefrontal cortex, retrosplenial, left angular gyrus and early visual cortex covaried with memory precision (corrected $p < 0.05$, see Figure 3.5A, and see Table 3.2). The observed covariation indicates that activity in the observed regions of the recollection network signals the behavioural variation of mnemonic precision on the recall task, illustrated by bar plots in Figure 3.5B.

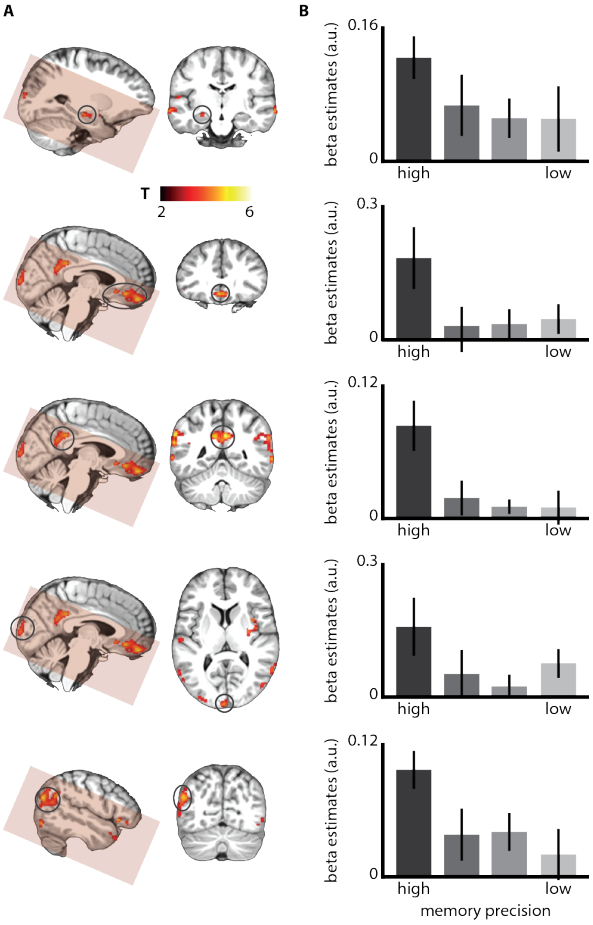



**Figure 3.5: Activity in the recollection network predicts mnemonic precision**
Statistical maps for the parametric analysis of trial-by-trial memory precision. A precision score was calculated by subtracting the absolute trial errors from the maximum error possible (90 degrees). The field of view (FOV) of functional scans is overlaid on sagittal maps.
A) Several regions in the recollection network showed higher activity for trials in which participants made more precise mnemonic decisions. From top to bottom, the regions highlighted are: left hippocampus, medial prefrontal cortex, retrosplenial cortex, early visual cortex and angular gyrus. Colours indicate T-values. Maps were thresholded at $p < 0.05$ (cluster-corrected). Effects are highlighted by grey ellipses.
B) The bar plots illustrate the parametric nature of the effect in the regions in A) by showing the parametric effects for the peak voxels from A), divided into four bins by memory performance (from high to low memory precision).

Several neurocomputational models hypothesize an important role for the hippocampus during memory retrieval (Marr, 1971; Eichenbaum et al., 1992; Squire et al., 2004). We leveraged our rapid fMRI sequence (repetition time of 1.1 s) to investigate whether connectivity between the hippocampus and other regions involved in the task, was modulated by the precision of mnemonic decisions. The left hippocampus was used as a seed for a psychophysiological interaction (PPI) analysis (see Figure 3.6A, left map). We observed that medial prefrontal cortex showed variable connectivity to the hippocampal seed region as a function of memory precision (see Figure 3.6A; small volume-corrected at $p < 0.05$). The peak of the reported effect was located at MNI coordinates x=2, y= 40, z= -14 with a peak Z-value of 3.4. Illustrations of this parametric effect are shown in the bar plots in Figure 3.6B.

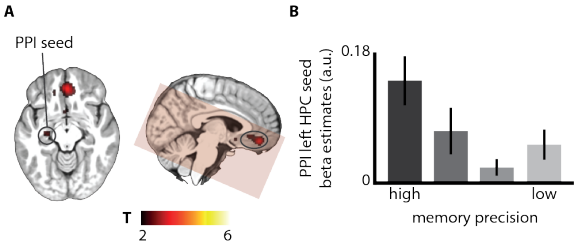



**Figure 3.6: Connectivity between hippocampus and medial prefrontal cortex modulates mnemonic precision**
A) The parametric effect in left hippocampus (see Figure 3.5) was used as a seed region for a psychophysiological interaction (PPI) analysis (see the left axial map). Medial prefrontal cortex showed increased connectivity to the left hippocampal seed region for trials in which participants' memory was more precise. Colours indicate T-values. Maps were thresholded at $p < 0.005$, uncorrected, for display purposes. Effects are highlighted by grey ellipses.
B) The bar plots show the parametric effect of connectivity from left hippocampus to medial prefrontal cortex, separately for the four memory precision PPI regressors.

## 3.4. Discussion

In this study, we investigated whether cortical memory representations can predict the precision of mnemonic decisions. We combined a parametric cued recall task with multivariate analyses to assess whether reinstated neural patterns during recall relate to variations in mnemonic precision, and related trial-by-trial precision to coordinated activity in regions of the recollection network. We could predict association-specific mnemonic reinstatement on the basis of neural patterns in early visual cortex. More accurate decisions were associated with stronger cortical reinstatement, as in-

dexed by our forward model, strongly suggesting that cortical reinstatement strength varies continuously and is echoed in a similarly continuous variation of mnemonic precision. Furthermore, we observed that hippocampal, medial prefrontal, lateral parietal and retrosplenial activity during recall covary with trial-by-trial memory precision, consistent with the hypothesis that a core recollection network (Rugg and Vilberg, 2013) including hippocampus mediates cortical reinstatement (Marr, 1971; Tulving, 1983).



Memory retrieval can be seen as a process in which perceptual input is matched against stored memory representations, with the goal of selecting the most appropriate representation to guide actions (Shadlen and Kiani, 2013). Reinstatement of mnemonic information in cortex is thought to underlie memory retrieval: greater or stronger reinstatement should lead to more accurate memory decisions (Morris et al., 1977; Tulving, 1983). Memory performance has been probed by several memory paradigms, many of which employ dichotomous old/new item recognition tests, in which participants are shown previously seen (encoded) and unseen (most often visual) stimuli, and decide whether or not the stimuli are 'old' or 'new' for them (Yonelinas et al., 2010). It is assumed that individuals will respond 'old' to an item if they can recollect qualitative information about the specific study event, or if the item is judged to be sufficiently familiar. If individuals are required to rate confidence, then recollection should lead to relatively high confidence responses, whereas familiarity will be mapped monotonically across a wider range of confidence, with the more familiar items leading to more confident recognition responses (Yonelinas et al., 2010). In source and associate memory tasks, in which participants must indicate the source or associate of a cue item, familiarity is expected to be less useful in supporting these discriminations than in item recognition (Yonelinas et al., 2010). In the present study, we used a task that allowed us to probe the accuracy of mnemonic decisions at a more fine-grained level than previously employed memory measures. Here, the effective response space of 180 degrees yielded a distribution of memory precision over trials. The participants' behavioural accuracy on this parametric memory task correlated with the accuracy of neural model estimations, but only for the trials 'in memory', indicating that the reinstated recollection signal in cortex varies continuously across trials, and that this trial-by-trial variation has an influence on mnemonic decisions (i.e., better reinstatement leads to higher memory precision). This is consistent with earlier work that showed a differential effect of reinstatement for correct than incorrect memory trials (Kahn et al., 2004; Hofstetter et al., 2012; Staresina et al., 2012; Kuhl

et al., 2013; Gordon et al., 2014), but significantly extends these findings by showing that this relationship is continuous in nature.

We show that left hippocampus, medial prefrontal cortex, left angular gyrus and retrosplenial cortex predict mnemonic precision on a trial-by-trial level. Several neurocomputational models posit that the hippocampus mediates successful cortical reinstatement (Marr, 1971; Eichenbaum et al., 1992; Alvarez and Squire, 1994; Norman and O'Reilly, 2003; Squire et al., 2004). Indeed, a recent animal study showed the causal involvement of the hippocampus in successful fear memory retrieval (Tanaka et al., 2014). Also in human fMRI studies, stronger hippocampal activity has been observed for correct than for incorrect memory reinstatement trials (Davachi et al., 2003; Duzel et al., 2003; Kuhl et al., 2011; Liang et al., 2013; Staresina et al., 2013; Gordon et al., 2014). Recent studies found correlations between hippocampal activity and encoding-retrieval pattern similarity in parahippocampal cortex (Staresina et al., 2012) and inferior frontal gyrus (Ritchey et al., 2013). The other regions we observed in our study, have all been implicated in content-independent, retrieval-related effects, and together are dubbed the 'core recollection network' (Rugg and Vilberg, 2013). The recollection network comprises the hippocampus and parahippocampal cortex, along with ventral parietal cortex, retrosplenial/posterior cingulate cortex, and medial prefrontal cortex, almost all of which covaried with mnemonic precision in our task. It has been proposed that, in interaction with regions manifesting content-selective retrieval effects (i.e., sensory cortex), this network supports the retrieval and maintenance of consciously accessible memory representations (Rugg and Vilberg, 2013). Retrieval-related activity in these regions, most notably in the angular gyrus and in the hippocampus, co-varies with the confidence and accuracy of source memory judgments (Glanzer et al., 2004; Slotnick and Dodson, 2005; Mickes et al., 2009; Yu et al., 2012; Thakral et al., 2015). Finally, we show that connectivity between hippocampus and medial frontal cortex modulates mnemonic precision. Hippocampal and medial frontal activity have been linked to scene construction and spatial memory (Hassabis and Maguire, 2007; Hassabis et al., 2007; Doeller et al., 2008), but also the formation of associative links (Davachi, 2006; Zeithamova et al., 2012) and constructive episodic simulation (Addis et al., 2007; Schacter and Addis, 2007; Barron et al., 2013). Our data suggest that cross-talk between these regions is pivotal for the precision of mnemonic decisions, consistent with the idea that prefrontal cortex can bias the hippocampus towards context-specific memory representations after a retrieval cue (Miller and Cohen,

2001; Preston and Eichenbaum, 2013).

In conclusion, we observed stimulus-specific reinstatement of neural activity patterns in early visual cortex, which related to mnemonic precision on a trial-by-trial level. These findings provide evidence for a continuous variation of cortical reinstatement, which predicts variation in the precision of mnemonic decisions. Activity in several recollection regions and coordinated connectivity between hippocampal and medial prefrontal cortex activity modulates this fine-grained variation in memory performance.

## 3.5. Supplementary materials

**Table 3.1:** Summary of regions that show univariate effects MNI coordinates for significantly active regions (from anterior to posterior) during the recall task ($p < 0.05$, cluster-corrected, cluster size > 50 voxels).

| Contrast | AAL label | X | Y | Z | Z-value |
|---|---|---|---|---|---|
| audio | Insula_R | 32 | 24 | -4 | 5.15 |
| | Insula_L | -30 | 24 | -2 | 4.17 |
| | Temporal_Pole_Sup_L | -56 | 12 | -4 | 4.71 |
| | Caudate_L | -10 | 2 | 12 | 5.78 |
| | Temporal_Mid_R | 64 | -42 | -14 | 5.05 |
| | Parietal_Inf_L | -32 | -56 | 38 | 5.57 |
| | Cerebelum_6_R | 28 | -64 | -32 | 4.37 |
| recall | Insula_R | 38 | 18 | 6 | 4.64 |
| | Rolandic_Oper_L | -46 | 0 | 6 | 5.25 |
| | Thalamus_L | -14 | -20 | 8 | 4.56 |
| | Thalamus_L | 0 | -20 | -8 | 4.45 |
| | Parietal_Inf_L | -34 | -44 | 38 | 4.91 |
| | Cerebelum_6_L | -34 | -50 | -32 | 5.15 |
| | Cerebelum_6_R | 20 | -52 | -24 | 5.51 |
| | Temporal_Mid_R | 44 | -64 | 4 | 6.09 |
| | Occipital_Mid_L | -40 | -66 | 6 | 5.56 |
| | Occipital_Mid_R | 30 | -70 | 30 | 5.27 |
| | Parietal_Sup_L | -16 | -72 | 50 | 4.62 |
| | Occipital_Mid_L | -28 | -74 | 26 | 4.49 |
| match | Cingulum_Mid_L | 2 | -28 | 26 | 5.69 |
| | Occipital_Mid_L | -36 | -92 | -6 | 7.04 |

**Table 3.2:** Summary of regions that track mnemonic precision MNI coordinates for all regions (from anterior to posterior) that were significantly modulated by memory precision during the recall ($p < 0.05$, cluster-corrected, cluster size > 50 voxels).

| Contrast | AAL label | X | Y | Z | Z-value |
|---|---|---|---|---|---|
| recall | Rectus_L | -2 | 46 | -22 | 3.8 |
| | Temporal_Pole_Sup_L | -36 | 24 | -28 | 3.92 |
| | Temporal_Inf_R | 50 | 10 | -40 | 3.74 |
| | Insula_R | 38 | 4 | 12 | 3.46 |
| | Temporal_Sup_L | -60 | 0 | 2 | 3.73 |
| | Hippocampus_L | -26 | -18 | -14 | 3.2 |
| | Temporal_Mid_L | -68 | -20 | -10 | 3.84 |
| | Temporal_Sup_R | 66 | -22 | 16 | 3.49 |
| | SupraMarginal_L | -64 | -24 | 14 | 3.55 |
| | SupraMarginal_R | 52 | -30 | 24 | 3.51 |
| | Temporal_Mid_L | -66 | -44 | -2 | 3.71 |
| | Temporal_Mid_R | 66 | -48 | 2 | 3.99 |
| | Cingulum_Mid_R | 6 | -48 | 34 | 4.14 |
| | Angular_L | -60 | -58 | 22 | 4.41 |
| | Occipital_Inf_L | -50 | -74 | -6 | 3.53 |
| | Cuneus_R | 14 | -84 | 42 | 3.55 |
| | Occipital_Mid_L | -44 | -86 | 0 | 3.45 |
| | Calcarine_L | -4 | -98 | 12 | 3.52 |

# 4

# Prospective event representation through hippocampal regularity learning [hipant]

**Sander E. Bosch, Branka Milivojevic, Peter W.A. Smulders, Floris P. de Lange, Christian F. Doeller**

This chapter is in preparation as: SE Bosch*, B Milivojevic*, PWA Smulders, FP de Lange and CF Doeller. Prospective event representation through hippocampal regularity learning (* = equal contributions)

## 4.1. Introduction

For adaptive behaviour, it is important to be able to expect and predict upcoming events. These expectations are based on previous experiences, which form the building blocks for prediction and imagination (Buckner, 2010). The hippocampus, a key region for the representation of memory and space (O'Keefe and Nadel, 1978), is excellently suited for the support of this prospective function, as it contains cells sensitive to location (O'Keefe and Dostrovsky, 1971; Hafting et al., 2005) and time (MacDonald et al., 2011; Eichenbaum, 2014). Electrophysiological studies in freely navigating animals show that hippocampal place cells code for upcoming positions of an animal in the environment (Diba and Buzsaki, 2007; Dragoi and Tonegawa, 2011), indeed suggesting a prospective role for this memory region. This prospective spatial activity might generalize to the representation of future events in humans (Buckner, 2010): the network underlying episodic future thought is strikingly similar to that for autobiographical recall (Hassabis et al., 2007; Schacter and Addis, 2007). Analyses that combine data across studies suggest there is convergent activation for future thought and retrieval in the hippocampus, posterior cingulate, parietal and medial frontal cortex (Schacter et al., 2008; Spreng et al., 2009).



Consistent with the existence of time cells in hippocampus, which may code specific moments in time or temporal positions (MacDonald et al., 2011; Eichenbaum, 2014), previous human neuroimaging studies on sequence learning have shown that the hippocampus is involved in learning sequential regularities (Schendan et al., 2003; Doeller et al., 2005, 2006; Kumaran and Maguire, 2006; Bar, 2009; Schapiro et al., 2014), with greater activity for random (low predictability) than ordered (high predictability) sequences (Strange et al., 2005). Recently, Schapiro and colleagues (Schapiro et al., 2012) reported that the hippocampus encodes regularities by increasing the representational similarity of objects that follow each other. However, since the authors only investigated pairs of events immediately following each other, it was not possible to distinguish temporal proximity from a prospective signal across a longer sequence of events.

In this study, we investigated the dynamics of regularity learning of three-stimulus sequences (triplets) using fMRI, and examined the effect of regularity learning on the neural similarity between the stimulus representations in the hippocampus. Participants were presented with images, the order of which was subject to certain statistical regularities: the stimulus set was organised into four sequences of three images (triplets). For

two of these triplets, the order of the stimuli was always the same (transitional probability for all stimuli was 1) and in that sense the stimuli in those triplets were fully predictable. We expected that this would lead to strongly associated stimuli within those triplets. For the other two triplets, the order of the first two stimuli was always the same (transitional probability for 1st to 2nd was 100%), while the third image in the sequence could be one of two equally probable stimuli (transitional probability for 2nd to 3rd was 50%). Thus, the final stimulus in those triplets was unpredictable. We expected that this would lead to weakly associated stimuli in those triplets. During regularity learning, we expected that the hippocampus would show higher activity for unpredictable than for predictable sequences, consistent with previous reports (Schendan et al., 2003; Doeller et al., 2005; Kumaran and Maguire, 2006). Furthermore, we expected that this sensitivity for predictability would lead to lasting differences in stimulus representations in hippocampus. By comparing the neural similarity between the first two items and the crucial third item in the predictable and unpredictable triplets before and after regularity learning, we were able to investigate whether the hippocampal prospective code is sequential and represents the first upcoming item, or whether the prospective code is deterministic and represents all upcoming events once sufficient information has been accumulated. In the former case, the representation of the third stimulus should become more similar to the immediately preceding second stimulus for the predictable compared to the unpredictable triplets. On the other hand, if the hippocampal similarity change reflects prospective information deterministically, we might expect the representations of the third item to become more similar to the first item which signals it, in this case the first item in the triplet.



## 4.2. Materials and Methods

### 4.2.1. Participants

Thirty-one participants (19 female, average age 25.7, range 19.5-33.7) gave written informed consent and participated in this study. Ten participants were excluded from the analysis due to technical difficulties during data acquisition (6) or excessive movement (4 participants moved >6 mm). Data from the remaining twenty-one participants (12 female, average age 24.7, range 19.5-29.8) were included in the reported analyses. All participants were right handed, had normal or corrected-to-normal vision and had no history of psychiatric or neurological disorders. They received monetary compensation or course credit as payment for participation. The research

was approved by the local ethics committee (CMO Arnhem-Nijmegen).

### 4.2.2. Stimuli

Stimuli consisted of coloured photographs (400x400 pixels) of faces, houses and objects, scaled to fit into a white-background circular display approximately 9.6° of visual angle (see Figure 4.1 for examples). Eighteen Caucasian male faces were retrieved from the Radboud Faces Database and scaled such that internal facial features fit well within the circular display, while the circle obscured hair and clothing. Pictures of eighteen houses were downloaded from Dutch real estate sites. The pictures contained a sideway view of the houses with at least two walls, windows and doors, and a visible roof. The objects were obtained from Moreno-Martínez and Montoro (Moreno-Martinez and Montoro, 2012). Twenty objects could be categorized as animate (fruits, vegetables, animals, flowers) and another twenty as inanimate (clothing, vehicles, furniture, desk materials, musical instruments and stimuli used in sports and games). All objects were scaled to fit into the circular display. For each participant, a subset of these stimuli was selected using a Latin square design to control for potential differences in response to different stimuli. This subset consisted of two faces, two houses, four inanimate objects and four animate objects and was used in the sequence-learning task and the pre- and post-learning tasks. The remaining stimuli were used for the localizer task (see below). Stimuli were presented using Presentation software version 16.2 (Neurobehavioral Systems, Albany, California, United States) and displayed on a rear-projection screen using a luminance-calibrated EIKI projector (1,024 x 768 resolution, 60 Hz refresh rate) against a uniform grey background.

### 4.2.3. Procedure

The fMRI session consisted of four tasks (see Figure 4.1A). Before and after the sequence-learning task (~38 min, see Figure 4.1B) a representational change task was run, in which participants viewed pictures while performing a detection task. These tasks lasted ~7 minutes each. Subsequently, participants performed a localizer task, in which pictures of houses and faces were passively viewed (~13 min; data not analysed for this manuscript). Finally, an anatomical scan (~5 min) and a gradient-field map (~2 min) were acquired. Prior to the fMRI session, participants performed a short practice session of the sequence-learning task (~2 min, 12 trials). After the fMRI session, participants completed a subsequent-memory task outside of the scanning environment.

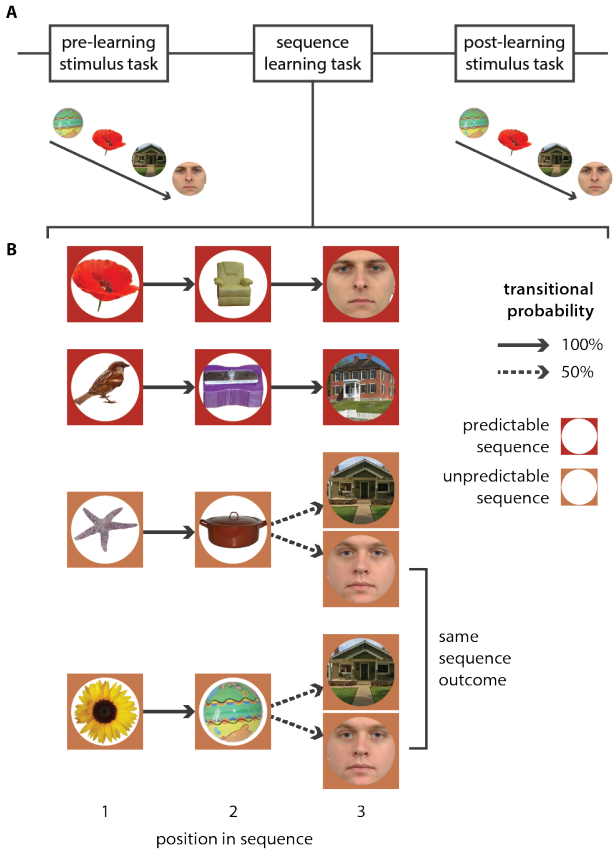



**Figure 4.1: Sequence-learning paradigm**
A) A schematic illustration of the fMRI session structure. Participants learned statistical regularities between triplets of picture stimuli (see B). Before and after this sequence-learning task, they were presented with the same picture stimuli, presented in (the same) random order. This allowed for a comparison of neural similarity between the stimuli as a function of regularity learning.
B) In the sequence-learning task, participants were presented with stimuli, presented in triplets, that adhered to statistical regularities. On each stimulus, participants performed an animacy judgment by pressing one of two buttons. There were four triplets in total. Two of these were fully predictable (stimuli with red borders): their constituent stimuli were always presented in succession. The other two sequences were not fully predictable (stimuli with yellow borders): the transitional probability between stimulus 2 and 3 was 50%, making the sequences unpredictable. Note that the third stimuli of the two unpredictable sequences were the same, ensuring that each stimulus was presented an equal number of times.

### **4.2.4.** Localizer task

A functional localizer was run for objects, faces and scenes. Participants were presented with 16s blocks during which images of objects, faces or

houses were presented, interleaved with fixation-only periods which lasted for 12 ± 4 seconds. Every stimulus category was presented three times and each block consisted of a total of 16 different images, each presented for 750 ms with an inter-stimulus interval of 250 ms. The block order was counterbalanced within participants. Participants were instructed to press a button when they saw the same picture twice in a row (1-back task), and maintained fixation on a small cross presented in the centre of the screen.

### **4.2.5.** Sequence-learning task

In the sequence-learning task, participants were presented with pictures of faces, houses and objects and were required to make an animacy judgments on each picture by pressing a button with their right index finger for one category and left index finger for the other (counterbalanced between participants) while maintaining fixation on a centrally-presented fixation cross. Participants were also instructed that the order of stimulus presentations contains certain regularities, and that it was their task to determine what those regularities are and to remember them. Stimuli were ordered into four different triplets, always starting with two objects (one animate, one inanimate) and ending with either a face or a house (see Figure 4.1B). Two of the triplets had a transitional probability of 100% between its three constituent stimuli, and were thus fully predictable (see Figure 4.1B, red triplets). The other two triplets contained a 0.5 transitional probability between the second and the third stimulus, which could either be a face or a house, rendering these triplets partly unpredictable (see Figure 4.1B, yellow triplets). This design ensured that the animacy judgment to the third stimulus in a given triplet could be predicted by the objects preceding it for the predictable triplets, while this was not the case for the unpredictable triplets, since the equally probable face or house stimuli required different responses. In order to keep the number of presentations equal for every stimulus, the same face and scene were used for both unpredictable triplets (see Figure 4.1B, yellow triplets). To keep the response contingencies similar between the predictable and unpredictable triplets, the response category of the objects in the first two positions was controlled: the first two objects would either always be animate followed by inanimate or inanimate followed byanimate (counterbalanced between subjects). The picture stimuli were presented for 200ms with an inter-stimulus interval of 6300 ± 1500ms. A slightly longer ISI of 8500 ± 1000ms was used between the last stimulus of one triplet and the first stimulus of the next. Each triplet was presented a total of 26 times. For the unpredictable triplets, there were 13 repetitions which ended with a face and 13 repetitions ending with a house. The

sequence-learning task lasted for approximately 50 minutes, split over four twelve-minute blocks, interleaved with breaks. The duration of the breaks was determined by the participant.

### **4.2.6.** Representational change task

To determine whether stimuli associated through sequential presentations elicited more similar neural representations, participants performed a representational change task before and after the sequence-learning task. The stimuli in these representational change tasks were the same 12 stimuli as in the sequence-learning task (4 animate and 4 inanimate objects, 2 faces and 2 houses). Stimuli were presented 9 times each for 1 second, and were separated by inter-stimulus intervals of 1,3 or 5 seconds (distributed over 40%, 40% and 20% of the trial, respectively). The proportion of ISIs was biased towards shorter durations to keep the inter-stimulus intervals short on average, while still being able to de-convolve BOLD responses. To ensure that the participants attended the stimuli, participants performed an orthogonal task, in which they detected whether a stimulus contained greyscale patches or not and indicated their choice with a button press. On approximately 11% of trials (1 out of 9 presentations), a stimulus appeared with 5% of pixels converted to greyscale (distributed evenly over the stimulus in 8-pixel clusters) while the luminance was kept the same. Full-colour stimuli were used on the remaining trials. Only the trials with full-colour stimuli were used in the MRI analysis. To ensure that any change in representational similarity between the pre- and post-learning blocks reflected representational change as consequence of learning, rather than changes in signal similarity due to difference in temporal proximity of the stimuli, we constructed a unique order of stimuli and inter-stimulus intervals for each participant, which was used for both the pre and the post blocks. To control for temporal autocorrelation between events in the pre- and post-blocks, stimulus order was pseudorandomised such that each of the 12 stimuli were presented once per mini-block in a random order.

### **4.2.7.** Subsequent memory task

After the fMRI session, participants completed a computerised task to assess their knowledge of the statistical regularities between the stimuli in the sequence-learning task. In this subsequent memory task, three stimuli appeared on the screen simultaneously, two from one triplet and one from another triplet (a distractor stimulus). One of the stimuli, the test stimulus, was presented in the upper half of the screen, while the other two, a target stimulus and a distractor stimulus, were presented below it

in a triangular formation. The participants were asked to decide which of the stimuli in the lower half of the screen were associated with the stimulus presented above. The distractor was matched to the target stimulus in category (animate object, inanimate object, face, or house) to ensure participants based their answers on stimulus identity rather than stimulus category. Subsequently, they indicated their certainty on a scale from 1 to 4. All possible within-triplet stimulus associations were tested (position1-position3, position1-position2 and position2-position3). To ensure that participants were not learning the expected associations during this task, they were only given feedback on their performance after completing the test.



### **4.2.8.** fMRI acquisition

Participants were scanned in a Siemens Tim Trio 3T scanner equipped with a 32 channel head coil. Whole-brain T2* weighted BOLD fMRI images were acquired using a 3D Echo Planar Imaging (Poser et al., 2010) sequence (64 slices, TR = 1.8s, voxel size = 2 × 2 × 2 mm, TE = 25 ms, flip angle = 15°, field of view = 224 × 224 mm, GRAPPA acceleration factor = 2). Using the AutoAlign Head software by Siemens, we ensured that the orientation of our field of view was tilted -25 degrees from the transverse plane for each of our participants, ensuring the same tilt relative to the individual participant's head position. In addition, T1-weighted structural images (MPRAGE, voxel size = 1 × 1 × 1 mm, TR = 2.3 seconds) and a field map (GRE, voxel size = 3.5 × 3.5 × 2 mm, TR = 1.02 seconds, TE1 = 10 ms, TE2 = 12.46 ms, flip angle = 90°; FOV = 224 × 224 mm; slice orientation = -25° pitch rotation from the transverse plane) were acquired.

### **4.2.9.** fMRI data preprocessing

fMRI data were analysed using the Automatic Analysis Toolbox v4 (Cusack et al., 2015). Functional imaging data were initially motion corrected and coregistered. The T1 structural scan was segmented using FreeSurfer v5.1 functions to obtain grey matter, white matter and CSF maps. For the univariate analyses, the functional images were normalised to the Montreal Neurological Institute (MNI) template and then smoothed using a 10 mm Full-Width at Half-Maximum(FWHM) 3D kernel.

### **4.2.10.** Univariate analysis of the sequence-learning task

The functional data from the sequence-learning task were modelled in a general linear model (GLM). This model contained six regressors of interest, representing the stimulus onsets for each of the three positions in the

triplets for the predictable and unpredictable sequences separately, but collapsed across the two predictable and the two unpredictable sequences. Left and right button presses were modelled in a separate regressor. These regressors were convolved with a canonical hemodynamic response function (HRF). Six movement parameters were included as nuisance regressors. We ran contrasts for the main contrast of predictability and for the interaction between predictability and position in sequence.

### **4.2.11.** General linear modelling of the representational change tasks

The functional data of the pre- and post-learning tasks were modelled in one GLM. The model contained twenty-four regressors per representational change task (for the pre- and post-learning representational change tasks separately), each containing half of the repetitions for one stimulus image (i.e. 8 objects, 2 faces and 2 houses). We constructed two regressors per stimulus image per representational change task to be able to compare the neural similarity of each stimulus with itself and other stimuli as a function of sequence learning (see subsection 4.2.12). Additional regressors represented button presses for each task. Six motion parameters were included as nuisance regressors. We constructed contrasts to investigate predictable vs unpredictable stimuli and their interaction with stimulus position in the sequence. Reported statistics are at $p < 0.001$, uncorrected.



### **4.2.12.** Searchlight representational similarity analysis

We used representational similarity analysis (RSA) to analyse the multivoxel pattern of neural activity (Kriegeskorte et al., 2008) and applied a roving searchlight approach on a hippocampal region of interest (ROI) based on Freesurfer volume reconstructions (van Leemput et al., 2009, constructed by combining the 'CA1', 'CA2-3' and 'CA4-DG' reconstructions,). The resulting masks were split in half along the y-axis to obtain an anterior and a posterior hippocampal region of interest. We examined the Pearson's correlation coefficients between patterns of activity within spherical searchlights throughout the grey matter of the ROI volume. RSA was used to assess whether parts of the hippocampus showed an increase in neural similarity as a function of learning for stimuli which were predictable, and thus strongly associated within the triplet, compared to unpredictable stimuli which should have had weaker associations within the triplet. From each spherical searchlight, we extracted the multivoxel activity pattern (2 voxel radius, including a minimum of 30 grey matter voxels), from each of the 24 pre- and post-learning beta images. We then constructed a balanced regressor-by-regressor contrast matrix for the hypothesized represen-

tational similarity pattern, with a mean value of 0. The observed similarity space of each sphere was then fitted to the contrast matrix, using a general linear model. The resulting parameter estimates were assigned to the centre voxels of each sphere. We then warped the resulting statistical maps for each participant to the MNI space, smoothed the normalized maps (FWHM: 2 mm) and used these to compute second-level T-statistics. Since we hypothesized an increase in representational similarity, one-tailed significance values are reported.

## 4.3. Results



Participants performed well in the representational-change tasks (pre-learning: 95.4%; post-learning: 96.4%), indicating they paid attention to the stimuli. On the sequence-learning task, participants could accurately categorise the items (M=95.70% correct, SE=0.51%), and there was no significant effect of stimulus predictability ($F(1,20) = 2.54$, $p = 0.126$), stimulus position in the sequence ($F(2,40) = 1.449$, $p = 0.248$) or interaction between those two factors ($F(2,40) = 2.70$, $p = 0.087$). In the subsequent-memory task, participants associated the stimuli in the sequences with each other with above-chance accuracy (Bonferroni corrected; first-second: M = 87.25% correct, SE=16%; $T(16) = 9.50$, $p < 0.001$; second-third: M = 73% correct, SE=22%; $T(16) = 4.22$, $p < 0.001$; first-third: M = 65.69% correct, SE=22%; $t(16)=2.91$, $p < 0.05$). There were no differences between predictable and unpredictable sequences ($p > 0.05$).

During the sequence-learning task, participants performed an animacy judgment on each stimulus. For the predictable sequences, participants could learn to predict the upcoming stimuli and the corresponding responses by learning the statistical regularities underlying the sequence order. In contrast, the irregular transition from the second to the third stimulus should prevent this behavioural facilitation for the unpredictable sequences. We hypothesized that participants could improve their response time performance for expected stimuli. Reaction times (RTs) on the animacy judgments were analysed in a 2x3 repeated-measures ANOVA with predictability and t position in the triplet as factors. Participants responded faster to predictable stimuli (M=632ms; SE=31ms) than to unpredictable stimuli (M=655ms; SE=30ms; $F(1,20) = 5.12$, $p = 0.035$, see Figure 4.2). We also observed that reaction times differed for the stimulus positions in the sequence ($F(2,40) = 17.03$, $p < 0.001$), reflecting faster RTs for stimuli in the second position (M=596.45ms, SE=33.51ms) compared to those

in the first (M=663ms, SE=30ms) or third (M=671ms, SE=31ms) position. This pattern of results may reflect a facilitated motor response for the second stimulus, which was predictable for both the predictable and unpredictable triplets: in all triplets, the first two (object) stimuli always followed each other and the required responses were always from opposite categories (see Figure 4.1B). Surprisingly, we did not observe an interaction between stimulus predictability and stimulus position ($F(2,40) = 0.42$, $p = 0.656$), suggesting that the expected behavioural facilitation for the final stimulus in predictable sequences was carried forward in time to include the preceding stimuli in those triplets. Note that this RT advantage for predictable triplets cannot be explained in terms of stimulus-level practice, as each stimulus was presented the same number of times, albeit in different configurations for the unpredictable sequences (see Figure 4.1B).



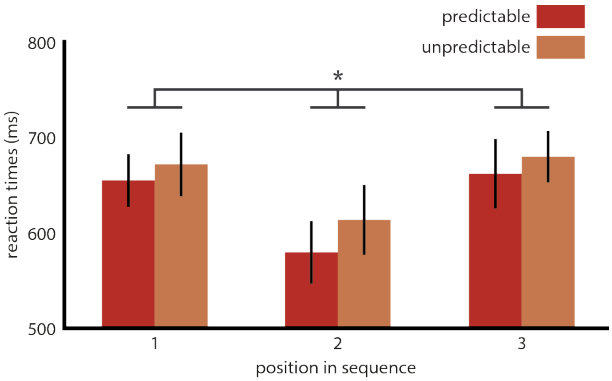



**Figure 4.2: Stimulus predictability speeds up reaction times**
Participants responded faster to stimuli that belonged to a predictable (red) sequence than to those belonging to unpredictable (yellow) sequence, regardless of stimulus position in the sequence. The second stimuli in the sequence had a faster response than the other two items for both predictable and unpredictable sequences, probably due to the predictability of the second stimulus given the first (see Figure 4.1B).

To investigate our hypothesis pertaining to the predictability of sequential information, brain responses between predictable and unpredictable triplets were contrasted, collapsing triplets ending in scenes and faces for both conditions. Although the critical manipulation between unpredictable and predictable triplets occurred in the third position, learning the regularities in the triplets may result in differences between all stimuli that were associated with the predictable and unpredictable last stimuli in the sequence. Indeed, medial prefrontal cortex and right posterior hippocampus showed a main effect of triplet predictability, characterised by higher activity for unpredictable than predictable stimuli (at $p < 0.001$, uncorrected, see Fig-

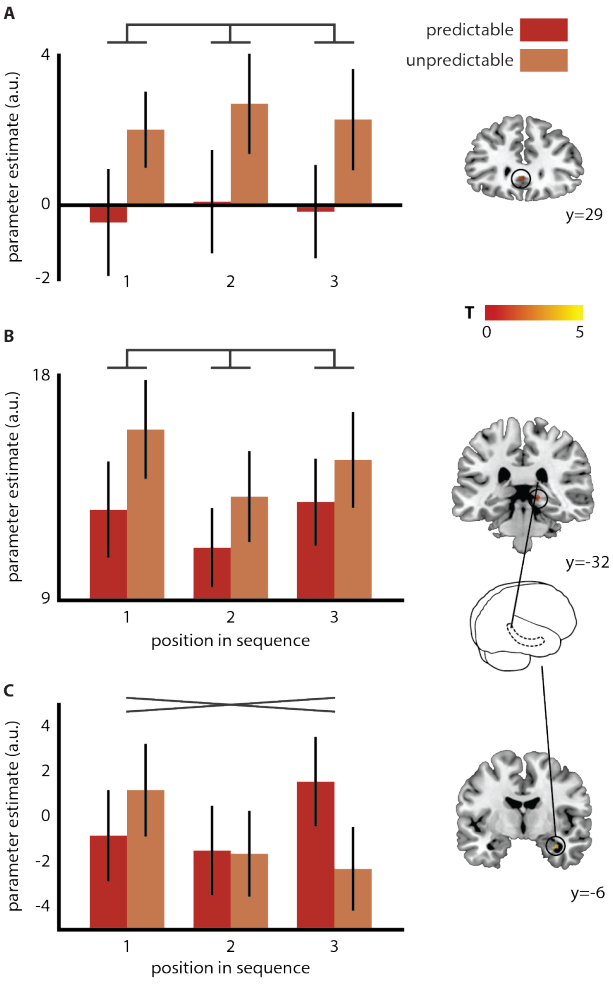



**Figure 4.3: Univariate effects of sequence predictability**
A) Activity in medial prefrontal cortex and B) right posterior hippocampus was higher for stimuli belonging to unpredictable (yellow) sequences than those in predictable (red) sequences, regardless of stimulus position in the sequence. The plot shows parameter estimates for predictable and unpredictable stimulus positions. The image on the right shows a statistical map of the plotted effect. Colours indicate T-values. The statistical maps were thresholded at $p < 0.001$, uncorrected.
C) Right anterior hippocampus showed an interaction between predictability and stimulus position: for predictable sequences, activity increased with stimulus position, while unpredictable sequences showed the opposite pattern. Parameter estimates for this interaction are plotted. The image on the right shows a statistical map indicating the location of the effect. Colour indicate T-values. The statistical map was thresholded at $p < 0.001$, uncorrected.

ure 4.3A and Figure 4.3B, respectively), indicating these regions are sensitive to the differences in predictability between the sequence types. In a next step, we asked whether there were regions in the brain that represented an interaction between stimulus position in the triplet and predictability, representing a differential build-up of sequential information for predictable and unpredictable sequences. Right anterior hippocampus showed such an interaction, with progressively lower activity for unpredictable sequences, but progressively higher activity for predictable sequences as a function of stimulus position (linear interaction, $F(1,20) = 14.20$, $p = 0.001$ see Figure 4.3C), indicating this region is sensitive to predictability as a function of time for a given sequence.



To further investigate the effect of the learned regularity structure on the representation of the presented stimuli, we used representational similarity analysis (Kriegeskorte et al., 2008) on the data from the representational change tasks. We expected that neural representations of stimuli which were associated as a consequence of sequential co-occurrence should become more similar to each other, selectively in the post compared to the pre block. Furthermore, we expected that this effect should be more prominent for predictable sequences compared with unpredictable sequences since their transitional probability was higher. On the basis of earlier reports (e.g. Schapiro et al., 2012), we expected that representational similarity in regions in the hippocampal formation would increase for stimuli that were strongly associated to each other as a consequence of learning the triplet structure. Conversely, representational similarity in regions in the hippocampal formation was not expected to change for items with an unpredictable relation to each other (see Figure 4.4A for a schematic illustration of this interaction logic). We tested this hypothesis separately for third-to-second stimulus comparison and the third-to-first comparison in hippocampal ROIs (see Methods). We observed that in the anterior hippocampus, neural similarity between the third-to-first comparison increased as a function of learning, for predictable over unpredictable sequences ($T(20) = 1.85$, $p = 0.039$; see Figure 4.4B). The posterior hippocampus did not show this learning-induced effect on neural similarity ($T(20) = 0.93$, $p = 0.183$). Interestingly, the sequence-learning effect was not present for the third-to-second stimulus comparison in the regions of interest, possibly reflecting the reduced task relevance of the second stimulus in each sequence compared to the first and third (see also the behavioural finding). These results indicate that the hippocampus codes for temporal regularities by increasing the neural similarity of stimuli that are associated by

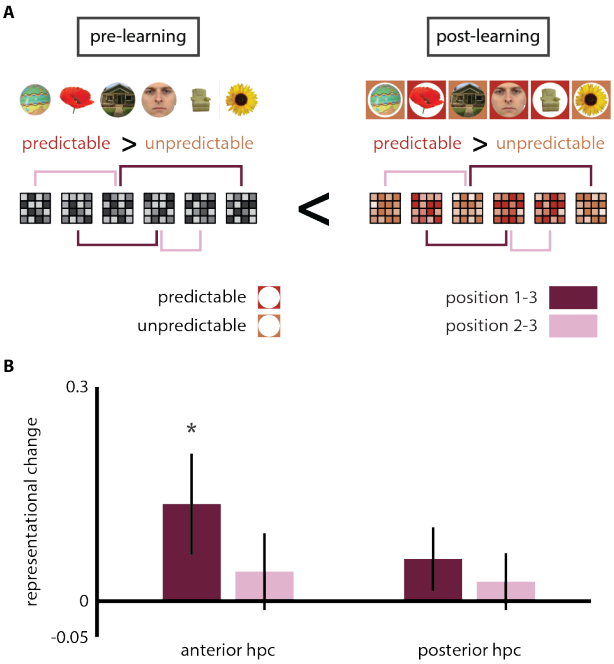



**Figure 4.4: Neural similarity increases after learning for predictable stimuli**
A) A schematic illustration of the representational similarity analysis. Pre- and post-learning, participants were presented with stimuli in the same random order. Neural responses to these stimuli were extracted and correlated. The interaction between predictability and time of presentation (pre- or post-learning) was investigated: the similarity difference between predictable (red) and unpredictable (yellow) stimuli was compared between post-and pre-learning, separately for stimulus 3 to 1 in each sequence (purple) and stimulus 3 to 2 (pink).
B) The representational change of post- > pre-learning for predictable > unpredictable, for anterior and posterior hippocampus. The representational change was significant in anterior hippocampus, but only for the comparison between stimulus 3 to 1. * = $p < 0.05$, one-tailed.

predictable transitional probabilities. These stimuli do not have to be temporally proximal, but instead might reflect the relevance of stimuli for the sequence representation: since our first item was already fully predictive of the last item, the second item was less relevant for the prediction of the end of the sequence, which was reflected in higher similarity between the first and third item in the sequence.

## 4.4. Discussion

In this study, we investigated prospective coding during and after hippocampal sequence learning. Participants learned regularities between stimulus presentations, which could facilitate their response times during the task. We found that participants indeed could improve their response times for items presented in predictable triplets compared to those which were a part of unpredictable triplets. Hippocampus and medial prefrontal cortex showed sensitivity to sequence predictability, highlighting their role in distinguishing the transitional probabilities between events. Finally, we show that as a result of this regularity learning, stimulus representations in anterior hippocampus showed increased pattern similarity, indicating that this region codes represents the learned transitional probabilities by changing the neural similarity of its constituent parts.



Participants showed faster reaction times to stimuli from predictable than unpredictable sequences. This finding dovetails with other studies on predictability that found that expectations can facilitate the speed and accuracy of perception (Carpenter and Williams, 1995; Bogacz et al., 2006; Diederich and Busemeyer, 2006; Puri and Wojciulik, 2008; Turk-Browne and Scholl, 2009; Hanks et al., 2011; Krol and El-Deredy, 2011; van Ravenzwaaij et al., 2012; Jiang et al., 2013). Neural correlates of predictions guiding perception have been observed in visual (Summerfield et al., 2006a; White et al., 2012; Jiang et al., 2013; Kok et al., 2014), auditory (Chennu et al., 2013), somatosensory (Carlsson et al., 2000), and olfactory (Zelano et al., 2011) cortex. Interestingly, we observed behavioural facilitation for all stimulus positions in the predictable sequences, even though there only was a difference in predictability for the third stimulus position. This suggests that strong associations may have been formed between the stimuli within the predictable sequences, which could transfer any behavioural advantage for one of the stimuli to the others by association.

We hypothesized that the hippocampus would be sensitive to the predictability of the learned sequences (Davachi and DuBrow, 2015). Indeed, posterior hippocampus generally showed higher activity for stimuli in unpredictable than in predictable sequences. Anterior hippocampus also showed sensitivity to predictability. These findings are consistent with earlier reports of hippocampal involvement in sequence learning (Schendan et al., 2003; Kumaran and Maguire, 2006; Bar, 2009; Kalm et al., 2013; Schapiro et al., 2014). Specifically, anterior hippocampus has been shown to adapt when a probabilistic relation between stimuli is learned (Strange

and Dolan, 2001). Furthermore, this region was found to respond more to random (low predictability) than ordered (high predictability) sequences (Strange et al., 2005). Here, the sensitivity to predictability interacted with the position of stimuli within the triplets: we observed increasing activity over the course of predictable, but decreasing activity over the course of unpredictable sequences. Our findings suggest that the anterior hippocampus codes uncertainty prospectively, possibly by reconstructing the upcoming stimulus representations (Addis and Schacter, 2008; Schacter et al., 2008; Addis et al., 2009). The medial prefrontal cortex also showed more activity for unpredictable than predictable stimulus sequences. This is consistent with previous work, showing that the medial prefrontal cortex is active during associative learning of stimuli that are separated in time (Kesner et al., 1994; Blumenfeld and Ranganath, 2006; Murray and Ranganath, 2007; Ezzyat and Davachi, 2011; Hales and Brewer, 2011). Furthermore, detection of regularities across experiences is reflected by functional coupling between the hippocampus and the ventromedial prefrontal cortex (Zeithamova et al., 2012). Clinical research has shown that lesions to the frontal cortex lead to impairments in sequence learning and order memory (Shimamura et al., 1990; McAndrews and Milner, 1991; Marshuetz, 2005; Meier et al., 2013).



Finally, we predicted that the effect of regularity learning would be reflected in lasting changes to hippocampal stimulus representations. We found that stimulus representations in the hippocampus became more similar as a function of the regularities between them: neural pattern similarity between stimuli in predictable triplets became greater after learning than between stimuli in unpredictable triplets. Interestingly, this similarity change was only present for the first and last stimuli of the sequences, indicating the hippocampus can represent non-contiguous sequence information about associated stimuli by increasing the similarity of the neural representations for the respective stimuli in these sequences. Our findings fit with a number of recent studies on hippocampal representations after sequence learning (Paz et al., 2010; Schapiro et al., 2012; Kalm et al., 2013; Hsieh and Ranganath, 2014). In one study, it was observed that pattern similarity in the hippocampus was greater for objects in their learned sequential positions than for the same objects in random positions and different objects in identical sequential positions (Hsieh and Ranganath, 2014). Another study in epileptic patients showed that the firing rate of hippocampal neurons to stimuli in a sequence becomes more similar over sequence repetitions. This increase of similarity corresponded to an increase in mem-

ory performance across participants (Paz et al., 2010). In a recent study, Schapiro and colleagues (Schapiro et al., 2012) found that after multiple presentations of pairs of stimuli with whose temporal regularity structure remained constant, the neural pattern similarity between these stimuli was increased in the hippocampus and MTL, such that exposure to the first stimulus elicited a prediction for the next stimulus. This similarity increase was absent for pairs of stimuli with weaker (less predictable) regularity structures. Although this indicates hippocampal involvement in the learning of regularity structures, these studies could not distinguish a prospective code for sequentially proximal stimuli from a possible deterministic code based on prospective relevance. We expand on these findings by showing that the hippocampus can also represent within-sequence stimulus relations that are not temporally proximal, but instead reflect the relevance of these stimuli for the representation of the sequence. These results provide more evidence for a role for the hippocampus in representing deterministic prospective event information.



In conclusion, we find that hippocampal sequence learning can facilitate behaviour and leads to changed neural representations in hippocampal patterns, such that the onset of a learned sequence is associated with the forward reinstatement of a hippocampal representation of the remainder of the sequence. These findings shed light on the role of the hippocampus in sequence learning and prospective event representation.

# 5

# Memory representations shift from hippocampus to medial frontal cortex through memory consolidation [temcon]

**Sander E. Bosch, Alexander R. Backus, Christian F. Doeller**

This chapter is in preparation as: SE Bosch*, AR Backus* and CF Doeller. Memory representations shift from hippocampus to medial frontal cortex through memory consolidation (* = equal contributions)

## 5.1. Introduction

The formation of long-term memories involves a rapid initial storage of newly acquired information, and a subsequent gradual integration of this information into existing associative networks. The hippocampus (HPC) plays an important role in the rapid storage of new information by indexing conjunctive information about newly acquired associations during encoding (Marr, 1971; Teyler and DiScenna, 1986; Teyler and Rudy, 2007). Through coordinated cortico-hippocampal reactivation, these neocortical representations can be integrated into structured neocortical associative networks, gradually diminishing the role of the hippocampal conjunctive memory representations (Marr, 1970; Sutherland and McNaughton, 2000; Frankland and Bontempi, 2005; Rasch and Born, 2007). The shift of hippocampal to neocortical memory representations over time has been dubbed systems consolidation (Squire, 1992; Alvarez and Squire, 1994). Consolidation can occur across long timescales, but also relatively short delays (upwards from a day) can cause changes in memory representations (Bosshardt et al., 2005b; Takashima et al., 2006, 2009).



Consistent with systems-level consolidation theory, several animal studies employing lesions or inactivations have reported a double dissociation between hippocampus and medial prefrontal cortex (mPFC): recent memories depend on hippocampus, while over time remote memory is supported by the mPFC (Maviel et al., 2004; Takehara-Nishiuchi et al., 2006; Takehara-Nishiuchi and McNaughton, 2008; Lesburgueres et al., 2011). These findings suggest that the binding role of the hippocampus for recently acquired memories may be transferred to the mPFC over time (Frankland and Bontempi, 2006; Takashima et al., 2006; Takehara-Nishiuchi and McNaughton, 2008; Goshen et al., 2011; Preston and Eichenbaum, 2013) and highlight the importance of hippocampal–neocortical interactions in the early stages of long-term memory formation (Wang and Morris, 2010).

However, human neuroimaging studies have produced mixed results. While most studies have reported higher activity in the hippocampus for recent than remote memory retrieval (Takashima et al., 2006; Sterpenich et al., 2009; Takashima et al., 2009; Yamashita et al., 2009; Watanabe et al., 2012; Ritchey et al., 2015), other studies have reported no change in activity (Stark and Squire, 2000; Janzen et al., 2008; Suchan et al., 2008), or even the reverse effect (Bosshardt et al., 2005a; Gais et al., 2007). Moreover, only some of these studies found that the medial prefrontal cortex was more involved during retrieval of remote than recent memories (Takashima

et al., 2006; Euston et al., 2007; Gais et al., 2007; Sterpenich et al., 2007). These mixed results may have been caused by differences between the memory paradigms that were used, or possible differences in behavioural performance for recent and remote memory retrieval. Furthermore, the shift of conjunctive representations from hippocampus to medial prefrontal cortex may not be apparent on a general amplitude level, but expressed more subtly through variations in neural patterns.

In the present study, we used a cued recall paradigm to investigate the representational roles of the hippocampus and medial prefrontal cortex as a function of time. Participants took part in two experimental sessions, in which they learned to associate pairs of visual stimuli (in three categories: faces, houses and bodies) and subsequently performed a cued recall task in the fMRI scanner. Crucially, the delay between learning and retrieval was different in the two sessions: either thirty minutes (recent session) or one week (remote session). We employed representational similarity analysis to investigate the conjunctive information present in hippocampus and medial prefrontal cortex during retrieval in both sessions. Specifically, we looked at conjunctive representations on two levels: one reflecting the general category of the retrieved association, and one reflecting the unique identity of the retrieved association. Since there is functional heterogeneity within the hippocampus (Poppenk et al., 2013), we hypothesized that these different types of conjunctive information might be stored in different parts of hippocampus. For example, the anterior and posterior hippocampus are differentially involved in spatial memory (Moser and Moser, 1998; Fanselow and Dong, 2010; Poppenk et al., 2013): general spatial context is represented in the anterior hippocampus, while the posterior hippocampus codes specific places (Poppenk et al., 2013; Evensmoen et al., 2015). This differentiation could generalize to non-spatial memories (Milivojevic and Doeller, 2013), leading to the hypothesis that category-level conjunctive information may be coded in the anterior hippocampus, while specific association-level information would be represented in posterior hippocampus. As memories can lose specificity with consolidation (Wiltgen and Silva, 2007; Winocur et al., 2007), we expected that these functional differences in the hippocampus could be reflected in differential contributions to the representation of memories over time. The medial prefrontal cortex is known for representing memories more gist-like and general over time (Lewis and Durrant, 2011; Winocur and Moscovitch, 2011), so we expected it to contain more general conjunctive representations for remote memories.

## 5.2. Materials and Methods

### 5.2.1. Participants

Twenty-four participants (12 females; aged 18-33 years; average age: 22.5 years) gave written informed consent and participated in the two-session experiment. All were in good health, with normal or corrected-to-normal vision and without history of psychiatric or neurological diseases. Participants were reimbursed for their participation. The study was approved by the local ethical review board (CMO region Arnhem-Nijmegen, The Netherlands). Two participants were excluded due to technical problems with the scanner during one of the sessions and one participant because of an insufficient performance level (d-prime < 1.0) during both sessions. Therefore, data of twenty-one participants (11 females; aged 18-33 years; average age: 22.6 years) were included in the reported analyses.



### 5.2.2. Stimuli

We used greyscale images of faces (Karolinska Directed Emotional Faces), houses (Stanford Vision Lab stimulus set) and human bodies (Bodily Expressive Action Stimulus Test set). All images were cropped to 200 x 200 pixel dimensions and normalized using the SHINE toolbox for MATLAB by adjusting the mean luminance and standard deviation of the intensity values for each pixel (see Figure 5.1B for examples). Stimuli were presented to participants using the Presentation software package (version 16.4; Neurobehavioural systems).

### 5.2.3. Procedure

Participants performed two sessions of the experiment, each consisting of an encoding phase outside and a recall phase in the fMRI scanner (see Figure 5.1A). In the 'recent' session, there was a delay of approximately thirty minutes between the encoding phase and the fMRI recall phase. The data from this recent session was separately analysed and discussed in another manuscript (Backus et al.). In the 'remote' session, there were seven days in between encoding and recall. The experimental sessions were on average planned 33 days apart, and contained different sets of stimuli. The order of the recent and remote sessions was counterbalanced across participants.

### 5.2.4. Paired associate learning prior to the fMRI recall task

Participants commenced with the initial encoding session outside the scanner, separated into six study and test cycles. During study cycles, participants learned twelve random associations between pairs of pictures. Associ-

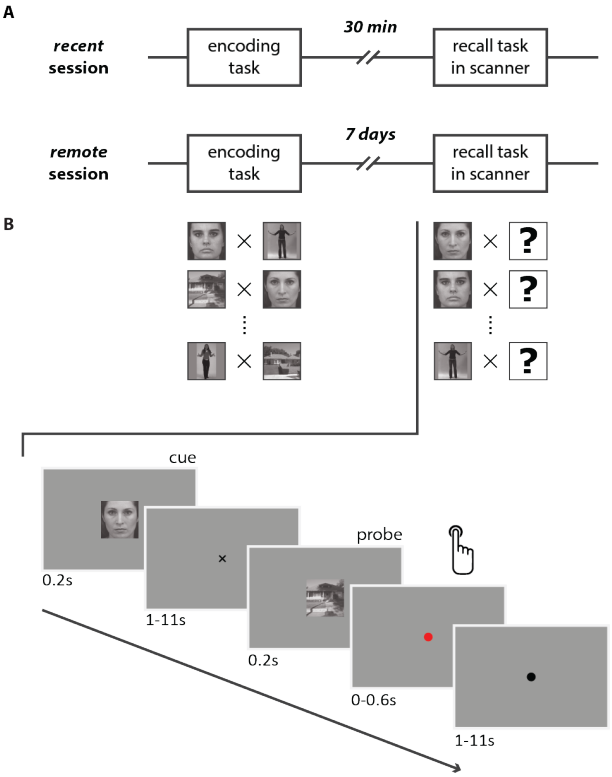



**Figure 5.1: Associative memory paradigm**
A) Schematic illustration of the sessions structure. All participants performed two experimental sessions: in one session, they encoded pairs of stimuli 30 minutes before performing an fMRI retrieval task, in the other session there was one week in between encoding and fMRI retrieval. The order of the sessions was counterbalanced across participants.
B) During encoding, participants learned to associate twelve pairs of three categories (face-house, house-body and body-face pairs) until criterion. During retrieval, they were cued with one member of a learned pair, and recalled its associate. Importantly, both stimuli from a pair could be used as cue. After a variable delay, a probe stimulus was presented. Participants indicated by button press whether or not the probe was the correct associate.



ations included face-house, face-body and house-body pairs (4 pairs of each type). In a study block, the twelve pairs were presented in random order. In each trial, the two stimuli of each pair were shown in succession (1000 ms on-screen, 1000 ms inter-stimulus interval). In between trials a 3000ms inter-trial interval was presented, during which a fixation dot was presented on screen. The order of presentation of the two stimuli per pair was counterbalanced across cycles. In the test blocks, 48 test trials were presented in which one of the stimuli of each pair was presented as a retrieval cue,

followed by a probe stimulus, which could either be the correct associate or a different stimulus from the same category. Either of the pair members could appear as a cue, with the order counterbalanced within and across cycles. The cue and probe stimuli were each presented for 200 ms. Cue and probe presentations were separated by a retrieval phase of 1000, 3000 or 5000 ms (counterbalanced across cues, pairs, correct versus incorrect probe and cycles) during which participants were asked to retrieve the specific associate of the cue. Participants were instructed to respond as fast as possible with their right hand, using two response buttons, and to indicate whether the probe was the correct or incorrect associate. Response mapping of these two buttons was counterbalanced across participants. The maximal response window was set to 600 ms. If participants did not respond within the response window, a "too late" text was presented for 1000 ms. The variable retrieval phase together with the short response window ensured that participants had to respond promptly to elicit immediate memory retrieval. After each response, feedback was provided by presenting the correct associate (1000 ms on screen). Trials were separated by variable inter-trial intervals of 1, 3 or 5 s (retrieval phase and inter-trial interval added up to 6 s in each trial). During a given test block, each association was tested 4 times. At the end of each test block, the percentage of correctly answered trials was displayed to the participant. We encouraged participants to reach a minimum of 80% correct trials in at least one of the test blocks to ensure high memory performance.



### **5.2.5.** Retrieval task in the scanner

After a 30 min break (recent session) or one week later (remote session), participants performed the retrieval task in the MRI scanner in 2 runs of approximately 25 minutes each, with a short half-time break in between lasting approximately 5 minutes. During each scan session, a total of 288 retrieval test trials were presented to the participant. Trial structure was identical to the combined test blocks of the encoding session. However, we did not provide feedback and set the retrieval phase and inter-trial interval lengths to 1, 6 and 11 s. The performance score was only displayed at the end of the recall task.

### **5.2.6.** fMRI acquisition

Neuroimaging data were acquired using a 3T MR scanner (TIM Trio; Siemens Healthcare) in combination with a 32-channel head coil. For the functional scans, we used a 3D EPI (Poser et al., 2010) sequence (voxel size: 2 x 2 x 2 mm; volume TR: 1800 ms; TE: 25 ms; flip angle: 15 degrees; 64 slices;

FOV: 224 x 224; orientation: -25 degrees from transverse plane; GRAPPA acceleration factor: 2; acceleration factor 3D: 2). Using the "AutoAlign" head software by Siemens, we ensured similar FOV tilt across participants. Functional scan runs contained approximately 1000 volumes. In addition, we acquired field maps using a gradient echo sequence (voxel-size: 3.5 x 3.5 x 2 mm; volume TR: 1020 ms; TE1: 10.00 ms; TE2: 12.46 ms; flip angle: 90 degrees; 64 slices; FOV: 224 x 224; orientation adjusted to functional sequence; descending slice order). At the end of the scanning session, we obtained a structural scan using an MPRAGE sequence (voxel-size: 1 x 1 x 1 mm; volume TR: 2300 ms; TE: 3.03 ms; flip angle: 8 degrees; FOV: 256 x 256; ascending slice order; GRAPPA acceleration factor: 2; duration: 5:21 mins).

### **5.2.7.** fMRI data preprocessing

We preprocessed MRI data using the Automatic Analysis framework (Cusack et al., 2015), which combines tools from SMP8, FreeSurfer v5.1 and the FMRIB Software Library v5.0, complemented by custom scripts. The preprocessing pipeline consisted of the following steps: we removed biases resulting from field inhomogeneities from the native structural images using the SMP8 'new segment' option. Furthermore, we denoised the structural images using an Adaptive Optimized Nonlocal Means filter (MRI denoising software). We realigned and unwarped the functional images using the fieldmap images, and coregistered the functional images to the obtained structural scan. We constructed a group structural template using the Advanced Normalization Tools (ANTs) toolbox v1.9.



### **5.2.8.** General linear modelling

Our analyses were restricted to the retrieval phase in each trial and we included all 288 trials for both the recent and remote recall sessions in our analyses. We modeled brain activity during the retrieval phase and inter-trial intervals by using three randomly selected trials of the same run and condition (with three different retrieval phase lengths). For each triplet, we ran a general linear model including a regressor for that triplet and another regressor for all other triplets and other task and nuisance variables, using standard SPM functions. In total, we obtained the beta images for 96 retrieval phase regressors and another 96 complementary inter-trial interval regressors (48 per functional run). Using this iterative method yields beta weights well-suited for multivariate pattern analysis on event-related designs (Mumford et al., 2012).

### **5.2.9.** Searchlight representational similarity analysis

We performed a searchlight analysis in our regions of interest to assess which of them contained multivoxel information about categorical and specific memory representations. After applying a grey matter mask, we extracted the multivoxel activity pattern within each spherical searchlight (4 voxel radius, including a minimum of 30 grey matter voxels), from each of the 96 retrieval phase beta images. Similarity measures between patterns were obtained by using Spearman correlation to account for nonlinear effects. We then constructed a balanced regressor-by-regressor contrast matrix for the hypothesized representational similarity pattern, with a mean value of 0. The observed similarity space of each sphere was then fitted to the contrast matrix, using a general linear model. The resulting parameter estimates were assigned to the center voxels of each sphere. We then warped the resulting statistical maps for each participant to the ANTS template space, smoothed the normalized maps (FWHM: 2 mm) and used these to compute second-level T-statistics. Finally, we transformed the second-level T-maps to MNI space.



### **5.2.10.** Conjunctive mnemonic information contrasts

To be sensitive to conjunctive memory retrieval in our analysis, we defined two contrasts. In the first, category-specific, contrast (see Figure 5.3A), we expected high pattern similarity when comparing the activity patterns of a specific association with another association of the same category type (face-house, house-body or face-body). For the comparison between patterns from associations from different categories, we expected high dissimilarity. The second contrast was association-specific (see Figure 5.3B), in which we expected high pattern similarity when comparing the multivoxel activity patterns of a specific association to a different instance of the same association ("associational similarity contrast"). Conversely, when we compared the patterns during retrieval of a specific association with the pattern in response to a different association, we expected high dissimilarity. To control for unspecific perceptual effects and to maximize our sensitivity for mnemonic representations in both of these contrasts, we introduce a "perception penalty" by excluding specific comparisons: whenever we compared neural patterns of two instances of the same association/ category type, the cue-associate order of one of the instances was always reversed. Conversely, when we compared instances of different associations/ category types, we made sure that cue-associate order was identical (see Figure 5.3) and (Backus et al.). Any perceptual (dis)similarity effects driven by the visual categories of the cue and associate were thus minimized.

### **5.2.11.** Univariate contrasts

To ascertain possible differences in the activity elicited by recent and remote retrieval, we smoothed the functional data from both sessions (FWHM: 8 mm) and applied an SPM general linear model including regressors for retrieval phases, inter-trial intervals, faces, scenes, bodies, test probes, retrieval cues and button presses for each functional run. Next, we contrasted the beta images of the retrieval phases with the beta images of the inter-trial intervals for each session separately. The resulting T-maps were warped to ANTS template space, then transformed to MNI space and contrasted in a second-level analysis (see Figure 5.6).

### **5.2.12.** Regions of interest

Freesurfer volume reconstructions were used as regions of interest. The hippocampal regions of interest were constructed by combining the CA1, CA2-3 and CA4-DG reconstructions (van Leemput et al., 2009). The resulting masks were split in half along the y-axis to obtain an anterior and a posterior hippocampal region of interest. To ensure a principled way of defining a region of interest for the medial prefrontal cortex, the left and right hemisphere cingulate labels from a Freesurfer cortical parcellation were used (Destrieux et al., 2010). These cortical volumes covered a large part of medial prefrontal cortex.



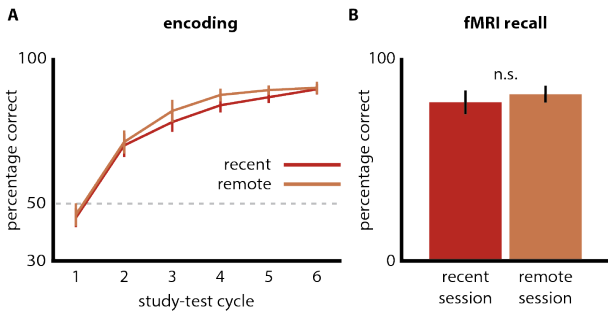



**Figure 5.2: Behavioural performance in the recent and remote sessions**
A) Participants performed six study-test cycles in the encoding phase of both experimental sessions. Their performance started around chance level, but increased steadily to criterion over the six cycles. There were no differences in learning rates between the two sessions.
B) During retrieval in the fMRI scanner, participants performed a cued recall task. There was no significant difference in performance between the recent and the remote memory session. n.s. = $p > 0.05$.

## 5.3. Results

Participants performed two sessions of an associative memory paradigm (see Figure 5.1B). In both sessions, participants (N = 21) learned the associations at similar rates (see Figure 5.2A). Importantly, there was no significant difference ($T(20) = -0.83$, $p = 0.416$) in the accuracy with which participants were able to remember the associations in the recent (M = 83.6% correct, SEM = 2.5%) and remote session (M = 85.3% correct, SEM = 1.8%; see Figure 5.2B). The observation that both learning rate and retrieval accuracy did not differ between the sessions indicates that any observed change in the neural patterns between recent and remote memory retrieval could not reflect a mere difference in behavioural performance.



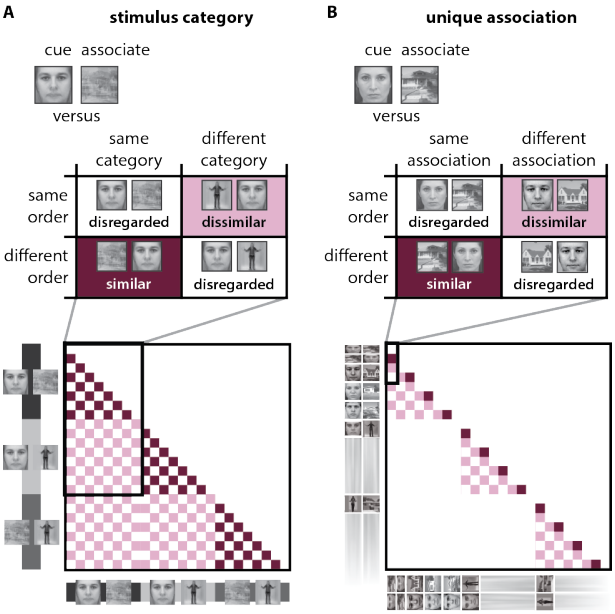



**Figure 5.3: Representation similarity analysis logic**
A) and B) show orthogonal representational similarity (RSA) contrasts, with A) capturing information about the stimulus category, and B) about the unique identity of the retrieved association. The top parts of the figure show a schematic of the associational similarity contrasts, with expected high regional representational similarity for comparisons of the same category/association, and low similarity for comparisons of different categories/associations, yielding a conjunctiveness metric for each voxel. Specific comparisons were excluded to penalize perceptually-driven effects (blank cells): within-association comparisons with identical cue or associate stimulus categories (top left quadrant in matrix), and between-association comparisons with different cue and associate stimulus categories (bottom right quadrant). The bottom parts show the full condition-by-condition RSA contrast matrices used in the searchlight approach. Each cell represents a specific comparison between two conditions. Darkness indicates degree of expected pattern similarity.

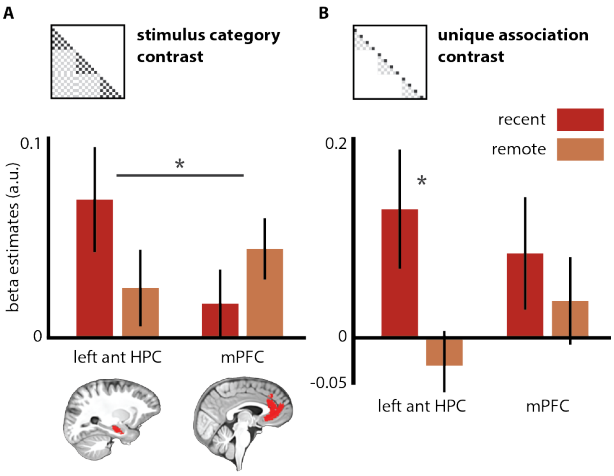



**Figure 5.4: Consolidation-induced representational shift from hippocampus to medial frontal cortex**
A) The left anterior hippocampus (left ant HPC) has more conjunctive information about the retrieved stimulus category during retrieval of recently acquired associative memories than of remote memories, whereas the medial prefrontal cortex (mPFC) shows more information for remote than recent memories. Left and right medial prefrontal cortex ROIs were combined in this illustration. Brain images show the regions of interest in red. * = $p < 0.05$.
B) During retrieval of recent associations, the left anterior hippocampus has more association-specific information about the identity of the retrieved stimulus content than for remote memories. * = $p < 0.05$.



We investigated the conjunctive information in the hippocampus and the medial frontal cortex during cued retrieval. Specifically, we were interested in differences between retrieval of associative memories for recently learned stimuli compared to remotely learned stimuli. We operationalized conjunctiveness as the amount of information about memory associations in spherical regions surrounding a single voxel ("search-lights"), assessed with representational similarity analysis. We constructed two contrasts, that each captured orthogonal aspects of the possible information present in our regions of interest (see Figure 5.3). The first contrast was sensitive to the retrieved association category (face-body, body-house or house-face; see Figure 5.3A). In other words, this contrast captured global information about the category of stimuli that was being retrieved, but not its specific identity. The second contrast was sensitive to the unique association (i.e. face 1, house 3, etc.; see Figure 5.3B), capturing information specific to the identity of the retrieved stimulus. These two contrasts were applied to

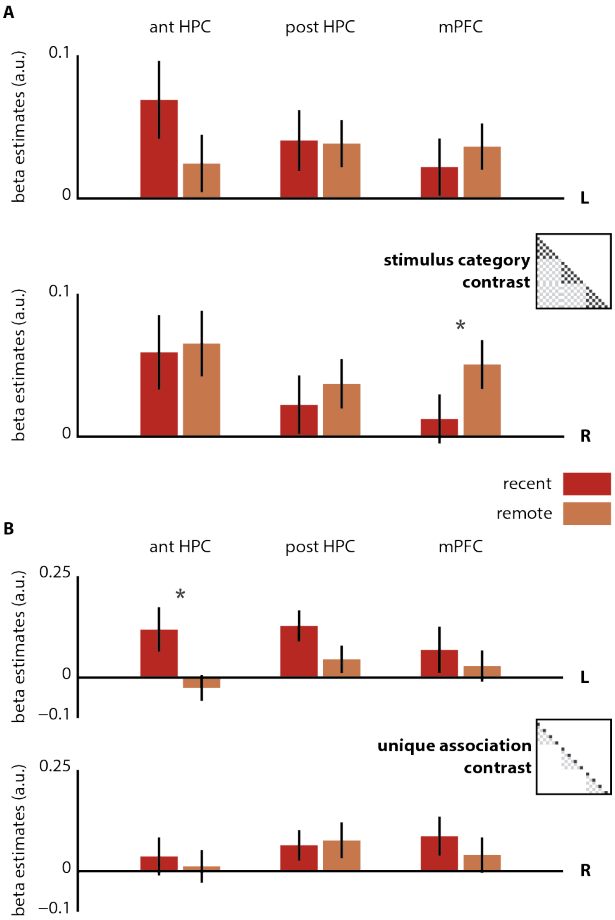



**Figure 5.5: Representational similarity for all regions of interest**
A) and B) show the amount of conjunctive information present in our six regions of interest: bilateral anterior hippocampus (ant HPC), posterior hippocampus (post HPC) and medial prefrontal cortex (mPFC), for the stimulus category and the unique association contrasts, respectively. * = $p < 0.05$.

the functional data in our regions of interest in a search-light analysis, resulting in a conjunctiveness score for each individual voxel. We expected higher neural pattern similarity when comparing instances of the same category type/specific association relative to comparing different associations (see Figure 5.3).

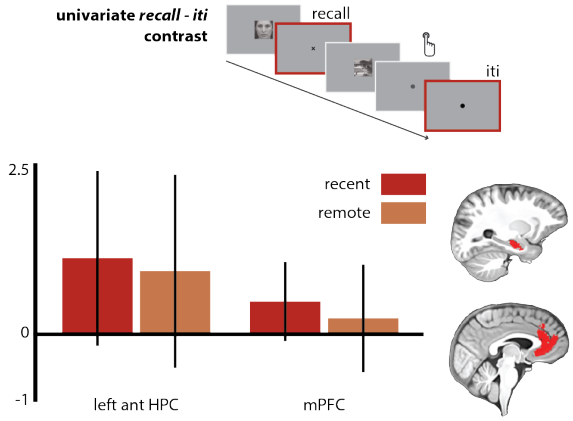



**Figure 5.6: No consolidation-induced difference in general signal amplitude**
To investigate whether our RSA results might be driven by univariate BOLD activation differences between the sessions, we contrasted recall and the inter-trial intervals (itis). There were no differences in the resulting parameter estimates, suggesting that the observed pattern similarity findings are not driven by a BOLD activity difference between recent and remote recall.



For the category contrast, we observed that left anterior hippocampus showed lower pattern similarity for remote than for recent associative memories, while medial prefrontal cortex showed higher pattern similarity over time ($T(20) = -2.11$, $p = 0.048$). This session-by-region dissociation was significant ($F(1,20) = 5.25$, $p = 0.033$; see Figure 5.4A), indicating a shift of the conjunctive representations within these regions as a function of memory delay. Similarly, for the unique association contrast, we also observed significantly higher pattern similarity in the left anterior hippocampus for recent than for remote associative memories ($T(20) = 2.35$, $p = 0.029$; see Figure 5.4B), suggesting that this region is more important for the representation of recently acquired associative links. Interestingly, posterior hippocampus did not show significant differences in neural similarity between recent and remote memories for either of the contrasts (see Figure 5.5). To make sure that the observed neural similarity effects were not due to BOLD signal differences between the two fMRI retrieval sessions, we compared the univariate signals during retrieval with those during the inter-trial intervals. There were no differences in the resulting parameter estimates between the recent and remote sessions in our regions of interest, indicating that the similarity effects we observed in hippocampus and medial frontal cortex were based on conjunctive information rather than mere general activation (see Figure 5.6).

## 5.4. Discussion

Systems-level consolidation theory posits a gradual shift of hippocampal-dependent memories to incorporation into associative neocortical networks (Squire, 1992; Alvarez and Squire, 1994). Using representational similarity analysis on cued retrieval data, we provide evidence for a shift in the location of conjunctive memory representations as a function of time. Recently acquired memories are represented in anterior hippocampus, but remote memories depend more dependent on medial prefrontal representations. Importantly, differences in behavioural performance and general fMRI signal amplitude between the experimental sessions could not account for the observed neural similarity dissociation.



The present results are in line with both theoretical work and previous empirical findings. Computational models demonstrate that the flexible nature of the hippocampus that enables it to store new information rapidly, renders stored representations vulnerable to interference (Marr, 1971). In contrast, the neocortex has a slower learning rate, allowing new information to be integrated into existing networks (Marr, 1970). These networks can store generalized and nonoverlapping memory representations efficiently in a structured manner (Marr, 1970; O'Reilly and Norman, 2002).

Previous studies on the effect of consolidation on hippocampal activity have yielded mixed results. Most studies have reported higher activity in the hippocampus for recent than remote memory retrieval (Takashima et al., 2006; Sterpenich et al., 2009; Takashima et al., 2009; Yamashita et al., 2009; Watanabe et al., 2012; Ritchey et al., 2015), consistent with consolidation theory. However, other studies found no change in activity (Stark and Squire, 2000; Janzen et al., 2008; Suchan et al., 2008), or higher activity for remote than recent memories (Bosshardt et al., 2005a; Gais et al., 2007). These mixed results might be due to the type of tasks and contrasts used: high- versus low-confidence recognition (Takashima et al., 2006; Suchan et al., 2008; Sterpenich et al., 2009; Takashima et al., 2009; Yamashita et al., 2009; Watanabe et al., 2012), targets versus foils (Stark and Squire, 2000) or recognized versus forgotten (Janzen et al., 2008) in a recognition task. In our study, participants encoded the associations till criterion in both sessions, ensuring equal strength of encoding. Equal performance for both recent and remote memory retrieval (see Figure 5.2B) arguably allowed us to better specifically compare recent and remote memory retrieval, because our comparisons were not dependent on retrieval success but instead on a

more stringent comparison between retrieval-related activity and an inter-trial interval baseline.

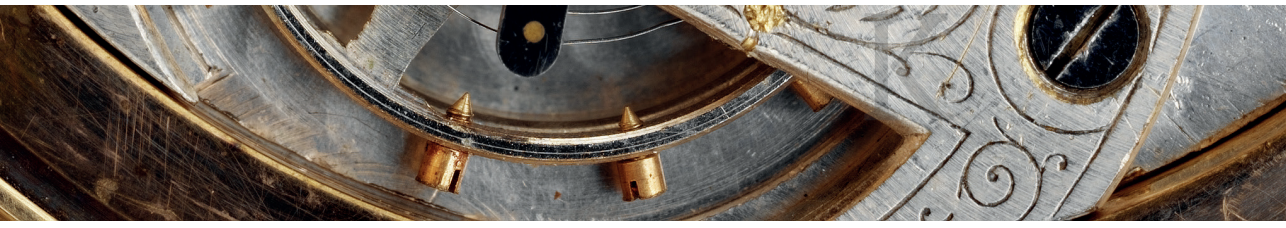
Even though we did not observe amplitude differences between recent and remote memories, there were differences in the conjunctive information present in the activity patterns, providing evidence for a consolidation-induced shift of conjunctive representations. The anterior, but not the posterior, hippocampus showed a difference in the amount of conjunctive information it represented for recent and remote memories. This observation is partially consistent with previous studies: there are a few activity-based reports of delay dependence in anterior hippocampus (Takashima et al., 2006; Milton et al., 2011), but even more in the posterior hippocampus (Takashima et al., 2009; Yamashita et al., 2009; Watanabe et al., 2012). Furthermore, a recent study employing pattern similarity analysis on an associative recognition task showed that patterns in posterior hippocampus became less similar after a one-day delay compared to immediately following learning, whereas anterior hippocampal patterns represented the recognized items for both immediate and delayed retrieval (Ritchey et al., 2015). Also studies investigating recent and remote autobiographical memories have reported mixed effects in anterior and posterior hippocampus. In one study, the anterior hippocampus was shown to be more involved in retrieval of recent than remote autobiographical memories (Gilboa, 2004). Another study, employing pattern classification, observed a reduction of pattern information over time for autobiographical memories in posterior hippocampus, while patterns in the anterior hippocampus were predictive of the retrieved episode for both recent and remote memory retrieval (Bonnici et al., 2012, 2013). Our findings are thus embedded in a literature with mixed results, which may be due to differences in delays and memory tasks.

Whereas the hippocampus contained less information for remote than recent memories, we observed the opposite pattern in the medial prefrontal cortex. Both animal and human neuroimaging studies have suggested that the medial prefrontal cortex is important for the retrieval of long-term memory, suggesting that this region may be the location of the proposed neocortical networks used for long-term memory storage (Marr, 1970; Goshen et al., 2011; Preston and Eichenbaum, 2013; Xu and Sudhof, 2013). Studies in rodents have shown that lesioning or inactivating the mPFC does not influence recent memories, but specifically disrupts remote memories. In a range of paradigms, this effect has been shown (Frankland et al., 2004;

Maviel et al., 2004; Takehara-Nishiuchi et al., 2006; Teixeira et al., 2006; Takehara-Nishiuchi and McNaughton, 2008; Lesburgueres et al., 2011). Consistent with this, neuroimaging studies have shown delay-dependent shifts of retrieval-related activity from the hippocampus to mPFC: memory retrieval was associated with increased mPFC activity over time, whereas the hippocampus showed decreasing activity (Takashima et al., 2006; Euston et al., 2007; Gais et al., 2007; Sterpenich et al., 2007; Takashima et al., 2009). Our results provide important new information to this line of research by showing that these activity differences may reflect a representational shift of conjunctive information as a result of consolidation.

Previous work on spatial memory suggests that the anterior hippocampus represents general spatial context, while the posterior hippocampus represents specific places (Poppenk et al., 2013; Evensmoen et al., 2015). We expected this effect to map onto our levels of conjunctive information during non-spatial retrieval (Milivojevic and Doeller, 2013). Our representational analyses indicate that during retrieval of recent memories, anterior hippocampus contains conjunctive information about the retrieved association on both a general category level and a specific association level. This indicates that anterior hippocampus initially codes conjunctive information at multiple levels of specificity. Over time, this representational role diminishes for both level of conjunctive information. The role of the medial prefrontal cortex, however, increases with time, but only for a more general level of conjunctive information. This is consistent with the proposed role of the medial prefrontal cortex in representing memories more gist-like and general over time (Wiltgen and Silva, 2007; Winocur et al., 2007; McKenzie and Eichenbaum, 2011). Our findings thus show a representational shift of general and specific conjunctive information in the hippocampus to a general conjunctive representation in medial prefrontal cortex.

In conclusion, we observed differences in the involvement of anterior and posterior hippocampus to memory retrieval at different time points after learning. Consistent with systems-level consolidation theory, the representational involvement of hippocampus diminished, while medial prefrontal cortex became more important for general remote memory representations. Although the representational involvement of the hippocampal subregions during consolidation will need to be clarified in future work, the present study extends existing literature by showing delay-dependent conjunctive coding at different levels in hippocampus and neocortex.



# 6

# General discussion

## 6.1. Introduction

In this thesis, I set out to investigate the main question: "How do the hippocampus and neocortex support memory retrieval?" I combined memory paradigms and novel analysis techniques from different field to investigate this main research question in four experimental chapters. I approached the main question in two ways: from the perspective of sensory cortex, where memories are reinstated, and from the perspective of the hippocampus, which codes for conjunctive information about the retrieved memories. In Chapter 2 and Chapter 3, I investigated retrieval from the cortical perspective by looking at the reinstatement of memory representations in sensory cortex (Chapter 2) and its relation to memory performance (Chapter 3). In the two remaining chapters, I looked at the role of the hippocampus as an index for conjunctive information between associated events as a function of associational strength (Chapter 4) and time delay between learning and retrieval (Chapter 5).

First, I will review the key observations that were discussed in the experimental chapters of this thesis. Subsequently, I will evaluate how these observations have furthered our knowledge in the field of memory. Then, I provide an outlook with research questions that future studies may answer. I will end this chapter with a conclusion.



## 6.2. Key observations

During memory retrieval, the hippocampus and neocortex are thought to interact to support the reinstatement of memories. In four experimental chapters, aspects of this reinstatement phenomenon were investigated. We made the following observations in these chapters:

1. Retrieval is associated with reinstatement of memory representations in early visual cortex (Chapter 2 and Chapter 3)

2. These representations carry information about the identity of the retrieved event (Chapter 2 and Chapter 3)

3. The reinstated representations in early visual cortex resemble those during passive perception (Chapter 2)

4. The quality of the reinstated pattern predicts precision on a memory task (Chapter 3)

5. Activity in the hippocampus covaries with the quality of the reinstated pattern (Chapter 2)

6. Activity in the recollection network (hippocampus, medial prefrontal cortex, angular gyrus, and retrosplenial cortex) covaries with memory performance (Chapter 3)

7. Hippocampus carries conjunctive information about newly acquired associations between stimuli (Chapter 4 and Chapter 5)

8. The hippocampus represents the predictability between these stimulus associations (Chapter 4)

9. Over time, the role of the hippocampus in representing conjunctive information about associations diminishes, while the medial prefrontal cortex becomes more important for conjunctive memory representation (Chapter 5)

## 6.3. Evaluation

To evaluate how the results answer the central question of how the hippocampus and regions in the neocortex support the reinstatement of previous experiences to guide behaviour, I will discuss the key observations outlined above in three subquestions: "How does the hippocampus represent associations?", "How does the sensory cortex represent memory representations during retrieval?", and "How do the hippocampus and neocortex interact during retrieval?".



### 6.3.1. How does the hippocampus represent associations?

During encoding, information is routed from early sensory cortices to neocortical association areas, which in turn project to the entorhinal cortex (ERC). The ERC receives and sends this multimodal information to the hippocampus (van Strien et al., 2009). The functional architecture of especially hippocampal subfield CA3 is well-equipped to auto-associate inputs that are processed close together in time through its recurrent connectivity (Grossberg, 1971; Kesner et al., 2008). The association of multiple events is thought to form a memory trace, which contains conjunctive information about the events that were bound together (Marr, 1971; Teyler and DiScenna, 1986). When at a later moment in time part of a pattern is fed into the CA3 autoassociative network, this input pattern may be pattern-completed into the stored memory trace (O'Reilly and McClelland, 1994; Norman and O'Reilly, 2003), thereby making the stored conjunctive information available again.

In Chapter 5, we show that the hippocampus indeed contains conjunctive information about the associations during retrieval, consistent with a number of recent studies on employing pattern analyses (Chadwick et al., 2010; Bonnici et al., 2012; Watanabe et al., 2012; Bonnici et al., 2013; Ritchey et al., 2015). This conjunctive information is represented both at a general association-category level as well as at an specific association-identity level. In Chapter 5, the retrieval process was triggered explicitly by presenting one member of an associated pair of stimuli. Our participants were instructed to retrieve the associated stimulus and indicate whether a probe stimulus matched their remembered associate. However, in Chapter 4, retrieval of the associated stimuli was not necessary during the representational change tasks, in which participants looked for greyscale patches in presented images. Interestingly, the hippocampal activity patterns for previously associated stimuli showed an increase in similarity after learning nonetheless, indicating that this retrieval process can happen automatically.



In Chapter 4, we investigated how predictability of one stimulus following another influences hippocampal representations. As observed before , the hippocampus showed higher activity for unpredictable than predictable stimuli during sequence learning (Strange and Dolan, 2001; Strange et al., 2005), consistent with the idea that the hippocampus acts as a mismatch detector (Jensen and Lisman, 1996; Colgin et al., 2009; Kumaran and Maguire, 2009). As a result of this learning, hippocampal patterns became more similar for stimuli that were strongly associated with each other during learning (transitional probabilities of 1). However, this similarity increase did not reflect temporal proximity between the associated stimuli, but rather their relevance for the sequence representation. Previous work considered paired associations and could not distinguish between proximity and relevance (e.g. Schapiro et al., 2012). These findings indicate that hippocampal conjunctive representations can 'skip' over less relevant parts of a learned sequence, and only represent the stimulus associations necessary for the prediction of an upcoming sequence.

Taken together, our results show that during learning, the hippocampus is sensitive to the associational strength of presented stimuli, such that it detects unpredictable transitions between associates, consistent with its hypothesized role in pattern separation (McNaughton and Morris, 1987; Treves and Rolls, 1994). After learning, the hippocampus represents conjunctive information about relevant members of stimulus associations, in

line with ideas of the hippocampus as a region of convergence for conjunctive information (Marr, 1971; Teyler and DiScenna, 1986; Damasio, 1989; Teyler and Rudy, 2007).

### 6.3.2. How does the sensory cortex represent memory representations during retrieval?

Previous studies showed reactivation of encoding-related areas in higher-order sensory areas (e.g. Nyberg et al., 2000; Wheeler et al., 2000). In Chapter 2 and Chapter 3, we showed that the early visual cortex can also support memory reinstatement, indicating that depending on the task at hand, memory representations for higher-order sensory or detailed low-level feature representations can be reinstated in their respective sensory areas. The representations that were reinstated carried information about the retrieved events: pattern classifiers could successfully predict the identity of the specific retrieved visual associations, whereas most previous studies could only provide evidence for category-specific (e.g. faces or objects) reinstatement (Polyn et al., 2005; Lewis-Peacock and Postle, 2008; Johnson et al., 2009; Liang et al., 2013; Gordon et al., 2014). The quality with which this information is reinstated related to precision on a memory task, providing evidence for the functional role of reinstatement for behaviour. Previous studies showed that reinstatement effects are greater for correct than for incorrect memory judgements in content-selective cortical regions (Kahn et al., 2004; Kuhl et al., 2011; Hofstetter et al., 2012; Staresina et al., 2012; Gordon et al., 2014; Kuhl and Chun, 2014). However, the results in Chapter 3 show that this link between reinstatement and behaviour is not all or nothing, but rather continuous: on a trial-by-trial level, memory performance and reinstatement strength are related.

Whereas previous studies found similarity between encoding and recall (Johnson et al., 2009; Ritchey et al., 2013; Gordon et al., 2014), they could not exclude that the reinstated mnemonic representations were influenced by factors such as attention or executive strategy at encoding (Chun and Turk-Browne, 2007), retrieval (Vicente-Grabovetsky et al., 2012) or both (Summerfield et al., 2006b). In Chapter 2, we used a well-controlled design to show that the patterns during active recall resembled those during passive perception of the same stimuli. This is remarkable, because it indicates that during reinstatement, a top-down process, the neural pattern in early visual cortex approximates bottom-up perception of a stimulus: cortical reinstatement can bring vivid low-level features back to the mind's eye. Even the lowest levels of the visual hierarchy thus seem to play a role

in memory processes, rather than just serving as an entry point for sensory information (Rao and Ballard, 1999). Several studies have shown that activity patterns in visual cortex are predictive of specific visual stimulus properties (Kamitani and Tong, 2005), the attentional state of the observer (Kamitani and Tong, 2005; Jehee et al., 2011), unconscious perception of a stimulus (Haynes and Rees, 2005) and the identity of viewed natural images (Kay et al., 2008). However, also during working memory (Harrison and Tong, 2009; Serences et al., 2009; Xing et al., 2013) and imagery (Albers et al., 2013) visual activity patterns contain stimulus-specific information about the maintained or imagined stimulus. These shared neural representations between perception and working memory, imagery and memory reinstatement (see Chapter 2) suggest that all these processes might be implemented similarly in sensory cortex (Tong, 2013) and highlight the role of sensory cortices as a dynamic blackboard for the integration of bottom-up sensory and top-down processing (Mumford, 1991; Bullier, 2001; Roelfsema, 2005; Addis et al., 2007). This is consistent with the predictive coding theory, which posits that the brain continuously tries to predict incoming and future input on the basis of experiences, and thereby to minimise the difference between input and prediction (Friston, 2005). In such a framework, retrieval-based predictions are important at every level of processing: even simple bottom-up perception can be shaped by top-down prediction. Perhaps this is why we observe such striking similarity between the visual patterns during active recall and passive perception.



Taken together, our results show that reinstatement can bring back memory representations to the sensory cortices where they were initially processed during encoding. These representations are stimulus-specific and may resemble not only encoding-related, but also passive-perception-related patterns of activity. The strength with which a memory representation is reinstated can predict the precision of memory-based decisions. These findings fit well with the theory of cortical reinstatement as a mechanism for memory retrieval (Tulving, 1983; Rugg et al., 2008; Danker and Anderson, 2010).

### **6.3.3.** How do the hippocampus and neocortex interact during retrieval?

From the previous sections, we have learned that during retrieval, the hippocampus represents conjunctive information about learned associations, while the sensory cortex represents specific information about the event that is retrieved. The hippocampus is thought to mediate successful cortical reinstatement (Marr, 1971; Eichenbaum et al., 1992; Alvarez and

Squire, 1994; Norman and O'Reilly, 2003; Squire et al., 2004), possibly by using its conjunctive representation to reactivate specific cortical traces related to the association (Carr et al., 2011). Indeed, a recent animal study showed that the hippocampus is causally involved during successful fear memory retrieval (Tanaka et al., 2014). Also in human fMRI studies, stronger hippocampal activity has been observed for correct than for incorrect memory reinstatement trials (Davachi et al., 2003; Duzel et al., 2003; Kuhl et al., 2011; Liang et al., 2013; Staresina et al., 2013; Gordon et al., 2014). Recent studies found correlations between hippocampal activity and encoding-retrieval pattern similarity in parahippocampal cortex (Staresina et al., 2012) and inferior frontal gyrus (Ritchey et al., 2013). In Chapter 2 and Chapter 3, we extend these findings by showing that activity in the hippocampus covaries with reinstatement strength in sensory cortex (Chapter 2) and with fluctuations in trial-by-trial memory performance (Chapter 3), corroborating the importance of cortico-hippocampal interactions for reinstatement and memory-based behaviour. However, the hippocampus and content-selective sensory cortex are not the only regions involved during memory retrieval: a number of non-content-selective regions also show higher activity for successful retrieval, including parahippocampal, retrosplenial/posterior cingulate, lateral parietal, and medial prefrontal cortices (Duarte et al., 2011; Hayama et al., 2012; Rugg and Vilberg, 2013). Together with the hippocampus, these regions have been dubbed the recollection network, because they show higher activity for recollection than for familiarity (Rugg and Vilberg, 2013). Specifically, activity in the angular gyrus and in the hippocampus was shown to be sensitive to confident and correct source memory judgments (Glanzer et al., 2004; Slotnick and Dodson, 2005; Mickes et al., 2009; Yu et al., 2012; Thakral et al., 2015). In Chapter 3, we showed that activity fluctuations in left hippocampus, medial prefrontal cortex, left angular gyrus and retrosplenial cortex predict mnemonic precision on a trial-by-trial level, consistent with these regions' putative role in the support and maintenance of consciously accessible memory representations (Rugg and Vilberg, 2013).



Two regions in the recollection network were consistently involved in the experiments described in this thesis: the hippocampus and medial prefrontal cortex. In Chapter 3, we report that during retrieval, connectivity between hippocampus and medial frontal cortex modulates memory precision, which dovetails with the idea that prefrontal cortex can bias the hippocampus towards context-specific memory representations after a retrieval cue (Miller and Cohen, 2001; Preston and Eichenbaum, 2013). Fur-

thermore, both hippocampal and medial prefrontal cortex were sensitive to the associational strength between stimuli presented in a sequence during learning (Chapter 4). Previous studies have suggested involvement of the hippocampus (Schendan et al., 2003; Kumaran and Maguire, 2006; Bar, 2009; Kalm et al., 2013; Schapiro et al., 2014) and medial prefrontal regions (Shimamura et al., 1990; Kesner et al., 1994; Marshuetz, 2005; Hales and Brewer, 2011) in the representation of sequential events. Hippocampal and medial frontal activity have been linked to scene construction and spatial memory (Hassabis et al., 2007; Hassabis and Maguire, 2007; Doeller et al., 2008), but also the formation of associative links (Davachi, 2006; Zeithamova et al., 2012) and constructive episodic simulation (Addis et al., 2007; Schacter and Addis, 2007; Barron et al., 2013).

Additionally, cross-talk between these regions may support the integration of information across events (Ranganath et al., 2005; Gais et al., 2007; van Kesteren et al., 2010; Zeithamova et al., 2012) into associational knowledge networks called schemas (Bartlett, 1932; Tse et al., 2007; van Kesteren et al., 2010; Wang and Morris, 2010). The results from Chapter 5 are consistent with this integration hypothesis: we showed that the hippocampal involvement in representing conjunctive information diminishes with time, while the medial prefrontal cortex showed the opposite pattern. Both animal and human neuroimaging studies have suggested that the medial prefrontal cortex is important for the retrieval of long-term memory (Frankland et al., 2004; Maviel et al., 2004; Takashima et al., 2006; Takehara-Nishiuchi et al., 2006; Teixeira et al., 2006; Euston et al., 2007; Gais et al., 2007; Sterpenich et al., 2007; Takehara-Nishiuchi and McNaughton, 2008; Takashima et al., 2009; Lesburgueres et al., 2011), suggesting that this region may be the location of the proposed neocortical networks used for long-term memory storage (Marr, 1970; Goshen et al., 2011; Preston and Eichenbaum, 2013; Xu and Sudhof, 2013). Our findings extend this literature by showing that this shift from hippocampus to medial prefrontal cortex reflects the transfer of conjunctive information. Taken together, these results support the theory that hippocampus and neocortical areas interact to support successful reinstatement of memory representations in sensory cortex, mediated by subtle activity fluctuations in the regions of the recollection network. Specifically the interaction between the medial prefrontal cortex and the hippocampus may integrate conjunctive representations into neocortical associational networks for long-term storage (Preston and Eichenbaum, 2013).

Summarized, the results from the four experimental chapters form a coherent picture, that answer parts of our main question: "How do the hippocampus and neocortex support memory retrieval?" In the four experimental chapters, I have studied the nature of hippocampal and cortical representations during retrieval, as well as their interaction. In particular, I was interested in the quality of the cortical and hippocampal memory representations, how their quality relates to retrieval success, and the fate of these representations over time. The results paint the following picture of how the hippocampus and neocortex reactivate: when encoding new information, the hippocampus is sensitive to the strength of associations between encoded stimuli (Chapter 4). The conjunctive information about associated stimuli is represented in the hippocampus (Chapter 5) by storing relevant stimulus associations in similar neural representations (Chapter 4). Through consolidation, the representational role of the hippocampus diminishes, whereas the medial prefrontal cortex takes over the representation of general conjunctive information (Chapter 5). Upon presentation of a retrieval cue, the hippocampus retrieves this conjunctive information and reinstates the associated memory representation in sensory cortex (Chapter 2, Chapter 3 and Chapter 5). The quality of the reinstated representation is signalled by the activity in hippocampus (Chapter 2) and predicts memory performance (Chapter 3) on a trial-by-trial level. This reinstatement process in hippocampus and sensory cortex is mediated by the recollection network, whose activity relates to memory precision: specifically , connectivity between the hippocampus and medial prefrontal cortex supports memory performance (Chapter 3).



## 6.4. Outlook

The results from the studies in this thesis have answered and clarified research questions, but also raised new questions. I will discuss two avenues that future research may take.

### 6.4.1. The link between memory and prediction

We have seen that in sensory cortex, memory reinstatement and perception share similar representations (Chapter 2). Furthermore, even when participants are not explicitly retrieving associations, the hippocampus still shows sensitivity to these learned associations by increasing the neural similarity between its constituent parts (Chapter 4). This might indicate that the hippocampus continuously tries to predict upcoming events on the basis of retrieval-mediated predictions (Buckner, 2010). A few electrophysiological

studies in freely navigating animals suggest that the hippocampal place cells code for upcoming positions of an animal in the environment (Diba and Buzsaki, 2007; Dragoi and Tonegawa, 2011), indeed suggesting a prospective role for the hippocampus. Furthermore, the hippocampus is involved in episodic future thought (Hassabis et al., 2007; Schacter and Addis, 2007). How similar exactly retrieval and simulation are, is an exciting avenue for future research: how do hippocampal predictions influence the processing of incoming information through for example attention? Does the same mechanism support effortful retrieval and implicit predictions?

### **6.4.2.** Anterior hippocampus versus posterior hippocampus

Anterior and posterior hippocampus are thought to differ in their memory functions, both in the spatial and non-spatial memory domains (Moser and Moser, 1998; Milivojevic and Doeller, 2013; Poppenk et al., 2013). The anterior hippocampus (which is the ventral part of hippocampus in rats) is thought to be more involved in global episodic memory representation, as evidenced by the relatively large place fields of its place cells (Kjelstrup et al., 2008) and its involvement in representing coarse object and landmark locations (Ekstrom et al., 2011; Evensmoen et al., 2015), as well as gist-like memory representations (Poppenk et al., 2008; Gutchess and Schacter, 2012). The posterior hippocampus, in contrast, may be more involved in specific memory representations (Davachi, 2006; Eichenbaum et al., 2007; Ranganath, 2010; Milivojevic and Doeller, 2013). In the studies described in this thesis, we consistently observe involvement for the anterior hippocampus during retrieval, even though participants were asked to retrieve specific memories. One interesting suggestion is that due to the repeated co-occurrence of the associated stimuli during retrieval, a new, more general representations might evolve (Kumaran and McClelland, 2012; Milivojevic and Doeller, 2013). Future research should try to identify what levels of conjunctive information is represented in the hippocampus, where these representations are stored, how they interact with neocortical representations and how they link to memory behaviour.



## **6.5.** Conclusion

In this thesis, I set out to understand the mechanisms by which the neocortex and the hippocampus support memory retrieval. I conducted four experimental studies to tackle this question from two different perspectives: from the sensory cortex, in which the memory representations are reinstated, and from the hippocampus, in which associations are bound and

indexed. From these studies, we conclude that memory retrieval is associated with stimulus-specific reinstatement of memory representations in early visual cortex. The activity patterns in sensory cortex during reinstatement resemble those during perception, and predict precision on a memory task on a trial-by-trial basis. Memory performance is furthermore modulated by activity in a network of non-content-selective regions. Hippocampal activity covaries with the strength of cortical reinstatement and memory performance. In the hippocampus, conjunctive information about associated events is represented at multiple levels. This conjunctive representation is dependent on the associative strength between the constituent parts of an association. Over time, the hippocampus loses its representational function, but medial prefrontal cortex may take over the conjunctive representation of general associations. In future studies, it will be important to 1) investigate the similarities between the memory and prospective functions in the hippocampus and neocortex, and 2) further explore the levels at which conjunctive information is represented, their respective locations in the hippocampus and their roles in guiding memory-based decisions. The Time Traveller may conclude that if memory retrieval is 'mental time travel', the interaction between the hippocampus and neocortex can be seen as the time machine that makes this possible.

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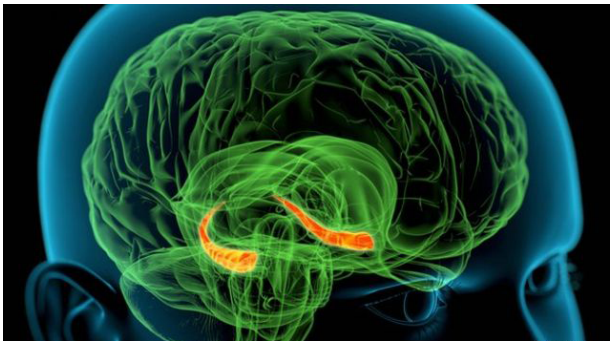
# Nederlandse samenvatting

De tijdreiziger van H.G. Wells beschrijft herinneren als 'mentaal tijdreizen'. Als we ons een meegemaakte gebeurtenis levendig herinneren, lijkt het soms inderdaad alsof we terugreizen in de tijd naar het moment van die gebeurtenis: we zien, horen en ruiken misschien zelfs de onderdelen van de herinnering. Het terughalen van herinneringen is cruciaal in het dagelijks leven. We gebruiken continu wat we nog weten van eerdere ervaringen om ons gedrag aan te passen op wat we verwachten dat gaat gebeuren. Maar hoe werkt het terughalen van herinneringen eigenlijk in de hersenen? In dit proefschrift heb ik dit mechanisme onderzocht door middel van vier experimentele studies. Een speciale rol lijkt weggelegd voor de hippocampus.



**Figuur 6.1: De hippocampus (in oranje) zit diep weggestopt in de hersenen**
Roger Harris/Science Photo Library

De hippocampus, een evolutionair oude structuur in het brein, is erg belangrijk voor het geheugen. De hippocampus zit diep weggestopt in de hersenen (zie Figuur 6.1) en is vanwege zijn vorm genoemd naar het Griekse woord voor zeepaardje. Veel van wat we weten van het geheugen en de rol die de hippocampus hierin speelt, komt van patiëntstudies. Het bekendste voorbeeld is Henry Molaison, beter bekend onder zijn initialen H.M., die leed aan ernstige epilepsie. De oorzaak van zijn epileptische aanvallen lag in de beide temporaalkwabben, waar de hippocampi zijn gesitueerd. Tijdens een chirurgische ingreep werden zijn hippocampi verwijderd in de hoop dat hiermee de aanvallen in hevigheid en frequentie zouden verminderen. Na

deze ingrijpende operatie ontwikkelde H.M. specifieke geheugenproblemen. Zo kon hij zich recent geleerde informatie niet meer herinneren, terwijl de herinneringen van zijn jeugd gespaard bleven. Interessant genoeg kon hij nog wel nieuwe motorische vaardigheden leren en onthouden.

Sinds de eerste patiëntstudies hebben we veel geleerd over de rol van de hippocampus in het geheugen. De hippocampus wordt nu gezien als de hersenstructuur die informatie krijgt van alle sensorische gebieden en deze informatie samenvoegt tot herinneringen. In de jaren '80 bedacht Endel Tulving hoe het brein het mogelijk maakt om gebeurtenissen te herinneren. Hij voorspelde dat de sensorische corticale hersengebieden (visueel, auditief, tast, smaak en geur) die actief waren tijdens de originele gebeurtenis, opnieuw actief zouden worden tijdens het herinneren van die gebeurtenis. Hij noemde dit fenomeen cortical reinstatement en verwachtte dat de hippocampus hierin een belangrijke rol zou spelen.

Pas vrij recent is het mogelijk geworden om direct te bestuderen wat er in de hersenen gebeurt tijdens het herinneren. Voor de studies in dit proefschrift heb ik gebruik gemaakt van functional magnetic resonance imaging (fMRI). Bij fMRI wordt de hoeveelheid bloed in en toevoer naar hersengebieden gemeten. Elk molecuul hemoglobine (Hb) kan tot vier zuurstofmoleculen transporteren door de bloedbaan. Als een Hb-molecuul geen zuurstof heeft, ligt de ijzerkern van het molecuul bloot, wat het magnetisch veld van de MRI verstoort. Zuurstofarm bloed zorgt dus voor een slechter signaal dan zuurstofrijk bloed. Als een hersengebied actief wordt, verbruikt het zuurstof en glucose. Om ervoor te zorgen dat het hersengebied niet 'droog' komt te staan, komt er een hemodynamische respons op gang. Dit betekent dat er vers, zuurstofrijk bloed naar het actieve gebied wordt gepompt. Dit verse bloed zorgt voor een beter MRI-signaal. Op deze manier is het mogelijk op een indirecte manier actieve hersengebieden te lokaliseren.

In de studie in Hoofdstuk 2 heb ik onderzocht of de theorie van Endel Tulving klopt. Eerder onderzoek toonde al aan dat hogere sensorische gebieden opnieuw actief worden wanneer proefpersonen zich iets herinneren, maar het was onduidelijk wat deze activatie reflecteerde. Betekende de reactivatie dat precies dezelfde representatie als tijdens het waarnemen weer werd gereactiveerd op dezelfde plek? Met andere woorden, is perceptie enigszins gelijk aan geheugen in de sensorische cortex? Om deze vraag te beantwoorden, heb ik simpele stimuli gebruikt: auditieve tonen en visuele oriëntaties. Aangezien bekend is waar en hoe deze stimuli worden gere-

presenteerd in het brein, wist ik precies waar ik de activatie en reactivatie moest verwachten. Participanten leerden associaties tussen de tonen en de visuele oriëntaties. In de MRI-scanner kregen ze de tonen weer te horen en moesten ze zich herinneren welke oriëntatie daarbij hoorde. Ik keek specifiek naar de activatiepatronen in de visuele cortex, waar ik de reactivatie verwachtte. Aan de hand van patronen van visuele hersenactiviteit tijdens het herinneren kon ik voorspellen welke oriëntatie de proefpersonen zich herinnerden. Daarnaast kon ik aantonen dat deze patronen tijdens het herinneren erg lijken op de patronen tijdens passieve waarneming van dezelfde visuele oriëntaties. Tulving had dus gelijk: als je je iets herinnert, wordt de originele representatie weer gereactiveerd in de sensorische cortex. Ik vond dat hoe sterker de reactivatie in de visuele cortex, hoe sterker de activatie in de hippocampus. De hippocampus lijkt dus belangrijk te zijn voor de reactivatie.

In Hoofdstuk 3 bouwde ik voort op de resultaten van Hoofdstuk 2. Ik onderzocht hoe de reactivatie in de visuele cortex en hippocampus samenhangt met hoe goed proefpersonen scoorden op een geheugentaak. Proefpersonen leerden weer associaties tussen tonen en visuele oriëntaties. In de MRI-scanner hoorden ze de tonen en herinnerden zich de bijbehorende oriëntatie. Hierna kregen ze een lijnsegment te zien op het scherm, dat ze konden roteren tot de oriëntatie die ze zich herinnerden. Op deze manier kon ik onderzoeken of de mate van reactivatie in de visuele cortex samenhangt met de geheugenscore van de proefpersonen. Dit bleek inderdaad zo te zijn: hoe sterker de reactivatie, hoe hoger de geheugenscore. Verder vond ik dat een hogere geheugenscore samenging met een hogere activatie in de hippocampus. Deze studie toonde dus aan dat de mate van cortical reinstatement invloed heeft op de geheugenscore van proefpersonen tijdens een geheugentaak.

Waar Hoofdstuk 2 en Hoofdstuk 3 gefocust waren op de reactivatie in de visuele cortex, heb ik in Hoofdstuk 4 bekeken hoe de hippocampus de associaties representeert. Zoals hierboven al beschreven, is de hippocampus belangrijk voor het associëren en verbinden van verschillende sensorische elementen. Maar hoe gebeurt dat als de elementen na elkaar in een sequentie worden gepresenteerd? In deze studie kregen proefpersonen in de MRI-scanner plaatjes te zien (gezichten, huizen en objecten), waarvan sommige plaatjes altijd op dezelfde andere volgden. De taak van de proefpersonen was om te vinden welke plaatjes samen een sequentie van drie vormden. Bij twee sequenties was dat gemakkelijk; de plaatjes volgden elkaar altijd op.

Bij twee andere sequenties was het laatste plaatje niet te voorspellen. Het doel was om te onderzoeken of de hippocampus deze sequenties anders zou representeren. Proefpersonen reageerden sneller op plaatjes uit voorspelbare dan uit deels onvoorspelbare sequenties. De hippocampale representaties van plaatjes in de voorspelbare sequenties waren meer gelijk aan elkaar dan die van de onvoorspelbare sequenties. De hippocampus 'groepeerde' de plaatjes dus aan de hand van de voorspelbaarheid. Dit betekent dat de hippocampus bij elkaar horende stimuli kan samenbinden, ook al worden ze na elkaar gepresenteerd.

In Hoofdstuk 5 onderzocht ik de rol van de hippocampus tijdens het herinneren van 'oude' versus 'recente' herinneringen. Zoals eerder beschreven, kon patiënt H.M. zich zijn jeugd nog wel herinneren. Is de hippocampus wel altijd nodig voor het herinneren van informatie? Of wordt deze rol met de tijd overgenomen door een ander hersengebied? De consolidatietheorie voorspelt dat de hippocampus inderdaad geleidelijk minder belangrijk wordt voor het herinneren van informatie, terwijl de mediaal prefrontale cortex deze rol langzaamaan overneemt. Ik wilde weten of de informatie over de associatie van verschillende elementen (de conjunctieve informatie) inderdaad verplaatst van de hippocampus naar de mediaal prefrontale cortex. Proefpersonen leerden associaties tussen gezichten, huizen en lichamen en moesten zich in de MRI-scanner herinneren welke plaatjes bij elkaar hoorden. In één sessie leerden ze deze associaties 30 minuten voordat ze de scanner ingingen; in een andere sessie (met nieuwe associaties) zat er een week tussen leren en herinneren in de scanner. De hippocampus bevatte meer conjunctieve informatie voor recent dan langer geleden geleerde informatie, terwijl de mediaal prefrontale cortex juist meer informatie bevatte voor 'oude' herinneringen. In deze studie vond ik dus bewijs voor de consolidatietheorie.

Het 'mentaal tijdreizen' van de tijdreiziger is nu onderwerp van veel wetenschappelijk onderzoek. De studies in dit proefschrift hebben vanuit verschillende perspectieven bijgedragen aan het ontrafelen van het mechanisme dat ervoor zorgt dat we ons eerder geleerde informatie kunnen herinneren. De hippocampus staat in dit mechanisme centraal: het bindt tijdens perceptie verschillende sensorische elementen aan elkaar. Dit kunnen elementen zijn vanuit één zintuig (Hoofdstuk 5) of verschillende zintuigen (de tonen en oriëntaties uit Hoofdstuk 2 en Hoofdstuk 3), maar ook elementen die sequentieel worden waargenomen (Hoofdstuk 4). Als op een later moment een element van een associatie opnieuw wordt gepresenteerd, vult de

hippocampus de associatie aan en reactiveert de bijbehorende representatie in de sensorische cortex om gedrag te beïnvloeden. Als herinneren mentaal tijdreizen is, kan de interactie tussen de hippocampus en de neocortex dus gezien worden als de tijdmachine die dit mogelijk maakt.

# List of publications

## Journal articles

1. **Bosch SE***, Backus AR*, and Doeller CF (in preparation) Memory representations shift from hippocampus to medial frontal cortex through memory consolidation.

2. **Bosch SE***, Milivojevic B*, Smulders PWA, de Lange FP and Doeller CF (in preparation) Prospective event representation through hippocampal regularity learning.

3. Backus AR*, **Bosch SE***, Ekman M, Vicente-Grabovetsky A, Doeller CF (in revision) Mnemonic convergence in the human hippocampus.

4. **Bosch SE**, Doeller CF (in revision) Cortical reinstatement predicts precision of mnemonic decisions.

5. **Bosch SE**, Jehee JF, Fernandez G, Doeller CF (2014) Reinstatement of associative memories in early visual cortex is signaled by the hippocampus. *Journal of Neuroscience*, **34**, 7493-7500.

6. **Bosch SE**, Neggers SF, Van der Stigchel S (2013) The role of the frontal eye fields in oculomotor competition: image-guided TMS enhances contralateral target selection. *Cerebral Cortex*, **23**, 824-832.

7. van der Ham IJ, van Zandvoort MJ, Meilinger T, **Bosch SE**, Kant N, Postma A (2010) Spatial and temporal aspects of navigation in two neurological patients. *Neuroreport*, **21**, 685-689.

* denotes equal contributions.

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Beginnen aan het dankwoord is niet gemakkelijk. Het voelt als de kers op de spreekwoordelijke (zelfgebakken) taart zetten: je wil hem precies goed plaatsen. Dit proefschrift is mede mogelijk gemaakt door een heleboel mensen. Het is een hopeloze taak om te proberen aan ieder van hen recht te doen, maar *here goes*.

Richting het einde van mijn onderzoeksstage in Londen in 2010, stond ik op een avond met de senior postdoc van de groep, Christian Doeller, in de pub *The Swan* (of was het *The Lamb?*). Christian, na dat stevige 'sollicitatiegesprek' vertelde jij me dat je misschien naar Nijmegen zou komen, en als dat zo zou zijn, ik je mocht komen versterken in je kersverse *Memory and Space* groep. Zo geschiedde, en wat hebben we veel meegemaakt. Gedurende mijn promotie is de groep tot een vaste waarde binnen het DCCN gegroeid, met de bijbehorende beurzen, mooie papers en media-optredens. Het had ook niet anders kunnen lopen: je bent een perfect voorbeeld van 'work hard, play hard'. Ik heb bewondering voor je ambitie en doelgerichtheid, maar zeker ook voor je humor, je vriendelijkheid, je vermogen om bier te drinken en natuurlijk je dansmoves. Ik ben er trots op dat jij regelmatig de 'last PI standing' was op sociale Donders-evenementen! Daarnaast waardeer ik je optimisme, dat ervoor zorgde dat problemen met nare reviews en frustrerende data al snel niet zo onoverkomelijk meer leken. Bedankt voor je bezielende begeleiding en vriendschap. Ik hoop dat we nog veel kunnen samenwerken in de toekomst.

Uit onze eerste brainstormsessies in 2011 kwamen grote plannen. Met ons gecombineerde optimisme bedachten Christian en ik dat geheugen in de vroege visuele cortex te bestuderen moest zijn. Wij hadden echter allebei geen idee hoe we dat moesten bewerkstelligen. Janneke, bedankt voor het warme welkom in je VisComp-groep en de introductie tot de wondere wereld van het visuele systeem! Ik heb veel geleerd van je scherpe kijk op experimenteel design en je uitgebreide kennis van wat er gebeurt in de visuele cortex.

Uit Utrecht kende ik vaag een jongen van mijn MSc-opleiding, die ik weer tegenkwam in Nijmegen. Hij kwam als PhD-student in de groep, kreeg een kantoor vlakbij het mijne, en de rest is geschiedenis. Alex, we zijn wel eens broers genoemd binnen het DCCN (bosbac fusion, haa!). Hele treinreizen, werkdagen, kroegavonden en conferentienachten (uitkijkend over San Diágo bay) hebben we geouwehoerd en gelachen over filmquotes, wetenschap, het leven en alles ertussenin. Laten we nog vaak tot sluit blijven zitten in café Vredenburg!

Soms, of eerder regelmatig, verscheen er een hoofd vanuit kamer 1.16 in de deuropening: "Hee hoi!", met de vraag om thee te drinken, over de wereld te praten of te honkballen. Jolien, wat een goede avonturen hebben we beleefd. Van wetenschapsgroentjes tot doctoren, ik heb altijd genoten van je mooie perspectief op leven en werk, je vrolijke drukte met allerhande projecten en de altijd klaarstaande hete (of warme/lauwe/koude) thee!

Kindled by Christian's enthusiasm and ambition, the Doellerlab has grown from a two-man group (100% attendance at group lunch!) into a big and lively group of hippocampal enthusiasts. Ben, Sasha, Alex, Tobias, Branka, Peter, Daniel, Nils, Silvy, Jacob, Lorena, Meryl, Lanjo (pls), Nynke, Naomi, Stephanie, David, Staudi and Jackeline, thank you for all the fun during group meetings, DCN drinks, retreats (Schnitzel Samstag), Katja's Bodyscan (she has a working hippocampus!), and of course our US conference experiences! I will never forget the limousine ride in Seattle, the barbecues at our San Diego mansion, the epic Doellerwall at the poster presentations, eerie nightfall at the Salton Sea, and watching rockets at the space museum in DC.

VisComp lab, Janneke, Ruben, Jasper, Klaudia, Rosanne, Koen, Andrea, thank you for including me in your group meetings and lunches. You've taught me all I know about vision! Ruben, I very much enjoyed working together on the creation of our baby girl, DoReti.

Due to the renovation I've had the opportunity to share offices with quite a few Donderians. Joost, you already were a DCCN icon when I first came to you for the check-in in room 1.18 on a sunny March morning in 2011. Thank you for showing me the way in this weird triangular building. Tom, there are few people with a mind as quick and piercing as yours. I could listen to your on-point rants about whatever topic for hours :). Flora, I liked our chats and loved singing Clouseau songs with you during karaoke

nights. Elexa, Mao and Dan, thanks for our brief but pleasant time in a now refurbished room on the first floor. Erik and Iske, I enjoyed the months in our admin/PhD-postdoc-limbo office. All the best for you!

The Donders is a vibrant place, mostly due to the Social Donderians. I can't do justice to every social Donderian, but Jolien, Alex, Eelke, Jeanette, Anke Marit, Loek, Mirjam, Jeroen, Linda, Ruud, Isabella, Tom, Iske, Flora, Ruben, Eelco, Verena, Winke, Tim, Susanne, Richard, Lieneke, Monja, Marlieke, René, Sasha, Sean, Til, Lennart, Arjen, thank you for your contributions to a happy work environment! I enjoyed your company and our adventures during the Dagjes Uit, Thursday lunches, karaoke nights, conferences and drinks.

The DCCN is a well-oiled research machine that runs on inspiring scientific leadership by David, Peter, Guillèn, Christian, Floris, Ivan, Roshan, Christian, Janneke, Alan, Karin and Ole. However, a machine needs maintenance and proper administration to run smoothly. Marek, Erik, Edward, René, Uriel, Mike, Jessica, Hong and Sander, thank you for the technical support that makes doing science at the DCCN so easy. Sandra, Nicole, Ayse, Joost and Petra, thank you for running the administration so very well. Arthur and Berend, thank you for your tireless efforts to keep the DCCN running (with a smile!). Tildie, thank you for being the ever cheerful heart of the centre.

Paul, de koning van de kelder, jij krijgt een eigen paragraaf. Bedankt voor het delen van je wijsheid en kennis over je geliefde scanners, maar nog meer voor de leuke gesprekken en geintjes. Ik heb met veel plezier als super-certified user van je geleerd en op de scanners gepast. Ik hoop je nog vaak tegen te komen in de kelder (misschien toch een keer iets doen met dat Tetris-project!?).

Tijdens mijn promotie heb ik de eer gehad verschillende studenten te mogen begeleiden. Lonja, Lara en de vele lab rotation studenten, dank jullie voor jullie inzet en enthousiasme. Graag bedank ik ook mijn participanten (zeker degenen die mee hebben gedaan aan de grating-experimenten; het was geen lolletje) voor hun inzet en de data, mijn co-auteurs voor de o zo belangrijke tweaks aan de manuscripten en mijn reviewers (behalve reviewer #3 van project [morrea], hij/zij heeft mijn dank niet verdiend), die me hebben geleerd dat hoe zeer je ook gelooft in jouw interpretatie van de data, er altijd een ander perspectief te vinden valt.

Als ik na een lange dag Matlabben en een 'verfrissende' treinreis weer in Utrecht aankwam, kon ik meestal wel een verzetje gebruiken. Gelukkig stonden/staan er altijd vrienden voor me klaar die me energie kunnen geven. Marieke, Juul, Jesper, Jordi, Jan, Herwin, Lieke, Michelle, Wahyu, Magelien, Mark, Marina, Marlous, Michiel, Danjel, Stefanie, Jaap, Bob en Sander, mijn liefste VV de KK, of we nou in Cuijk, Utrecht of Amsterdam samenkomen, onze band is met de jaren alleen maar hechter geworden. Ik kijk alweer uit naar de komende weekenden, carnavals, sentimentele fases. Ik prijs me gelukkig dat ik bij jullie hoor.

Sinds 2005, vanaf het eerste jaar, wordt er op dinsdag gegeten, of er nu twee of tien mensen zijn. Hoewel de bierconsumptie door de jaren heen op de dinsdagavond ietwat is afgenomen, is de hoeveelheid (redelijk kritisch) geouwehoer onverminderd. Michiel, Aurin, Brand, Jaap, Jeroen, Rogier, Simon, Johan en Ralf, Bruuske mannen, wat zijn jullie een stel bazen. Ik kijk uit naar de vuist!

Mijn beste Dingles, het begon met een vrij willekeurige groep studenten bij de pubquiz in de Mick, maar inmiddels zijn we uitgegroeid tot een mooie club met weekendjes, (amateur-)voetbal, televisie-optredens (festival op Terschelling?) en de nodige dobbelspelletjes (HET,IE,NIE). Carlijn, Marc, Marieke, Martijn, Lianne, Mirjam, Ralph, Robert, Caroline, Tieme, Gijs, Michiel, Suzette en Yannick, laten we proosten!

Lieve pap en mam, bedankt voor jullie interesse en aanmoediging in alles wat ik ooit gedaan of geprobeerd heb. Bedankt voor het voeden van mijn nieuwsgierigheid en het zorgen voor een liefdevol en veilig nest om af en toe naar terug te keren. Ik hou van jullie. Paul en Monique, het voelt alsof ik twee thuizen heb in Cuijk. Bedankt dat jullie me hebben opgenomen in de Dekker-clan. Wie weet, misschien komen Marieke, Archibald/Brunhilda en ik wel snel terug naar Kuuk (Sander d'n Urste, 2022 regelt zichzelf tenslotte niet). Stijn, wat ben jij een topvent, ik ben er trots op je swagger te mogen noemen. Carli, lief zusje, je bent mijn heldin. Wat leuk dat je mijn paranimf wil zijn! Don't you ever change.

Lieve Marieke, elke dag met jou is weer een feest. Ik weet het al een hele tijd: met jou wil ik oud worden. Ik ben blij dat ik je mijn vrouw mag noemen en dat we binnenkort samen een nieuw leven mogen verzorgen. Bedankt voor je onvoorwaardelijke steun en liefde (en het koken elke avond). ibgmlvj

# Curriculum Vitae

**Sander E. Bosch**

Sander Bosch was born in Nijmegen on January 14, 1987. He graduated from high school at the Merletcollege Cuijk in 2004. He subsequently completed a BSc at University College Utrecht (2008, magna cum laude), where he combined courses in cell biology and neuroscience with (clinical) psychology and philosophy. Then, he pursued the MSc-programme Neuroscience & Cognition at Utrecht University, where he graduated in 2011 (cum laude).

During the course of his studies, he completed two research internships, the first of which at Utrecht University. In this project, he worked with Dr. Stefan van der Stigchel and Dr. Bas Neggers to investigate the role of the frontal eye fields in oculomotor control using MRI-guided transcranial magnetic stimulation. During the second research internship, at the Institute for Cognitive Neuroscience, University College London, he worked with Prof. dr. Neil Burgess, Dr. Chris Bird and Dr. Christian Doeller on memory reconsolidation in virtual reality environments.

In March 2011, Sander started his PhD-programme at the Donders Institute under supervision of Prof. dr. David Norris and Dr. Christian Doeller. He investigated the neural correlates of memory retrieval in several experiments, combining tasks from visual psychophysics with functional MRI. During his doctorate, he set up and coordinated the BSc-level course *Introduction to Cognitive Neuroimaging* and participated actively in several initiatives on knowledge dissemination to the general public, such as the Brain Awareness Week, the IMC Weekendschool and several popular science TV- and radio-shows.

Sander is currently a postdoctoral researcher in the group of Dr. Marcel van Gerven at the Donders Institute, where he investigates the interaction between perception and memory with deep neural networks and other computational models.

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